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Faculty of Health Sciences

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PHYSIOTHERAPY FOR CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

A dissertation submitted in fulfilment of the requirements for the degree Doctor of Philosophy (PhD) in Physiotherapy

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Date: December 2019

DECLARATION

I declare that this thesis titled 'Physiotherapy for central vestibular dysfunction in post-stroke patients in the sub-acute phase', which I hereby submit to the University of Pretoria for the degree PhD (Physiotherapy), is my own, original work and has not been previously submitted by me for a degree at this or any other tertiary institution.

Signature of Student Date: December 2019

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Philippians 4:13
'I can do all things through Him who strengthens me'

ABSTRACT

Background

Vestibular dysfunction arising from the central components of the vestibular system are associated with impaired balance. Due to decreased spontaneous recovery of the central vestibular system post-stroke, patients may develop maladaptive sensory strategies in the early months post-stroke in response to the absence of specific management to address vestibular dysfunction following a stroke.

Methods

A phase 1 cross-sectional survey was conducted to determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke (N=102). A phase 2 single-blind cluster randomised controlled trial (RCT) was conducted to determine the effect of vestibular rehabilitation therapy (VRT) integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group. After central vestibular dysfunction was diagnosed based on the outcome of the assessment of smooth pursuit or saccadic eye movement using videonystagmography (VNG) or the assessment of vestibulo-ocular reflex (VOR)-gain using video head impulse test (vHIT) during the cross-sectional survey, 60 patients were randomly allocated to either an experimental group (N=30) or control group (N=30). Patients in the experimental group received a combination of VRT integrated with task-specific activities as part of the treatment as an “add-on” intervention compared to patients in the control group who received task-specific activities alone during the two-week intervention period.

Results

A high prevalence of clinical features associated with central vestibular dysfunction, including impairment of smooth pursuit eye movement (97.1%-99.0%), utricle and superior vestibular nerve function (97.1%) and higher vestibular function (97.1%), were observed. A high prevalence of activity limitations associated with central vestibular dysfunction, including impaired functional ability (98.0%), ability to modify gait in response to changing task demands (97.1%) and functional balance (87.3%), were also observed in the current study.

Findings of the single-blind cluster RCT demonstrated that between-group comparison based on logistic regression adjusted for age, gender and race, patients in the experimental group that received VRT integrated with task-specific activities improved significantly more in oculomotor function, specifically saccadic movement (velocity and accuracy), level of depression and functional ability, compared to patients in the control group who received task-specific activities alone.

Conclusion

The high prevalence of clinical features and activity limitations associated with central vestibular dysfunction on body structure and function, as well as activity level in patients post-stroke, may suggest that the measurement of these clinical features and activity limitations associated with central vestibular dysfunction might be a robust biomarker that may be applied in the guidance and interpretation of treatment outcomes post-stroke.

Findings of the study adds to an increasing body of evidence that the CNS has the capability to compensate for central vestibular dysfunction and re-weight sensory inputs post-stroke. Input from the visual system may compensate for the loss of vestibular information and is thus a substitute as a reference for earth vertical in controlling posture and trunk stability.

Implication

Vestibular rehabilitation therapy integrated with task-specific activities are a low cost, safe and effective complement to standard treatment of stroke patients.

Key words: stroke, central vestibular dysfunction, prevalence, vestibular rehabilitation therapy, sensory re-weighting

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ABBREVIATIONS

Abbreviation	Meaning
10MWT	Timed Ten Metre Walk Test
ABC	Activities-Specific Balance Confidence
AD	Alzheimer's disease
ADLs	Activities of daily living
AGSI	Antigravity Spasticity Index
AICA	Anterior inferior cerebellar artery
ASMP	Auditory subjective median plane
BBS	Berg Balance Scale
BC	Brachium conjunctivum
BDI	Beck Depression Inventory
BESTest	Balance Evaluation Systems Test
BI	Barthel Index
BPPV	Benign paroxysmal positional vertigo
BVF	Bilateral vestibular failure
BVH	Bilateral vestibular hypofunction
CARE	Consensus-based Clinical Case Reporting Guideline Development
CCR	Cervico-collic reflex
CE	Confidence ellipse
CES-D	Centre for Epidemiological Studies Depression Scale
CIMP-QUEST	Cognitive Impairment Questionnaire
CN	Cranial nerve
COGNISTAT	Neurobehavioral Cognitive Status Examination
CI	Confidence interval
CKC	Closed kinetic chain
CONSORT	Consolidated Standards of Reporting Trials
CNS	Central Nervous System
COG	Center of gravity
COP	Center of pressure
CPGs	Clinical Practice Guidelines
cVEMP	Cervical vestibular evoked myogenic potential

CVI	Cerebral vascular incident
CVTT	Central ventral tegmental tract
DEM	Developmental Eye Movement
DGI	Dynamic Gait Index
DHI	Dizziness Handicap Inventory
dMRI	Diffusion magnetic resonance imaging
DSS	Digit symbol substitution
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
DVA	Dynamic visual acuity
EC	Eyes closed
EMG	Electromyography
ENG	Electronystagmography
EO	Eyes open
EQ-5D	European Quality of Life Score
FAC	Functional Ambulation Categories
FDG	Fluorodeoxyglucose
FEF	Frontal eye fields
FES	Functional electric stimulation
FIM	Functional Independent Measures
FMA-LE	Fugl-Meyer Assessment
fMRI	Functional magnetic resonance imaging
FNI	Functional Neglect Index
FTSTS	Five Times Sit-to-Stand
GST	Gaze-stabilization test
GVS	Galvanic vestibular stimulation
HADS	Hospital Anxiety and Depression Scale
HIT	Head impulse test
HIV	Human Immunodeficiency Virus
HV	Head-vertical
IA	Inter-aural
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health

IPAQ	International physical activity questionnaire
IQR	Interquartile range
LOTCA	Loewenstein Occupational Therapy Cognitive Assessment
LTD	Long-term depression
LVST	Lateral vestibulospinal tract
MADRS	Montgomery Asberg Depression Rating Scale
MAS	Modified Ashworth Scale
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MCP	Middle cerebellar peduncle
mCTSIB	Modified Clinical Test of Sensory Interaction on Balance
MLF	Medial longitudinal fasciculus
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MSO	Multisensory orientation
MST	Medial superior temporal
MT	Medial temporal area
MT/V5	Motion-sensitive areas
MVPT	Motor-Free Visual Perception Test
MVST	Medial vestibulospinal tract
N	Number
N1	First negative deflection on wave form
NDT	Neurodevelopmental treatment
NIHSS	NIH Stroke Scale
NO	Naso-occipital
NPC	Near point of convergence
OK	Optokinetic
OR	Odds ratio
OTR	Ocular tilt reaction
oVEMP	Ocular vestibular evoked myogenic potential
P1	First positive peak on wave form
P-value	Exceedance probability value
PASS	Postural Assessment Scale

PCA	Posterior cerebral artery
PET	Positron emission tomography
PICA	Posterior inferior cerebellar artery
PIVC	Parieto-insular vestibular cortex
PH	Prepositus-Hypoglossi
PKC	Protein kinase C
PPRF	Paramedian pontine reticular formation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
qEEG	Electroencephalography
rCGM	Regional cerebral glucose metabolism
RCTs	Randomised Controlled Trials
SCP	Superior cerebellar peduncle
SD	Standard deviation
SLS	Single-Leg Stance
SOT	Sensory Organization Test
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRQR	Standards for Reporting Qualitative Research
SSs	Simple spikes
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SV	Sway velocity
SVA	Static visual acuity
SVD	Subjective syndrome
SVV	Subjective visual vertical
T	Thalamus
TBI	Traumatic brain injury
TDCS	Transcranial direct current stimulation
TEUSAC	Test for Equilibrium Under Altered Sensory Conditions
TMS	Transcranial magnetic stimulation
TUG	Timed “Up and Go”

UBNI	Unawareness and Behavioural Neglect Index
UP	University of Pretoria
UVH	Unilateral vestibular hypofunction
V	Visual cortex
V1	Primary visual cortex
V1/V2	Visual-cortex
VAS	Visual analogue scale
VCR	Vestibulocollic reflex
VFPT	Visual feedback posturography training
vHIT	Video head impulse test
VISTA	Virtual International Stroke Trials Archive
VN	Vestibular nuclei
VNG	Videonystagmography
VOG	Video-oculography
VOR	Vestibulo-ocular reflex
VRT	Vestibular rehabilitation therapy
VSCIs	Very small cerebellar infarcts
VSEs	Visual scanning exercises
VSR	Vestibulo-spinal reflex
VST	Vestibulospinal tract
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION AND ORIENTATION TO THE STUDY

1.1. INTRODUCTION

Balance impairment is common after stroke and the management of balance deficits is considered part of routine clinical practice in individuals with stroke (Winstein *et al* 2016:29). Although it is well established in the literature that vestibular, visual and proprioceptive (somatosensory system) information is processed by the central vestibular pathways and integrated within the sensorimotor cortex to maintain an individual's sense of balance and position (Gimmon, Millar, Pak, Liu and Schubert 2017:3347), the researcher noticed that in clinical practice, the assessment and management of central vestibular dysfunction are occasionally treated as a separate problem and not integrated into standard post-stroke rehabilitation. Vestibular dysfunction arising from peripheral or central components of the vestibular system is associated with dizziness, impaired balance and significantly increased risk of falls (Cronin, Arshad and Seemungal 2017:538). Winstein *et al* (2016:29) described a synopsis of best clinical practices in the rehabilitative care of patients post-stroke, and indicated that if balance impairments post-stroke are undetected or left untreated, it may result in serious and undesirable events. The findings of the study (Winstein *et al* 2016:29) are supported by Cronin *et al* (2017:538) who indicated that vestibular dysfunction has a major influence on patients' mortality, morbidity, use of health-care resources and socioeconomic productivity. Due to poor spontaneous recovery of the central vestibular system post-stroke, patients may develop maladaptive sensory strategies in the early months post-stroke in response to the absence of specific management (assessment and intervention) to address vestibular dysfunction following a stroke (Bonan, Gaillard, Ponche, Marquer, Vidal and Yelnik 2015:521; Lacour and Bernard-Demanze 2015:285). The vestibular system consists of both the peripheral and central vestibular systems. The peripheral vestibular system comprises of the vestibular organs in the inner ear and the central vestibular system includes the associated extensive central nervous system projections from the peripheral vestibular organs in the inner ear to the cerebellum, brainstem and the thalamic relays to cortical

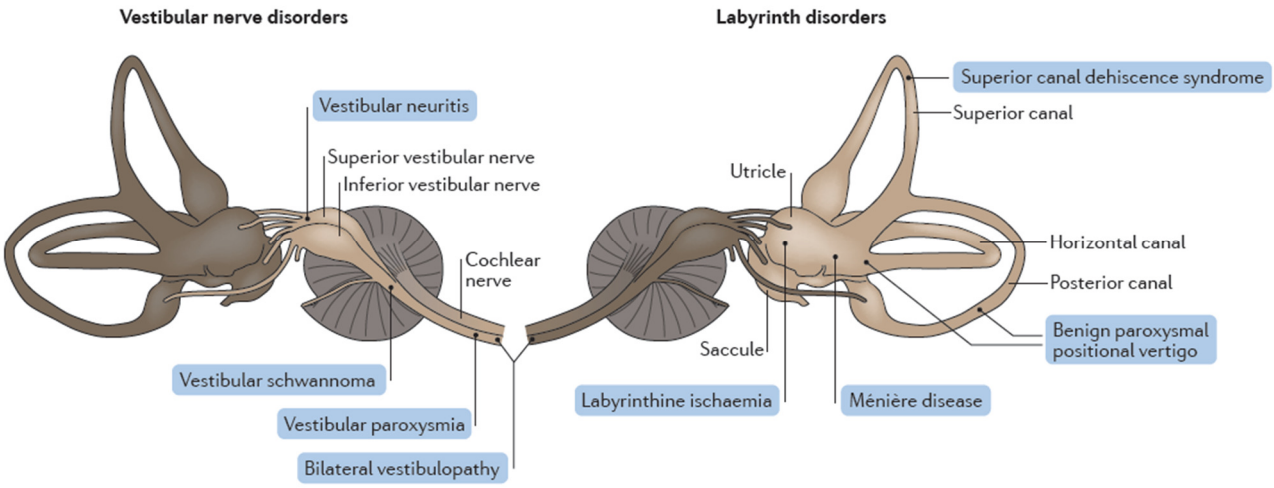
projections (Cronin *et al* 2017:538). The impairments of the peripheral and central vestibular system are discussed in Section 1.1.1.

1.1.1. Peripheral impairment versus central impairment

Traditionally, authors (Dieterich and Brand 2008:2538; Brandt and Dieterich 2017:352) distinguish between peripheral and central vestibular dysfunction based upon the anatomical site of the lesion. However, patients may present with similar following lesions sustained in either the peripheral or central vestibular system. Marsden, Playford, and Day (2005:670) indicated that a stroke may disrupt the corticobulbar projections that lie close to the corticospinal tract that terminate in the pons or upper medulla of the brainstem. These corticobulbar projections and brainstem output pathways are specifically involved in the vestibular control of balance. A stroke may thus cause a disruption of the corticobulbar pathway and the reciprocal connections on each side of the neuroaxis which may result in an asymmetric response between the two sides of the brainstem centre. A central lesion due to a stroke may result in decreased activity on one side of the brainstem centre and may also disinhibit the opposite side, thereby increasing its excitability (Marsden *et al* 2005:677). Similar asymmetries are observed in patients following peripheral vestibular system impairment such as a unilateral vestibular nerve lesion (Marsden *et al* 2005:677). Patients may therefore present with similar asymmetries following lesions sustained in either the peripheral or central vestibular system. It is therefore imperative to differentiate between the various impairments of the peripheral and central vestibular systems. Impairments of the peripheral vestibular system are discussed in Section 1.1.1.1.

1.1.1.1. Peripheral vestibular dysfunction

Peripheral vestibular dysfunction includes lesions of the vestibular nerve and labyrinth that include the semicircular canals and otoliths (Brandt and Dieterich 2017:352). Peripheral vestibular conditions that affect the vestibular nerve (left) and/or labyrinth (right) are presented in Figure 1.1.



(*The blue highlighted vestibular conditions in Figure 1.1 indicate the disorders that are associated with the lesions at the different sites of the peripheral vestibular system)

Figure 1.1.: Peripheral vestibular conditions that affect the vestibular nerve (left) and/or labyrinth (right) (Brandt and Dieterich 2017:352).

Typical peripheral vestibular nerve disorders include unilateral peripheral vestibulopathy (vestibular neuritis or vestibular schwannoma), bilateral vestibulopathy; and vestibular paroxysmia caused by neurovascular cross-compression (Figure 1.1). Labyrinthine disorders may include benign paroxysmal positional vertigo (BPPV) due to canalolithiasis or cupulolithiasis of the anterior, posterior or horizontal semicircular canals, Ménière's disease with endolymphatic hydrops, superior canal dehiscence syndrome due to a bony defect and labyrinthine ischaemia (Brandt and Dieterich 2017:352) (Figure 1.1). Impairments of the central vestibular system are discussed in Section 1.1.1.2.

1.1.1.2. Central vestibular dysfunction

Central vestibular dysfunction is diagnosed when lesions involve (a) the vestibular nuclei in the pontomedullary brainstem; (b) the vestibular pathways that project from the vestibular nuclei to the vestibulocerebellum (via the cerebellar peduncles); (c) brainstem; (d) thalamus; and (e) cortex. The bilateral structural organization of the central vestibular system from the vestibular nuclei to multisensory vestibular cortex is displayed in Figure 1.2.

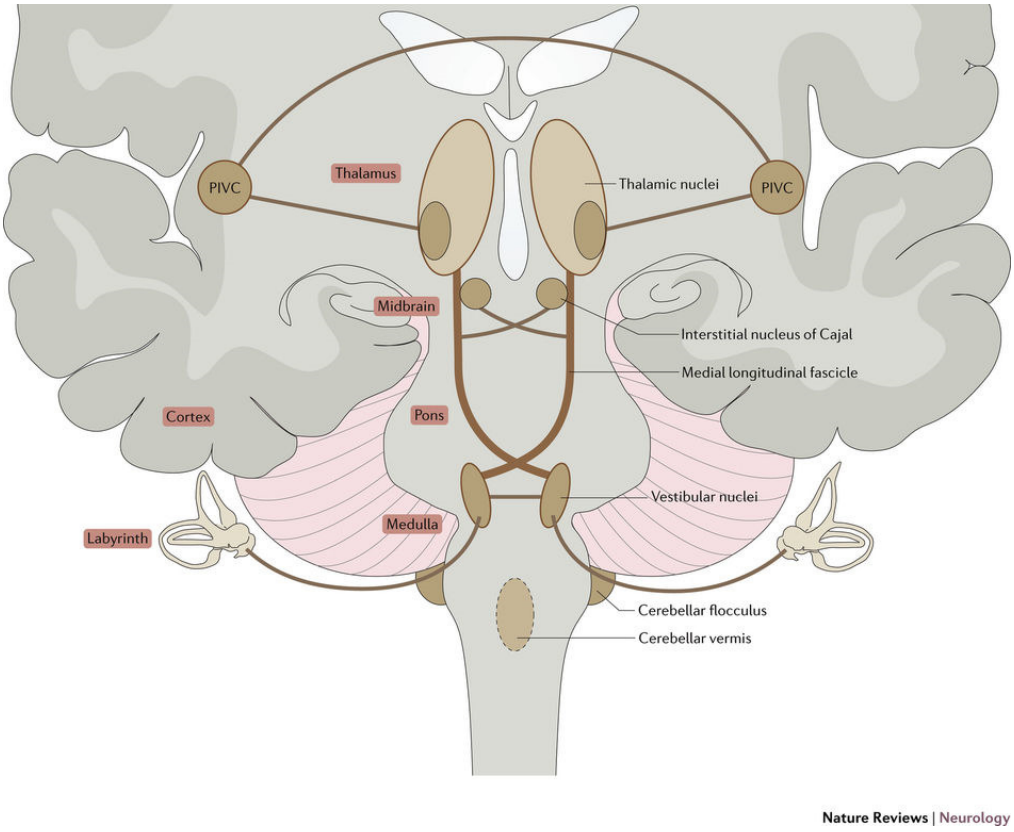


Figure 1.2.: Bilateral structural organization of the central vestibular system from the vestibular nuclei to multisensory vestibular cortex (Brandt and Dieterich 2017:352).

Vestibular input from the labyrinth and vestibular nerve ascends ipsilaterally and contralaterally, mainly via the medial longitudinal fasciculus (MLF), to the midbrain tegmentum which contains the interstitial nucleus of Cajal. Thereafter, pathways travel via dorsolateral thalamic nuclei to multisensory vestibular cortex areas that include the parieto-insular vestibular cortex (PIVC) and the medial superior temporal area (MST) of the visual cortex (not indicated in Figure 1.2). Four crossings between the bilateral vestibular nuclei pathways and cortical areas are observed. Three of the four crossings are observed in the brainstem, namely: (i) between the vestibular nuclei; (ii) at the lower pontine level (superior to the vestibular nuclei); and (iii) at the midbrain tegmentum. A fourth cortical crossing is observed through the splenium of the corpus callosum via transcallosal connections between the PIVC or the MST of the right and left hemispheres. The two main cerebellar structures involved in central vestibular function are the cerebellar flocculus and the cerebellar vermis (Brandt and Dieterich 2017:352). The bilateral structure and organisation of the vestibular system can be

divided in four (4) functional groups based on their anatomy and functional role, namely; (i) reflexive control of gaze during head and body movements at brainstem and cerebellar levels; (ii) control of balance at brainstem and spinal cord levels; (iii) perception of orientation, self-motion and sensorimotor control of voluntary movement and balance at cortical and sub-cortical levels; and (iv) higher vestibular function involving multisensory integration and cognition mediated mainly by the hippocampus and the temporo-parietal areas (Dieterich and Brand 2015:10; Brandt and Dieterich 2017:352). The structural neural connectivity of the central vestibular system is discussed in Section 1.1.2.

1.1.2. Structural neural connectivity of the central vestibular system

The clinical features associated with central vestibular dysfunction based on the anatomy and functional role of the bilateral structure and organisation of the central vestibular system described by Brandt and Dieterich (2017:352), is supported by findings described by Jang, Lee, Yeo and Kwon (2018:727) who investigated the structural neural connectivity of the vestibular nuclei using diffusion tensor tractography (DTT). Jang *et al* (2018:727) investigated the incidence of connection between the vestibular nuclei and the primary motor cortex, premotor cortex, primary somatosensory cortex, posterior parietal cortex, lateral prefrontal cortex, ventromedial prefrontal cortex, orbitofrontal cortex, thalamus, hypothalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus, reticular formation and cerebellum in 37 healthy subjects using DTT. Findings of the study demonstrated 100% connectivity between the vestibular nuclei and the cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus and reticular formation. These connected brain regions thus relate hundred percent to the functions of the vestibular nuclei (Brandt and Dieterich 2017:352; Jang *et al* 2018:727) and include control over (i) eye movements; (ii) sensorimotor control of voluntary movement and balance; and (iii) conscious perception of movement and spatial orientation. The vestibular nuclei also demonstrate high connectivity (over 70%) with the sensory-motor cortex (primary motor cortex [95.9%], primary somatosensory cortex [90.5%], premotor cortex [87.8%] and posterior parietal cortex [75.7%]), hypothalamus (86.5%) and lateral prefrontal cortex (70.3%). Lastly the vestibular nuclei also show connectivity with the ventromedial prefrontal cortex (51.4%) and orbitofrontal cortex (40.5%). In all brain

regions investigated, no significant difference (P>0.05) in connectivity of the vestibular nuclei was observed between the right and left hemispheres (Jang *et al* 2018:727). Lesions within these brain regions may thus result in central vestibular dysfunction as they demonstrate increased structural neural connectivity with the vestibular nuclei (Brandt and Dieterich 2017:352; Jang *et al* 2018:727). The model of disablement used in peripheral versus central vestibular dysfunction is discussed in Section 1.1.3.

1.1.3. Model of disablement used in peripheral versus central vestibular dysfunction

The International Classification of Functioning, Disability and Health (ICF) is a conceptual framework and classification to assess all aspects of health and disability (Grill, Furman, Alghwiri, Müller and Whitney 2013:297). During the development of the Clinical Practice Guidelines (CPGs) for vestibular rehabilitation of patients diagnosed with peripheral vestibular hypofunction (Hall *et al* 2016:133), a short list of categories (components of the Brief Core Set for Vertigo) based on the ICF model of disablement were used as the minimal standard for the assessment and description of functioning and disability. The three (3) specific domains of the ICF model included (1) body structure and function (body level); (2) activity (individual level); and (3) participation (societal level) (Hall *et al* 2016:133). The short list of categories (components of the Brief Core Set for Vertigo) based on the ICF model are presented in Table 1.1.

Table 1.1.: The short list of categories which included the minimal standard for assessment and description of functioning based on the International Classification of Functioning, Disability and Health (ICF) model (Hall *et al* 2016:133)

ICF CATEGORY	DESCRIPTION	ICF CATEGORY	DESCRIPTION
BODY FUNCTIONS		**ACTIVITIES AND PARTICIPATION**	
Mental functions		General tasks and demands	
b152	Emotional functions	d230	Carrying out daily routine
b156	Perceptual functions	Mobility	
Sensory functions and pain		d410	Changing the basic body position
b210	Seeing functions	d415	Maintaining a body position
b215	Functions of structures adjoining the eye	d450	Walking
b230	Hearing functions	d455	Moving around
b235	Vestibular functions	d460	Moving around in different locations
b240	Sensations associated with hearing and vestibular function	d469	Walking and moving, other specified and unspecified
b260	Proprioceptive function	d475	Driving
Neuromusculoskeletal and movement-related functions		Domestic life	
b770	Gait pattern functions	d640	Doing housework
BODY STRUCTURE			
Nervous system			
s110	Structure of brain		
s120	Spinal cord and related structures		

Table 1.1.: The short list of categories which included the minimal standard for assessment and description of functioning based on the International Classification of Functioning, Disability and Health (ICF) model (Hall *et al* 2016:133) (continued).

ICF CATEGORY	DESCRIPTION	
BODY STRUCTURE		
The eye, ear, and related structures		
s260	Structure of inner-ear	
Structures of the cardiovascular, immunological, and respiratory systems		
s410	Structure of cardiovascular system	

In the current study, the ICF was selected as the model of disablement within which the patients' levels of impairment, functional activity and participation as a result of the presence of clinical features associated with central vestibular dysfunction were determined and documented (Van Wyk, Eksteen, Becker and Heinze 2016:140). The presence of central vestibular dysfunction in patients post-stroke may be identified by the presence of specific clinical categories based on the clinical features patients may present with. The presence of central vestibular dysfunction may be categorised by impairment on the level of body structure and function that includes impairment of (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function, and (6) anxiety and/or depression. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level which includes; (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke. The conceptual framework of the current study which is based on the ICF-model (Lazaro, Roller and Umphred 2013:187), is presented in Table 1.2.

Table 1.2.: The conceptual framework based on the ICF-model used in the current study (Lazaro *et al* 2013:187).

International Classification of Functioning, Disability and Health (ICF)	
Level of body structure and function	**Activity and participation level**
Oculomotor control	Sensorimotor control of balance, mobility and gait
Reflexive control of gaze	Functional ability
Saccule and inferior vestibular nerve function	Participation in societal physical activities post-stroke
Utricle and superior vestibular nerve function	
Higher vestibular function	
Anxiety and/or depression	

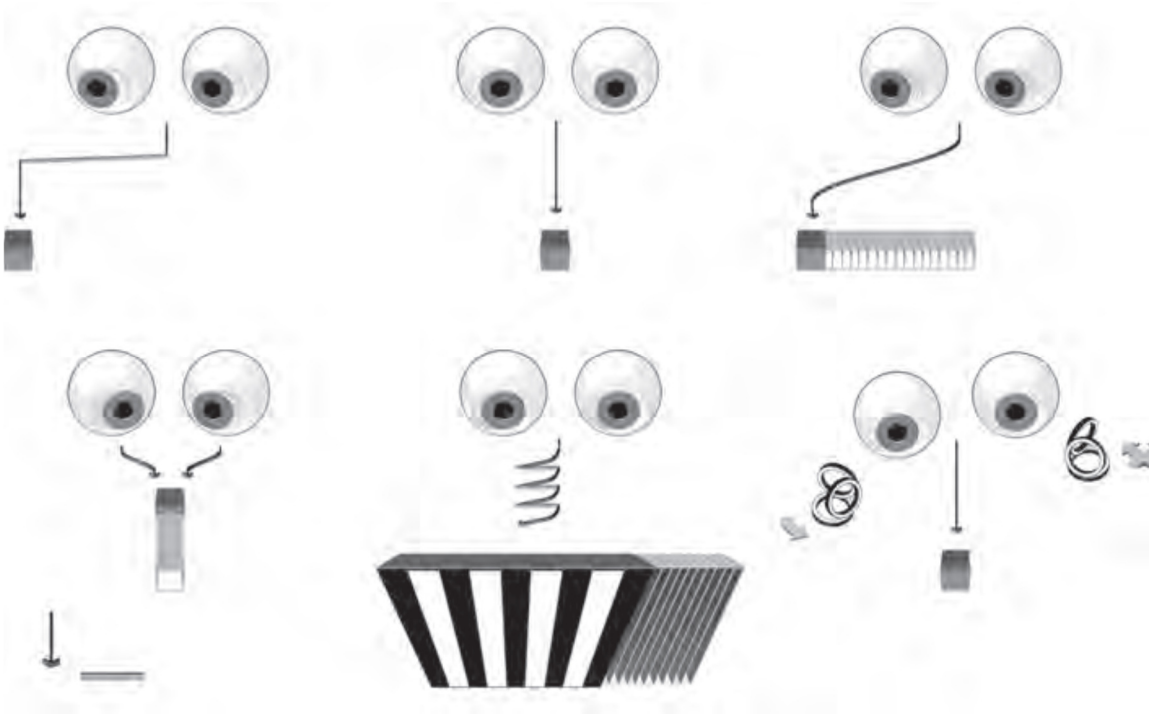
Each of the categories is discussed in Section 1.1.3.1 and Section 1.1.3.2.

1.1.3.1. Level of body structure and function

(i). Oculomotor function

As previously discussed (in Section 1.1.2), findings of the study by Jang *et al* (2018:727) demonstrated a hundred percent structural neural connectivity between the vestibular nuclei and the brain regions that are responsible for the control of eye movements (oculomotor control) (Brandt and Dieterich 2017:352; Jang *et al* 2018:727). Different types of eye movements are distinguished by their anatomical substrates, physiological properties and function (Kheradmand, Colpak and Zee 2016:103-117). The different types of eye movements are presented in Figure 1.3.

(a) (b) (c)



(d) (e) (f)

Figure 1.3.: Different types of eye movements (Lemos and Eggenberger 2014:471). (a) Saccadic eye movements are fast and precise eye movements that brings the image of an object of interest onto the fovea of the eye. (b) Visual fixation holds the image of a stationary object on the fovea of the eye to maintain a steady eye position on a target when the head is still. (c) Smooth pursuit eye movements keep an image of a moving target steady on the fovea of the eye to ensure clear vision (optimal visual acuity) of the target. (d) Convergence to smoothly and automatically turn the eyes in along the midline to observe near objects of interest with single vision. (e) Optokinetic reflex keeps the image of a large moving scene on the fovea of the eye. (f) Vestibulo–ocular reflex holds the image of a stationary object on the fovea to ensure stable images on the retina and clear vision (optimal visual acuity) during head movements (Leigh and Zee 2006:5; Hain and Helminski 2007:2; Pollock *et al* 2011:3; Chaikin 2013:867; Grill, Müller, Brandt and Jahn 2013:1; Lemos and Eggenberger 2014:471).

The role of each type of eye movement (Figure 1.3) is to keep the visual target stable on the macula of the eye, thus avoiding blurred vision, jumping and illusory movements (oscillopsia) during different functional tasks (Strupp *et al* 2014:542). Near point of

convergence (NPC) may be assessed using a Wolff wand placed along a patient's visual midline. The wand is then moved slowly towards the bridge of the nose of the patient and the NPC is recorded when the patient reports the presence of diplopia or the examiner observes one eye turning away from the wand (Schow, Harris, Teasdale and Rasmussen 2016:333). The optokinetic reflex may be quantified by placing a patient in a large, striped, rotating drum where after his/her entire visual field is stimulated to elicit optokinetic nystagmus (Davies 2004:37). Although the roles of convergence and the optokinetic reflex in oculomotor control are acknowledged, it will not be further addressed within this study as the above-mentioned assessment techniques are considered beyond the scope of this study. In the current study, oculomotor control and the impairment thereof will be limited to smooth pursuit eye movements, saccadic eye movements (Brandt and Dieterich 2017:352) and static visual acuity (Becker-Bense, Buchholz, Best, Schreckenberger, Bartenstein, Dieterich 2013:1103). The vestibulo-ocular reflex (VOR) and dynamic visual acuity are discussed under the clinical feature category of impaired reflexive control of gaze.

Although patients present with oculomotor impairment post-stroke, limited evidence on the association of oculomotor impairment and central vestibular dysfunction in patients who have suffered either an ischaemic or haemorrhagic stroke has been identified in the literature. Pollock *et al* (2011:2) reported that over 70% of stroke patients may present with impaired oculomotor control post-stroke. Though the association between central vestibular dysfunction and oculomotor impairment are well documented, Pollock *et al* (2011:2) did not distinguish between smooth pursuit and saccadic eye movements when they identified ocular motility impairment post-stroke. Despite the increased prevalence of oculomotor impairment post-stroke (Pollock *et al* 2011:2), the last mentioned authors also did not differentiate between the *prevalence* of impaired smooth pursuit eye movements and/or impaired saccadic eye movements respectively, but grouped all oculomotor conditions under a single clinical feature, namely 'eye movement disorders', when they reported on the prevalence of oculomotor impairment post-stroke.

Limited evidence on the prevalence, assessment and treatment of oculomotor impairment specifically reduced static visual acuity as a result of central vestibular dysfunction in patients post-stroke, has been identified in the literature. Current

literature (Edwards, Hahn, Baum, Perlmutter, Sheedy and Dromerick 2006:42; Rowe *et al* 2011:407; Shrestha, Upadhyayaa, Sharmaa and Gajurelb 2012:46; Siong *et al* 2014:433) estimates a prevalence between 15% and 70% of reduced static visual acuity post-stroke. None of these studies mentioned the role of the central vestibular system and static visual acuity. No objective vestibular assessment was included in the battery of tests used to determine the possible association between static visual acuity and central vestibular dysfunction post-stroke. Alternatively, Willis, Vitale, Agrawal and Ramulu (2013:1049) reported an association between decreased static visual acuity and vestibular dysfunction in a nationally representative sample of the US population. The study sample included N=4590 adults, 40 years or older, civilian non-institutionalised individuals through a complex, multistage probability design. Willis *et al* (2013:1049) demonstrated that individuals with decreased visual acuity or uncorrected refractive error also presented with vestibular dysfunction that resulted in impaired balance. Willis *et al* (2013:1049) reported that reduced visual information due to decreased visual acuity or uncorrected refractive error may weaken the VOR that results in decreased ability to maintain balance. Although the association between reduced static visual acuity and vestibular dysfunction has been established by Willis *et al* (2013:1049), the evaluation of visual acuity and the vestibular system were limited to the use of an autorefractor containing built-in visual acuity charts and the Romberg test of standing balance. It is important to highlight that although 2.8% of the study population reported a history of stroke (P<0.01) (Willis *et al* 2013:1049), no objective vestibular assessment was included in the battery of tests used to determine the possible association between static visual acuity and central vestibular dysfunction post-stroke. The second impairment on the level of body structure and function to be discussed is the impairment of reflexive control of gaze (Table 1.2).

(ii). Reflexive control of gaze

During activities of daily living (ADLs) rotational or translational head movements may reach velocities of up to 550°/s (Hermann, Pelisson, Dumas, Urquizar, Truy and Tilikete 2018:300). When visually-guided stabilising eye movements which include smooth pursuit eye movements or optokinetic reflex, are unable to sustain optimal visual acuity during high-velocity head motion, the VOR responds to changes in head acceleration with a latency of 5–7 ms to stabilise the gaze of the individual to achieve

best visual acuity during ADLs (Hermann *et al* 2018:300). Patients with a partial or complete loss of afferent (sensory) input from one or both sides may result in an asymmetry in the VOR pathway and function as result of a peripheral or central vestibular deficit. These patients may experience decreased visual acuity during head motion and an illusion of an unstable visual world during head movements (oscillopsia). Symptoms of oscillopsia and impaired visual acuity during head motion may have a severe impact on the quality of life of patients.

A recent study by Choi, Kim and Kim (2018:90) demonstrated that patients with lesions involving the central vestibular system that includes the vestibular nucleus, nucleus prepositus hypoglossi or flocculus may present with vestibular hypofunction as result of significantly reduced unilateral or bilateral horizontal VOR gains. Patients with diffuse cerebellar lesions may present with vestibular hyperfunction as result of an increased (hyperactive) horizontal VOR gains. Lesions involving the vestibular nucleus, MLF and cerebellum may demonstrate either decreased or increased vertical VOR-gains (Choi *et al* 2018:90). Choi *et al* (2018:90) indicated that the identification and definition of differences in patterns observed during the evaluation of the VOR may aid therapists to localise the lesions in the central vestibular system to facilitate the management of patients with impaired reflexive control of gaze post-stroke. Authors that investigated the presence of impaired reflexive control of gaze assessed by the VOR, limited their study populations to patients with pontine-cerebellar infarction (Chen, Todd, Halmagyi and Aw 2014:83), isolated floccular infarction (Park, Kim, Strupp and Zee 2013:1576; Baek *et al* 2015:279) and isolated unilateral vestibular nuclei infarction (Kim, Lee, Park, Choi and Kim 2014:121). Limited evidence on the prevalence, assessment and treatment of impaired reflexive control of gaze as a result of central vestibular dysfunction in patients who sustained either an ischaemic or haemorrhagic, hemispheric, subcortical, brainstem or cerebellar stroke has been identified in the literature (Park *et al* 2013:1576; Chen *et al* 2014:83; Kim *et al* 2014:121; Baek *et al* 2015:279). The third and fourth impairment on the level of body structure and function to be addressed is the saccular and inferior vestibular nerve as well as utricle and superior vestibular nerve function.

(iii). Saccular, inferior vestibular nerve function and utricle, superior vestibular nerve function

The vestibular end-organ consists of the semicircular canals which transduce angular acceleration and the otolith organs that include the saccule and utricle which transduce linear acceleration. The signal passes from the semi-circular canals, saccule and utricle to the vestibular nerve, the brainstem and cerebellar circuits, vestibular thalamic pathways, vestibulospinal tracts and to the vestibular cortical network (Cronin *et al* 2017:538). Cervical vestibular evoked myogenic potentials (cVEMPs) and ocular vestibular evoked myogenic potentials (oVEMPs) are relatively new tests of otolith function that can be used to objectively test the saccule and utricle of both ears independently (Rosengren and Colebatch 2018:481). An abnormal or absent VEMP indicates an impairment with the otolith receptors or the pathway of the reflex. Rosengren and Colebatch (2018:481) reported that the evaluation of the otoliths using VEMPs may aid therapists to localise the lesions in the central and peripheral vestibular system.

Patients with a lesion at or below the vestibular nucleus in the medial vestibulospinal tract (MVST) or spinal accessory nucleus would present with an isolated absent cVEMP. A patient with a lesion at or above the vestibular nucleus in the MLF or oculomotor nucleus would present with an absent oVEMP. Patients who present with a combined cVEMP and oVEMP abnormality would suggest a lesion in the vestibular nucleus or root entry zone (Rosengren and Colebatch 2018:481). It is important to highlight that although recovery of otolith function and VEMPs may occur following a peripheral vestibular nerve disorder such as vestibular neuritis (Figure 1.1), VEMPs in patients with central vestibular dysfunction may remain abnormal or absent even after central vestibular compensation has occurred (Rosengren and Colebatch 2018:481) (vestibular compensation following vestibular impairment is discussed in Section 1.1.4).

Authors who have investigated the presence of impaired saccular and inferior vestibular nerve function assessed by cVEMP, as well as utricle and superior vestibular nerve function assessed by oVEMP, limited their study populations to patients with cerebellar stroke (Su and Young 2011:923; Choi, Lee, Kim and Kim 2014:362), isolated floccular infarction (Park *et al* 2013:1576), brainstem lesions (Oh

et al 2013:770; Kim, Kim, Park and Kim 2016:2424) and isolated unilateral vestibular nuclei infarction (Kim *et al* 2014:121). Limited evidence on the prevalence, assessment and treatment of impaired saccular and inferior vestibular nerve function assessed by cVEMP as well as utricle and superior vestibular nerve function assessed by oVEMP as result of central vestibular dysfunction in patients who sustained either an ischaemic or haemorrhagic, hemispheric or subcortical stroke has been identified in the literature. The fifth impairment on the level of body structure and function as result of central vestibular dysfunction to consider is the impairment of higher vestibular function.

(iv). Higher vestibular function

The fifth impairment on the level of body structure and function as a result of central vestibular dysfunction (Table 1.2) to consider is the impairment of higher vestibular function. Apart from the role of the peripheral vestibular system to sense angular and linear acceleration of the head in order to stabilize the visual image on the retina during head movement by means of the VOR, the vestibular system also has a role in higher vestibular function that include visual-perceptual function and cognition (Hitier, Besnard and Smith 2014:59). Hitier *et al* (2014:59) indicated that four (4) different pathways are responsible for the transmission of vestibular information to cortical areas involved in higher vestibular function, namely: (1) the vestibulo-thalamo-cortical pathway; (2) a pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex; (3) a pathway via the nucleus reticularis pontis oralis, the supramammillary nucleus and the medial septum to the hippocampus; and (4) a possible pathway via the cerebellum and the ventral lateral nucleus of the thalamus (to the parietal cortex). Bigelow and Agrawal (2015:83) proposed a conceptual model that suggested the mechanism of cognitive dysfunction due to the vestibular system impairment. The conceptual model proposing the mechanism of cognitive dysfunction due to the vestibular system impairment (Bigelow and Agrawal 2015:83) is presented in Figure 1.4.

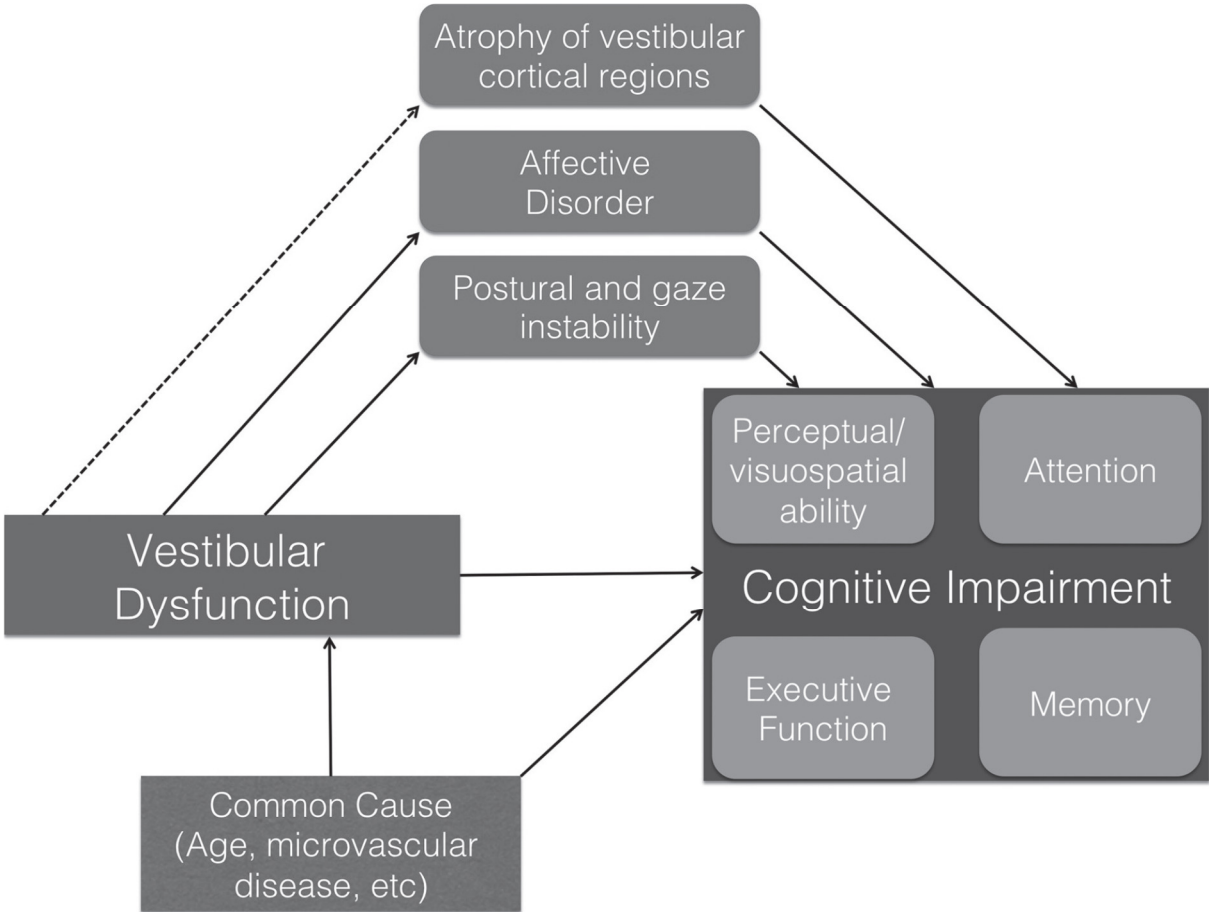


Figure 1.4.: Conceptual model proposing the mechanism of cognitive dysfunction due to the vestibular system impairment (Bigelow and Agrawal 2015:83).

The conceptual model by Bigelow and Agrawal (2015:83) supports the findings by Hitier *et al* (2014:59) that central vestibular dysfunction may result in atrophy of areas within the cortical vestibular network that may include the hippocampus that is responsible for higher vestibular function of memory and visuospatial ability. Recently, Kamil, Jacob, Ratnanather, Resnick and Agrawal (2018:765) investigated whether reduced vestibular function is associated with lower hippocampal volume in adults aged ≥60 years (N=103). Vestibular function testing included the assessment of saccular and utricular function using cVEMP and oVEMP respectively. Vestibular function testing also included the assessment of the horizontal semi-circular canal VOR using vHIT. A brain MRI scan was also performed during the same visit. Findings of the cross-sectional study indicated that reduced saccular function based upon a lower cVEMP amplitude was significantly associated ($p=0.003$) with lower mean hippocampal volume. Results of the study by Kamil *et al* (2018:765) supports the

findings of Bigelow and Agrawal (2015:83) and Hitier *et al* (2014:59) that central vestibular dysfunction may result in atrophy of areas within the cortical vestibular network that include the hippocampus that contributes to impaired higher vestibular function of spatial cognition, memory and visuospatial ability.

Semenov, Bigelow, Xue, du Lac and Agrawal (2016:243) assessed the association between vestibular and cognitive function in a nationally representative sample of U.S. adults aged ≥60 years (N=1303). Vestibular function was measured with the modified Romberg test and cognitive function was measured by the digit symbol substitution (DSS) score test. Findings of the study by Semenov *et al* (2016:243) indicated a significant independent association between vestibular function and cognitive function ($P<0.0001$). The presence of vestibular dysfunction may impair cognitive ability that may result in decreased functional ability ($P=0.001$) and falls ($P=0.017$). It is important to highlight that although 4.8% of the study population reported a history of stroke ($P=0.1014$), no objective vestibular assessment was included in the battery of tests used to determine the possible association between cognitive function and central vestibular dysfunction post-stroke (Semenov *et al* 2016:243). Harun, Oh, Bigelow, Studenski and Agrawal (2016:1137) included the assessment of saccular and inferior vestibular nerve function by cVEMP, utricle and superior vestibular nerve function by oVEMP and horizontal semicircular canal function (horizontal VOR-gain) in the battery of tests used to determine the association between vestibular and cognitive function in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to cognitively normal individuals (N=141) (Harun *et al* 2016:1137). Findings of the study by Harun *et al* (2016:1137) confirmed the association between vestibular impairment and cognitive decline. Interestingly, the loss of function of both otolith organs (saccule and utricle) was more prevalent in individuals with AD relative to age-matched controls. Although the assessment of saccular and inferior vestibular nerve function assessed by cVEMP, utricle and superior vestibular nerve function assessed by oVEMP and horizontal semi-circular canal function (horizontal VOR-gain) assessed by the video head impulse test (vHIT) were implemented in the study by Harun *et al* (2016:1137), the assessment of oculomotor impairment specifically smooth pursuit and saccadic eye movements were not included in the test battery to assess the association between vestibular impairment and cognition.

Alternatively, studies that investigated the association between the presence of oculomotor impairment and cognitive impairment (Dong *et al* 2013:337; Willard and Lueck 2014:75; Carrick *et al* 2016:3), did not discuss the role of the vestibular system in higher vestibular function. Findings of the study by Dong *et al* (2013:337) reported that stroke patients may present with subtle impairment of higher vestibular function that are reflected in the oculomotor system which includes saccadic eye movement impairment post-stroke (Dong *et al* 2013:337). Results of the study by Dong *et al* (2013:337) supports the findings of an earlier study by Cate and Richards (2000:326) which indicated that a good to excellent relationship (r=0.75) exists between oculomotor control and higher vestibular function, specifically visual-perceptual dysfunction, in patients post-stroke. The results of the study by Cate and Richards (2000:326) suggest that the evaluation of higher vestibular function (visual-perceptual function) should commence with assessment of oculomotor control so that the influence of oculomotor control on performance in more complex tests may be taken into consideration. Traditional higher vestibular function assessment with conventional paper-and-pencil tests that are completed in isolation, are not best practice. Omission of the assessment of oculomotor control may result in untreated oculomotor control that may influence the patient's higher vestibular function which include visual-perceptual function (Cate and Richards 2000:326) and cognition (Dong *et al* 2013:337) post-stroke.

In summary, although the presence of vestibular dysfunction categorised by impairment on level of body structure and function (Section 1.1.3.1) are established in various study populations, limited evidence on the prevalence, assessment and treatment of impaired higher vestibular function as result of central vestibular dysfunction in patients who sustained either an ischaemic or haemorrhagic, hemispheric, subcortical, brainstem or cerebellar stroke, has been identified in the literature. The sixth and final impairment on the level of body structure and function as a result of central vestibular dysfunction to consider is the presence of anxiety and/or depression post-stroke (Ali, Hazelton, Lyden, Pollock and Brady 2013:133).

(v). Level of anxiety and/ or depression post-stroke

Psychological impairments such as anxiety and depression may influence patients' functional ability, participation in rehabilitation, discharge destination, risk of falling, quality of life and social integration post-stroke (Ali *et al* 2013:133; Hepworth *et al* 2016:1). Although the association between the presence of oculomotor impairment, anxiety and/or depression post-stroke has been identified in the literature (Ali *et al* 2013:133; Hepworth *et al* 2016:1), the role of the vestibular system in the presence of anxiety and/or depression has not been discussed in the consulted literature. Bigelow, Semenov, du Lac, Hoffman and Agrawal (2016:367) evaluated the association between vestibular vertigo, cognitive impairment and psychiatric conditions in a nationally representative sample of US adults (N=20 950). The presence of vestibular vertigo, depression, anxiety and panic disorder was identified by means of a questionnaire. Findings of the study by Bigelow *et al* (2016:367) demonstrated strong and consistent association between vestibular dysfunction, psychiatric (depression, anxiety and panic disorder) and cognitive impairments in an analysis of a nationally representative sample of the US adult population (Bigelow *et al* 2016:367). The results of the study by Bigelow *et al* (2016:367) support the findings of the study by Bigelow and Agrawal (2015:83) (Figure 1.4) that the vestibular system is anatomically connected with cerebral cortex, hippocampus and amygdala. Vestibular impairment may result in impairment of both affective and cognitive circuits that further increases the probability to develop depression and/or anxiety following vestibular impairment (Bigelow *et al* 2016:367). Although the studies by Bigelow and Agrawal (2015:83) and Bigelow *et al* (2016:367) evaluated the association between the vestibular system and the presence of anxiety and/or depression, the assessment of oculomotor impairment, specifically smooth pursuit and saccadic eye movements; reflexive control of gaze; saccule, inferior vestibular nerve function and utricle and superior vestibular nerve function, were not included in the test battery to assess the association between vestibular impairment and the presence of anxiety and/or depression.

In Section 1.1.3.1., the clinical features associated with central vestibular dysfunction categorised by impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5)

higher vestibular function; and (6) anxiety and/or depression, are discussed. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level (Table 1.2) such as (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke. The first impairment on activity and participatory level to be discussed is impaired sensorimotor control of balance, mobility and gait (in Section 1.1.3.2).

1.1.3.2. Activity and participatory level

(i). Sensorimotor balance, mobility and gait

The restoration of functional balance in patients post-stroke is a prerequisite for independence in functional tasks such as transfers, walking and social participation (Påhlman, Gutiérrez-Pérez, Sävborg, Knopp and Tarkowski 2011:1952). Functional balance is achieved through complex sensorimotor control that requires; (i) the integration and continuous re-weighting of visual, vestibular and somatosensory information that contribute to the body's representation in space; (ii) coordination of multiple motor outputs throughout the body (Ting and McKay 2007:622; Guerraz and Bronstein 2008:392); and (iii) anticipatory and adaptive postural control mechanisms that are modulated by sensory information (Bonan, Marquer, Eskiizmirliler, Yelnik and Vidal 2013:713). In Section 1.1.3.1 the role of the vestibular system in sensing angular and linear acceleration of the head followed by the generation of the VOR to stabilise the visual image on the retina of the eye to ensure optimal visual acuity during head movement, is discussed. In Section 1.1.3.2 the role of the vestibular system in sensing angular and linear acceleration of the head followed by the generation of the vestibulocollic and vestibulospinal reflexes to adjust posture during head movement, is discussed. When head movement occurs, the vestibular branches of the 8th cranial nerve send information to the vestibular nuclei about changes in the orientation of the head where after the vestibular nuclei transmit motor commands through the vestibulocollic and vestibulospinal pathways to maintain balance of upright posture of body and head (Jang *et al* 2018:727).

Bonan *et al* (2004:268) demonstrated that chronic stroke patients (N=40) (19±15.5 months post-stroke) may continue to present with long term (>12 months) impaired ability to utilise vestibular, visual, and somatosensory inputs separately. Rehabilitation

programs aimed to improve postural control of patients post-stroke should consider the possible impairment of multisensory integration of vestibular, visual and somatosensory input and include exercises to be performed under varying interaction between conditions of vestibular, visual and somatosensory input deprivation and conflict (Bonan *et al* 2004:268). Another study by Bonan *et al* (2004:274) demonstrated that balance rehabilitation in chronic stroke (N=20) patients may be more effective with visual deprivation. Bonan *et al* (2004:274) postulated that stroke patients may increase their use of somatosensory and vestibular information during vision-deprived conditions to substitute for the absence of a visual compensatory strategy. The observed improvement in balance correlated significantly with gait velocity (P=0.03) and timed stair climbing (P=0.01). The researcher has identified the following limitations of the studies by Bonan *et al* (2004:268) and Bonan *et al* (2004:274): neither studies by Bonan *et al* (2004:268) and Bonan *et al* (2004:274) completed vestibular assessments to identify and quantify possible impairment on the level of body structure and function such as (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; and (4) utricle and superior vestibular nerve function as a result of central vestibular dysfunction during the duration of the study. The study population was limited to chronic stroke patients in the 'later reorganization' phase of vestibular compensation (Section 1.1.4) and to patients with relatively good functional balance as only patients who were able to walk without supervision and able to independently maintain balance on a moving platform during computerised dynamic posturography, were included in the study. The researcher has identified a lack of evidence related to the prevalence, assessment and treatment of impaired sensorimotor control of balance, mobility and gait due to central vestibular dysfunction in patients who sustained a hemispheric, subcortical, brainstem or cerebellar stroke. The second impairment on activity and participation level (Table 1.2) to consider is the impairment of functional ability.

(ii). Functional ability and participation in physical activity post-stroke

Central vestibular dysfunction in patients post-stroke is identified by the presence of clinical feature categories based on impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior

vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression (Section 1.1.3.1). Central vestibular dysfunction is also categorised by impairment on activity and participation level that includes impaired sensorimotor control of balance, mobility and gait as discussed in Section 1.1.3.2. Although these tests are good indicators of vestibular impairment, the tests do not indicate a patient's ability to use their vestibular function in daily life. It is therefore imperative to determine the effect of the presence of central vestibular dysfunction on patients' functional ability.

A significant proportion of patients following a stroke may present with unrecognised central vestibular dysfunction identified because the presence of impaired (1) oculomotor control; (2) reflexive control of gaze; (3) saccule, inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression as result of central vestibular dysfunction post-stroke, has not been identified objectively. Stroke patients may receive minimal management of their central vestibular dysfunction during rehabilitation which may result in decreased independence in ADLs, reduced motivation and depression (Hepworth, Rowe, Harper, Jarvis, Shipman and Rodgers 2015:146) that may have a wide-ranging impact on their functional performance post-stroke. The inability to perform basic ADLs such as walking, bathing, dressing and instrumental ADLs such as managing finances and taking medication according to prescription, may prevent independent living (Harun, Semenov and Agrawal 2015:1). A retrospective study of N=5017 community-dwelling individuals indicated that participants with vestibular dysfunction presented with statistically significant ($P<0.0001$) impairment in ADLs (Harun *et al* 2015:1). The presence of vestibular dysfunction was statistically significantly associated with difficulty in performing nine (9) different ADLs that included; (i) managing money; (ii) getting in and out of bed; (iii) standing up from an armless chair; (iv) walking up to 10 steps; (v) standing for long periods of time; (vi) walking for a quarter mile ; (vii) completing house chores; (viii) stooping/crouching/kneeling; and (iv) going out to community activities i.e. movies/social events (Harun *et al* 2015:1).

The strongest association between vestibular dysfunction and the ability to perform ADLs was the ability to manage money. This strong association may emphasise the

link between the vestibular system and higher vestibular function, specifically cognition (Harun *et al* 2015:1). The association between higher vestibular function, specifically cognition, as result of central vestibular dysfunction has been previously described in Section 1.1.3.1. Although strong evidence highlights the relationship between the presence of vestibular dysfunction and functional ability post-stroke, a lack of evidence has been identified to examine the association between impaired functional ability due to central vestibular dysfunction in patients who sustained a hemispheric, subcortical, brainstem or cerebellar stroke. The sub-acute phase post-stroke is discussed in Section 1.1.4.

1.1.4. Sub-acute phase post-stroke

The Stroke Recovery and Rehabilitation Roundtable taskforce (Bernhardt *et al* 2017:444) developed a framework that summarises the definitions of critical time points post-stroke based upon the currently known biology and pre-clinical research in both animal and human models of recovery post-stroke. The framework is presented in Figure 1.5.

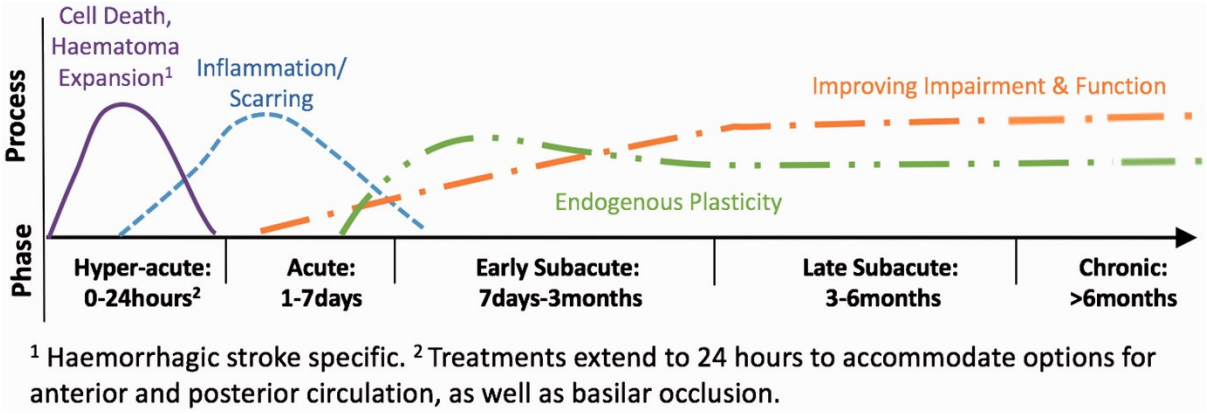


Figure 1.5.: Framework that summarises the definitions of critical time points post-stroke based upon the currently known biology and pre-clinical research in both animal and human models of recovery post-stroke (Bernhardt *et al* 2017:444).

In the current study, the sub-acute phase post-stroke is defined as the time period that range between seven (7) days to six (6) months post-stroke (Bernhardt *et al*

2017:444). This sub-acute phase post-stroke is a critical time period for neural plasticity and represents an important timeframe to maximise the potential of restorative interventions (Bernhardt *et al* 2017:444). The process of vestibular compensation following impairment of the peripheral and central vestibular system is discussed in Section 1.1.5.

1.1.5. Vestibular compensation

Vestibular compensation through the vestibular rehabilitation therapy (VRT)-approach is based upon the concept that the restoration of functional ability requires a systematic reintegration of the multiple sensory modalities that includes vestibular, visual and somatosensory (including proprioceptive) information essential for balance during the performance of functional tasks (Balaban, Hoffer and Gottshallf 2012:101). Neuronal and behavioural plasticity through vestibular compensation following damage to the peripheral vestibular system or alteration of the vestibular input due to ageing, head trauma, ototoxic drugs or vestibular pathologies, have been well documented (Lacour, Helmchen and Vidal 2016:54). The intrinsic plasticity of the central nervous system (CNS) to 'reorganise' following peripheral vestibular impairment is well documented, whereas literature on vestibular compensation following central vestibular dysfunction, specifically post-stroke, is limited (Lacour *et al* 2016:54). Recent decades of basic research into cellular and molecular mechanisms of vestibular compensation have produced important insights into functional plasticity of the CNS and its ability to compensate for vestibular impairment and 're-weight' sensory information through the process of vestibular compensation (Balaban *et al* 2012:101; Whitney, Alghadir and Anwer 2016:13). Firstly, the cellular and molecular mechanisms of vestibular compensation and VRT following central or peripheral vestibular dysfunction, are discussed in Section 1.1.5.1., followed by the components of the VRT-approach discussed in Section 1.1.5.2.

1.1.5.1. Cellular and molecular mechanisms of vestibular compensation and vestibular rehabilitation therapy following central or peripheral vestibular dysfunction

A schematic overview of the cellular and molecular mechanisms of vestibular compensation and VRT following central or peripheral vestibular dysfunction in patients (Balaban *et al* 2012:101) is displayed in Figure 1.6.

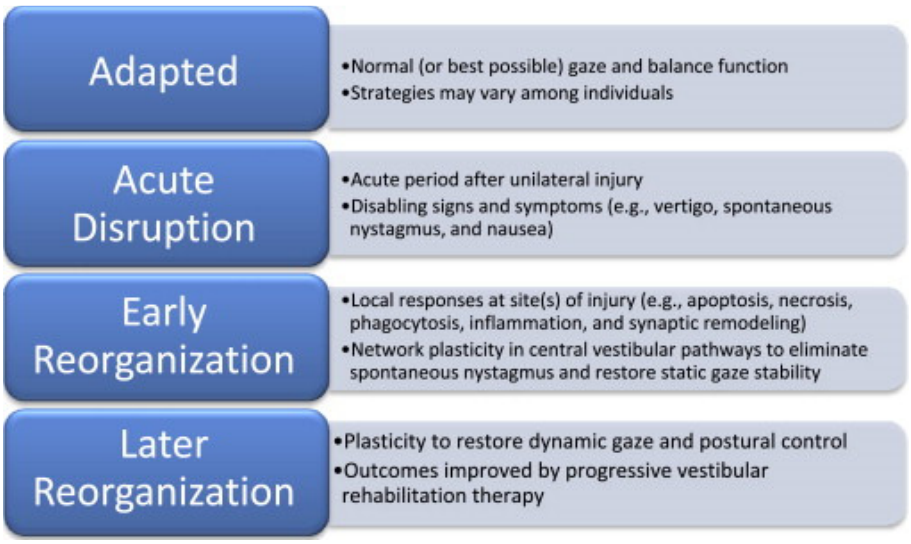


Figure 1.6.: Schematic overview of the cellular and molecular mechanisms of vestibular compensation and VRT following central or peripheral vestibular dysfunction in patients (Balaban *et al* 2012:101).

During the period of 'acute disruption', a post-stroke patient's stable adapted gaze and balance may be suddenly replaced with a chaotic orientation state due to central vestibular dysfunction following the stroke. The acute period is followed by a period of "early reorganization" that consists of an early biological response to (1) repair and facilitate remodelling at the site of injury; and (2) facilitation of plasticity in central vestibular pathways to eliminate spontaneous nystagmus as a result of the vestibular impairment and to restore static gaze stability. The period termed 'later functional reorganization', is targeted by VRT to facilitate plasticity to restore dynamic gaze and postural control of patients who present with central vestibular dysfunction post-stroke. The conceptual framework of the biological response following specifically central vestibular dysfunction in patients post-stroke (Balaban *et al* 2012:101) is supported by

findings from previously published literature by Becker-Bense *et al* (2013:1103) that demonstrated the downregulation of primary visual and motion-sensitive visual cortical areas in both cortical hemispheres to suppress blurred vision as result of oscillopsia caused by spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction following a lateral medullary stroke. Becker-Bense *et al* (2013:1103) indicated that the type of modulation observed in the cerebellum's inhibitory control on the vestibular nuclei which is mediated by vestibulo-cerebellar networks seems to occur in central vestibular disorders. The pattern of visual-vestibular interaction changes during modulation and activation processes of the vestibulo-cerebellar interaction mainly occur within the brainstem-cerebellar loops of the contralateral healthy side close to the impaired vestibular nucleus. Therefore, central vestibular compensation and recovery processes probably occur mainly in the brainstem-cerebellar loops after a medullary infarction (Becker-Bense *et al* 2013:1103). The positron emission tomography (PET) scans of patients were repeated at the six (6) months follow-up (N=7). The cerebellar hemispheres of these patients demonstrated decreased regional cerebral glucose metabolism (rCGM) as assessed by fluorodeoxyglucose (FDG)-PET compared to visual parieto-occipital areas that demonstrated increased rCGM within the contralateral hemisphere. Findings of the study further suggest that the observed changes were probably attributable to the processes of substitution in the later stage post-stroke (Becker-Bense *et al* 2013:1103). Findings of the study by Becker-Bense *et al* (2013:1103) adds to an increasing body of evidence that the CNS has the capability to compensate for vestibular dysfunction and re-weight sensory inputs (Whitney *et al* 2016:13).

The conceptual framework of the cellular and molecular mechanisms of vestibular compensation following specifically peripheral vestibular dysfunction in patients post-stroke (Balaban *et al* 2012:101) is supported by findings from Ahmad *et al* (2017: 1179) who investigated early visual-cortex (V1/V2) excitability using transcranial magnetic stimulation (TMS) in twelve (N=12) patients with bilateral vestibular failure (BVF). Findings from the study by Ahmad *et al* (2017:1179) provide neurophysiological evidence that cortically mediated adaptive mechanisms in the V1/V2 play a critical role in suppressing head movement–induced oscillopsia (an illusionary movement of the visual world) in patients with BVF. Ahmad *et al* (2017:1179) concluded that (1) centrally mediated oscillopsia adaptation following BVF may occur by downregulation

of V1/V2 cortical excitability; (2) patients with increased suppression of cortical excitability is associated with enhanced functional recovery from head movement–induced oscillopsia and reduced cortical responsiveness to visual motion; and (3) patients with head movement–induced oscillopsia may benefit from enhanced rehabilitation incorporating repeated visual motion paradigms to reduce cortical excitability that may translate to improved functional outcome.

In summary, the study sample of Becker-Bense *et al* (2013:1103) underwent resting-state 18F-FDG-PET with measurement of rCGM (range 4–12 days) after onset of an infarct. Results of the study demonstrated that vestibular compensation occurs in brainstem-cerebellar loops following vestibular nucleus lesions compared to vestibular compensation that occurs at the cortical level after peripheral lesions (Becker-Bense *et al* 2013:1103). The downregulation of primary visual and motion-sensitive visual cortical areas in both cortical hemispheres to suppress blurred vision as a result of oscillopsia, indicated that the patients were already in the 'early reorganisation' phase (Balaban *et al* 2012:101). Patients in the study by Ahmad *et al* (2017:1179) presented with a confirmed diagnosis of BVF at least one (1) year before participating in the study. Results of the study demonstrated downregulation of V1/V2 cortical excitability using TMS which indicated that vestibular compensation may continue to occur in the period termed 'later reorganization' based upon the conceptual overview of the cellular and molecular mechanisms of vestibular compensation following central or peripheral vestibular dysfunction in patients (Balaban *et al* 2012:101). Although VRT is indicated in the phase 'later functional reorganisation' based upon the conceptual overview of the cellular and molecular mechanisms of vestibular compensation following central or peripheral vestibular dysfunction in patients (Balaban *et al* 2012:101), the researcher hypothesizes that VRT may be already indicated in the 'early reorganisation' phase of vestibular compensation following central vestibular dysfunction due to stroke. Based on the findings of Becker-Bense *et al* (2013:1103), it is hypothesized that improved functional outcome may be achieved through the process of sensory substitution (sensory re-weighting) of the multiple sensory modalities that include vestibular, visual and somatosensory (including proprioceptive) information involved in balance to ultimately improve functional outcome in patients with central vestibular dysfunction post-stroke (Balaban *et al* 2012:101; Lacour *et al* 2016:54). Sensory substitution is the re-weighting of extra-vestibular input facilitated

by VRT (Lacour *et al* 2016:54). The processes of the VRT-approach are discussed in Section 1.1.5.2.

1.1.5.2. Vestibular rehabilitation approach

Limited evidence on the effect of VRT as result of central vestibular dysfunction in patients who sustained either an ischaemic or haemorrhagic, hemispheric, subcortical, brainstem or cerebellar stroke has been identified in the literature. A recent Cochrane review by McDonnell and Hillier (2015:3) assessed the effectiveness of VRT following unilateral peripheral vestibular dysfunction. The review included 39 studies involving 2441 adult, community-dwelling participants with unilateral peripheral vestibular disorders due to BPPV, acute unilateral vestibular loss, acoustic neuroma resection, removal of vestibular schwannoma, ablative vestibular surgery, Ménière's disease, labyrinthitis, neuritis and other mixed or idiopathic unilateral peripheral vestibular dysfunction pathologies. Although the review reported moderate to strong evidence to support VRT for persons with peripheral vestibular dysfunction, patients who presented with central vestibular dysfunction were excluded from the review.

Vestibular rehabilitation therapy (VRT) for treatment (rehabilitation) of central vestibular dysfunction consist of a programme of exercises designed to facilitate adaptation of the vestibular system, habituate the person to movement, teach sensory substitution and improve a patient's balance and postural control (Alghadir, Iqbal and Whitney 2013:1). The process of 'adaptation' for visual-vestibular interaction (gaze stabilisation) and eye/hand co-ordination uses repetitive and provocative movements of the head and/or eyes aimed to reduce error and restore VOR-gain (Cullen, Minor, Beraneck and Sadeghi 2009:171; Balaban *et al* 2012:101; McDonnell and Hillier 2015:3). The best stimulus to induce 'adaptation' is to produce an error signal that the CNS attempts to reduce by modifying the gain of the VOR (Herdman and Whitney 2007:311). Gaze stabilisation exercises to retrain VOR function are prescribed to stimulate retinal slip to optimise vision during head movement (Herdman and Whitney 2007:311).

Secondly, the process of 'habituation' is aimed to 'habituate' or reduce a patient's responsiveness to repetitive stimuli aimed to re-balance tonic activity within the

vestibular nuclei (Gans 2002:149; McDonnell and Hillier 2015:3). 'Habituation' is based on the inherent plasticity of the CNS and is more likely to be a compensatory or neuroplastic process (Han, Song and Kim 2011:184; McDonnell and Hillier, 2015:3), rather than a physiological synaptic habituation response. Positions and movements used during the process of 'habituation' may include moving from sitting to lying in supine, rolling from supine to left side lying, rolling from supine to right side lying, moving from supine to sitting, left and right Dix-Hallpike position; return to sitting from the Dix-Hallpike position; horizontal and vertical movement of the head and turning 180° to the left and right (Herdman and Whitney 2007:312). Thirdly, the process of substitution facilitates the use of individual or combinations of sensory input such as visual or somatosensory (including proprioceptive) information to facilitate vestibular compensation through the process of sensory re-weighting due to dysfunctional vestibular input (McDonnell and Hillier 2015:3). The rehabilitation programme may include substitution exercises such as saccadic eye movement training and the alteration of somatosensory cues, for example, let the patient stand on different surfaces, i.e., foam with eyes open and closed; challenges the vestibular system by letting the patient perform activities with and without visual input; modified centre of gravity exercises; and weight shifting (Whitney *et al* 2016:13). By removing or altering visual/somatosensory cues, the patient is forced to use remaining sensory–motor cues which will result in the fostering of responses by reacting on mainly vestibular cues (Herdman and Whitney 2007:311). Lastly, a comprehensive VRT exercise programme includes higher-balance activities aimed to improve an individual's balance and postural control. Standing and walking exercises are progressed by changing the patients' base of support and speed at which activities are performed (Alghadir *et al* 2013:1). Progression to dual-task activities is incorporated within safety limits as the patients' postural control (observed as improved functional ability) improves.

1.1.6. Practical experience of the researcher

Results of a previous study (Van Wyk, Eksteen and Rheeder 2014:856) conducted by the researcher supported findings from previously published literature (Nelles et al 2009:726) that stroke patients may present with impaired residual oculomotor visual performance and visual perceptual dysfunction that affect their functional outcome

post-stroke. Van Wyk *et al* (2014:856) demonstrated that an intervention of saccadic eye movement training with visual scanning exercises (VSEs) had a significant effect on patients' residual oculomotor visual performance assessed by the King-Devick Test and visual perceptual function assessed by the Star Cancellation Test post-stroke. The significantly improved residual oculomotor visual performance and visual perceptual function post-stroke translated to significantly improved ability to perform ADLs assessed by the Barthel Index post-stroke. The researchers realised that although results of the study indicated that intensive saccadic eye movement training improved patients' residual oculomotor visual performance and visual perceptual function with associated improvement in their functional ability, the assessment and intervention used in the study was only limited to a specific subgroup of the stroke population. The sample group of the study by Van Wyk *et al* (2014:856) only included patients with unilateral spatial neglect post-stroke. The researchers also realised that although the intervention focused on the visual system (visual scanning exercises integrated with task specific activities), the visual system also functions in conjunction with the vestibular and somatosensory (proprioceptive, cutaneous and joint receptors) systems to maintain postural orientation and stability during functional movement. Although it is well established in the literature that vestibular, visual and proprioceptive (somatosensory system) information is processed by the central vestibular pathways and integrated within the sensorimotor cortex to maintain an individual's sense of balance and position (Allison and Fuller, 2013:653; Gimmon *et al* 2017:3347), Van Wyk *et al* (2014:856) failed to mention the role of the central vestibular system in residual oculomotor visual performance, visual perceptual function and functional ability post-stroke.

This observation urged the researcher to conduct a literature review to determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients' post-stroke. The prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature are summarised in Table 1.3.

Table 1.3.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**	**Activity limitations associated with central vestibular dysfunction**		**Prevalence (%)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	5.0% (Rowe *et al* 2013:2) - 100.0% (Kikuchi and Yamasoba 2007:59)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	59.5% (De Haart, Geurts, Huidekoper, Fasotti and Limbeek 2004:886) - 100.0% (Wee and Hopman 2005:604; Brown et al 2006:76; Balci et al 2013:259)
	Saccadic eye movements	3.1% (Rowe *et al* 2013:2) - 77.1% (Herron 2016:72)		**Ability to modify gait in response to changing task demands**	None reported
	Static visual acuity	15.0% (Siong *et al* 2014:438) - 70.0% (Edwards *et al* 2006:45)			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	5.0% (Rowe *et al* 2013:2) - 100.0% (Chen *et al* 2014:83; Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279)	**FUNCTIONAL ABILITY**	**Functional ability**	None reported

Table 1.3.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**		
REFLEXIVE CONTROL OF GAZE	**Dynamic visual acuity**	60.0% (Niwa, Shimodozono and Kawahira 2015:203)		
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	28.9% (Kim *et al* 2016:2424) - 78.6% (Chen and Young 2003:990)		
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	26.7% (Kim *et al* 2016:2424) - 87.5% (Su and Young 2011:923)		
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	56.7% (Cate and Richards 2000:326) - 100.0% (Olk, Harvey and Gilchrist 2002:306; Kapoor, Ciuffreda and Han 2004:1667)		
	Visual-perceptual function	19.1% (Ng, Stein, Salles and Black-Schaffer 2005:2138) - 69.6% (Gottesman *et al* 2008:1439)		

Table 1.3.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**		
HIGHER VESTIBULAR FUNCTION	**Cognition**	38.7% (Påhlman *et al* 2011:1952)		
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	31.0% (Edwards *et al* 2006:45) - 53.0% (Ali *et al* 2013:133)		

Large variations in the reported prevalence of clinical features and activity limitations associated with central vestibular dysfunction were identified in the literature (Table 1.3). The researcher also observed that although various interventions for central vestibular disorders such as virtual reality, vibrotactile feedback and optokinetic stimulation had been described in the literature (Whitney, Alghwiri and Alghadir 2015:61; Van Wyk *et al* 2016:140), the management of clinical features and activity limitations associated with central vestibular dysfunction are treated as a separate problem and not integrated into standard post-stroke rehabilitation. This observation urged the researcher to conduct a literature review to determine the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients. The various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction in patients post-stroke identified in the literature are summarised in Table 1.4.

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	(1) Advice on adaptive strategies to optimise visual function, specifically smooth pursuit eye movements (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5; Herron 2016:72) (5) Orthoptic exercises (Rowe *et al* 2013:5) (6) Smooth pursuit eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda, Han, Kapoor and Ficarra 2006:9; Carrick *et al* 2016:3; Herron 2016:72) (7) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(1) Exercises performed in supine or prone position (Bonan *et al* 2004:274) (2) Exercises performed in a sitting position (Bonan *et al* 2004:274) (3) Exercises performed in four (4) point kneeling (Bonan *et al* 2004:274) (4) Exercises performed in an upright position (Bonan *et al* 2004:274; Smania, Picelli, Gandolfi, Fiaschi and Tinazzi 2008:313) (5) Balance training on a treadmill (Bonan *et al* 2004:274)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Saccadic eye movements**	(1) Advice on adaptive strategies to optimise visual function, specifically saccadic eye movements (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5; Herron 2016:72) (5) Saccadic eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9; Carrick *et al* 2016:3; Herron 2016:72) (6) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9) (7) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(6) Balance training on a stationary bicycle (Bonan *et al* 2004:274) (7) Walking on a foam rubber track with obstacles (Bonan *et al* 2004:274) (8) Individual physiotherapy embedded in an extensive, individualized neurodevelopmental treatment (NDT) rehabilitation program. The NDT program had a general emphasis on optimal use of the paretic body side (De Haart *et al* 2004:886).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Static visual acuity**	(1) Refractive correction (Lotery *et al* 2000:221; Shrestha *et al* 2012:46; Herron 2016:72) (2) Occlusion of a spectacle lens (Lotery *et al* 2000:221)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(9) Individualised physiotherapy sessions (Van Nes, van Kessel, Schils, Fasotti, Geurts and Kwakkel 2009:819) (10) Group sessions of physiotherapy (Van Nes *et al* 2009:819) (11) Vestibular rehabilitation therapy (VRT): balance and gait training, general strengthening and flexibility exercises, utilization of somatosensation and vision to aid in maintaining balance, vestibular adaptation exercises, substitution exercises (continued)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	(1) Advice on adaptive strategies to optimise visual function related to gaze stabilisation (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5) (5) Vestibular adaptation exercises (gaze stabilisation exercises) (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477; Herron 2016:72)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(11) (continued) VRT: education in the use of assistive devices and safety awareness techniques to avoid falls (Suarez, Arocena, Suarez, De Artagaveytia, Muse and Gil 2003:143; Brown, Whitney, Marchetti, Wrisley and Furman 2006:76; Balci, Akdal, Yaka and Angin 2013:259; Dai, Huang, Chou, Wu, Wang and Lin 2013:477). (12) Visual feedback posturography training (VFPT) using (2) force plates that provided continuous visual feedback of the position of the center of gravity in relation to the theoretical limits of stability during exercise. Patients were required to maintain postural stability on a stable/unstable surface.
	Dynamic visual acuity	None reported			

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	None reported	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(12) (continued) VFPT: The exercise program included dynamic weight shifting, leaning plus stepping tasks with different bases of support and temporal demands (larger distances, different movement directions and faster speeds (Balci *et al* 2013:259). (13) Basic balance and mobility home exercise programme that included strengthening of pelvic stabilisation muscles and improvement of balance and gait ability. The exercise program consisted of weight shifting in sitting, sit to stand activity, weight shifting in standing with hip abduction and extension (continued)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	None reported	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(13) (continued) Gait training such as marching on the spot, forward and backward walking with a progressively narrowing base of support (Balci *et al* 2013:259; Dai *et al* 2013:477). (14) Combination of balance training and visual therapy. Balance training included individualized sensory integration, vestibular and proprioceptive exercises. Visual therapy included training of binocularity, fixation, tracking, vergence, visual attention, accommodation, eye-hand coordination and binocularity (Schow *et al* 2016:333).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	(1) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9) (2) Advice on adaptive strategies to optimise residual oculomotor visual performance function (Rowe *et al* 2011:408) (3) Refractive correction (Rowe *et al* 2011:408) (4) Typoscope reading guide (Rowe *et al* 2011:408)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(1) Exercises performed in supine or prone position (Bonan *et al* 2004:274) (2) Exercises performed in a sitting position (Bonan *et al* 2004:274) (3) Exercises performed in four (4) point kneeling (Bonan *et al* 2004:274) (4) Exercises performed in an upright position (Bonan *et al* 2004:274) (5) Balance training on a treadmill (Bonan *et al* 2004:274)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	(5) Use of prisms (Rowe *et al* 2011:408) (6) Tracking exercises (Rowe *et al* 2011:408) (7) Low vision aids (Rowe *et al* 2011:408) (8) Occlusion of a spectacle lens (Rowe *et al* 2011:408) (9) Use of Peli prisms (Rowe *et al* 2011:408) (10) Convergence exercises (Rowe *et al* 2011:408) (11) Cortical visual impairment registration (Rowe *et al* 2011:408) (12) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(6) Balance training on a stationary bicycle (Bonan *et al* 2004:274) (7) Walking on a foam rubber track with obstacles (Bonan *et al* 2004:274) (8) Individual physiotherapy embedded in an extensive, individualized neurodevelopmental treatment (NDT) rehabilitation program. The NDT program had a general emphasis on optimal use of the paretic body side (De Haart *et al* 2004:886) (9) Individualised physiotherapy sessions (Van Nes *et al* 2009:819) (10) Group sessions of physiotherapy (Van Nes *et al* 2009:819)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Visual-perceptual function**	(1) Optokinetic stimulation to elicit smooth pursuit eye movements (Kerkhoff *et al* 2012:1164) (2) Vestibular rehabilitation therapy (Dai *et al* 2013:477) (3) Smooth pursuit eye movement training (Kerkhoff, Reinhart, Ziegler, Artinger, Marquardt and Keller, 2013:789; Kerkhoff *et al* 2014:557) (4) Saccadic eye movement training (Kerkhoff *et al* 2013:789); Kerkhoff *et al* 2014:557) (5) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(11) Vestibular rehabilitation therapy: balance and gait training, general strengthening and flexibility exercises, utilization of somatosensation and vision to aid in maintaining balance, vestibular adaptation exercises, substitution exercises, education in the use of assistive devices and safety awareness techniques to avoid falls (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Cognition**	(1) Comprehensive rehabilitation programme that included physiotherapy, occupational therapy and speech and language therapy (Ng *et al* 2005:2138)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(12) Visual feedback posturography training (VFPT) using (2) force plates that provided continuous visual feedback of the position of the center of gravity in relation to the theoretical limits of stability during exercise. Patients were required to maintain postural stability on a stable/unstable surface. The exercise program included dynamic weight shifting, leaning plus stepping tasks with different bases of support and temporal demands (larger distances, different movement directions and faster speeds (Balci *et al* 2013:259).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	(1) Combination of pharmacological and rehabilitation therapy (Nagaratnam, Ip and Bou-Haidar 2005:253) (2) Vestibular rehabilitation therapy (VRT) (Meli, Zimatore, Badaracco, De Angelis and Tufarelli 2007:185)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(13) Basic balance and mobility home exercise programme that included strengthening of pelvic stabilisation muscles and improvement of balance and gait ability. The exercise program consisted of weight shifting in sitting, sit to stand activity, weight shifting in standing with hip abduction and extension. Gait training such as marching on the spot, forward and backward walking with a progressively narrowing base of support (Balci *et al* 2013:259; Dai *et al* 2013:477).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)				
		Activity and participation level		
		Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
		SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT	**Ability to modify gait in response to changing task demands**	(14) Combination of balance training and visual therapy. Balance training included individualized sensory integration, vestibular and proprioceptive exercises. Visual therapy included training of binocularity, fixation, tracking, vergence, visual attention, accommodation, eye-hand coordination and binocularity (Schow *et al* 2016:333).

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)			
	Activity and participation level		
	Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
	FUNCTIONAL ABILITY	**Functional ability**	(1) Comprehensive rehabilitation programme (Ng *et al* 2005:2138) (2) Vestibular rehabilitation therapy (Dai *et al* 2013:477) (3) Active and passive exercises, resistance exercises and ambulation training (Dai *et al* 2013:477) (4) Computerised bedside saccadic eye movement training (Kerkhoff *et al* 2014:557) (5) Computerised bedside smooth pursuit eye movement training (Kerkhoff *et al* 2014:557)

Table 1.4.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)				
		Activity and participation level		
		Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
		FUNCTIONAL ABILITY	**Functional ability**	(6) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856)

Various interventions used in the treatment of clinical features associated with central vestibular dysfunction in patients post-stroke were identified in the literature (Table 1.4). Although Suarez *et al* (2003:143), Brown *et al* (2006:76), Balci *et al* (2013:259) and Dai *et al* (2013:477) demonstrated that patients with central vestibular dysfunction post-stroke improve with VRT, all four (4) studies posed multiple methodological limitations (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). A limitation on the use of VRT in the treatment of clinical features associated with central vestibular dysfunction in patients post-stroke were identified in the literature. The researcher therefore regarded the following processes as essential components in the management of patients with central vestibular dysfunction in the sub-acute phase post-stroke; (1) to determine the prevalence of clinical features of central vestibular dysfunction in the sub-acute post-stroke population; and (2) to determine whether VRT integrated with task-specific activities as a treatment approach may result in statistical significant improvement of clinical features of central vestibular dysfunction in patients in the early reorganisation (sub-acute) phase post-stroke.

1.2. PROBLEM STATEMENT

The presence of central vestibular dysfunction in patients post-stroke may be identified by the presence of specific clinical feature categories. The presence of central vestibular dysfunction may be categorised by impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level that includes; (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke (Section 1.1.3.1. to Section 1.1.3.2).

Insufficient evidence on the prevalence of central vestibular dysfunction that may be identified through the presence of above-mentioned clinical features based on impairment on the level of body structure and function, as well as activity and participation level in patients post-stroke, have been identified in the literature. The

researcher therefore identified the need to investigate the prevalence of central vestibular dysfunction in the sub-acute post-stroke population. Even though the association between central vestibular dysfunction and disability in performing activities of daily living is well established, the services available to patients with central vestibular dysfunction following a stroke are inconsistent at present. Identification of the possible presence of central vestibular dysfunction in the post-stroke population may facilitate the development of evidence-based treatment for patients who present with impaired (a) oculomotor control; (b) reflexive control of gaze; (c) saccule and inferior vestibular nerve function; (d) utricle and superior vestibular nerve function; (e) higher vestibular function; (f) anxiety and/or depression; (g) impaired sensorimotor control of balance, mobility and gait; (h) impaired functional ability; and (i) participation in physical activity due to the presence of central vestibular dysfunction post-stroke.

A further limitation on the use of VRT as part of, and integrated with, physiotherapy aimed to facilitate sensory re-weighting in the 'early reorganisation' phase post-stroke, has been identified in the literature. There is a need for research evidence on the use of VRT as part of, and integrated with, task-specific activities (the gold standard in post-stroke rehabilitation), to determine the effect of the intervention on body impairment level, functional activity and participation levels in the treatment of post-stroke patients in the sub-acute phase. A lack of evidence that examined the long-term effect of VRT integrated with task-specific activities on patients' activities related to participation has also been identified in the literature.

1.3. RESEARCH QUESTIONS, AIMS AND OBJECTIVES

As mentioned in Section 1.2., the researcher identified the need to investigate the prevalence of clinical features associated with central vestibular dysfunction in the sub-acute post-stroke population. A cross-sectional survey was conducted to determine the prevalence of central vestibular dysfunction that may be identified through the presence of specific clinical feature categories based on the ICF-model (Lazaro *et al* 2013:187). The presence of central vestibular dysfunction may be categorised by impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and

inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level that includes (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke (Section 1.1.3.1. to Section 1.1.3.2). The research questions, aims and objectives of phase 1 and phase 2 of the current study are described in Table 1.5.

Table 1.5.: Research questions, aims and objectives of phase 1 and phase 2 of the study.

	PHASE 1	PHASE 2
Main research question(s)	(a) What is the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in the sub-acute post-stroke population?	(a) Will VRT integrated with task-specific activities as treatment approach, result in statistically significant improvement of the clinical features and activity limitations associated with central vestibular dysfunction in the sub-acute phase post-stroke after two (2) weeks of rehabilitation compared to patients who only receive task-specific activities as treatment approach?
	(b) Which objective measures are used to assess the clinical features and activity limitations associated with central vestibular dysfunction in the sub-acute post-stroke population?	(b) Will VRT integrated with task-specific activities as treatment approach for patients who present with central vestibular dysfunction in the sub-acute phase post-stroke, have an effect on patients' participation in physical activities twenty (20) weeks after rehabilitation has been terminated, compared to patients who have only received the task-specific treatment approach?
Main aim(s)	(a) To determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke.	(a) To review and compile the treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction for patients who are in the sub-acute phase post-stroke.
	(b) To determine the specific objective measures and compile an assessment battery used to identify and measure the clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke.	(b) To determine the effect of VRT integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group.

Table 1.5.: Research questions, aims and objectives of phase 1 and phase 2 of the study (continued).

	PHASE 1	PHASE 2
Objective(s)	(a) To conduct a literature study to determine the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in patients post-stroke.	(a) To conduct a literature study to determine the various interventions used in the treatment of the clinical features and activity limitations associated with central vestibular dysfunction in patients post-stroke.
	(b) To conduct a literature study to determine the various objective measures used to identify and quantify the clinical features and activity limitations associated with central vestibular dysfunction in patients post-stroke.	

1.4. DELIMITATIONS AND ASSUMPTIONS

1.4.1. Delimitations

Delimitations of the study are: (1) the study population (phase 1 and phase 2) is delimited to only post-stroke patients in the sub-acute phase in Gauteng, South Africa. (2) The study population of phase 2 is delimited to a sample of patients identified during phase 1 of the study who present with clinical features associated with central vestibular dysfunction post-stroke and who are admitted at rehabilitation hospital settings in Gauteng, South Africa.

1.4.2. Assumptions

1.4.2.1. Ontological assumptions

The ontological assumption of this study was based on the fact that: (1) the patients have given accurate and honest information during the collection and completion of comprehensive biographical information during phase 1 of the study and self-reported outcome measures in phase 1 and phase 2 of the study; (2) the physiotherapist (principal investigator) have gathered and reported accurate and honest information during the assessment of the vestibular system with specific measurement tools and apparatus during phase 1 and phase 2 of the study; and (3) the physiotherapist (independent assessor) have gathered and reported accurate and honest information during the completion of outcome measures during phase 1 and phase 2 of the study. (4) The intervention has been carried out according to the study protocol in order to answer the research aims.

1.4.2.2. Epistemological assumptions

The primary researcher envisioned that the study would make a contribution to the body of knowledge to understand the multisensory integration of sensory input from the vestibular system, visual system and the somatosensory system to optimise postural control in post-stroke patients in the sub-acute phase. The assessment of the clinical features associated with central vestibular dysfunction on body impairment level might create research evidence on the multisensory integration of the vestibular system, visual system and the somatosensory system in maintaining postural orientation and stability during functional movement assessed on functional ability and participation levels. The researcher assumed that her knowledge and expertise in the

field would enable her to understand the processes of assessment and treatment of patients in the sub-acute phase post-stroke following a master's study on a similar topic. The researcher envisaged that her knowledge and expertise would also enable her to interpret the findings of each phase of the research process.

1.4.2.3. Methodological assumptions

In the current study, the first methodological assumption was that a cross-sectional survey would fall within the quantitative research paradigm and was the best method to answer the primary research question of phase 1 of the study. Interpretation of the results of the cross-sectional survey on post-stroke patients in the sub-acute phase completed during phase 1 of the study, would enable the researcher to achieve the main aim of phase 1 of the study.

The second methodological assumption of the study was that the prevalence of central vestibular dysfunction in patients who sustained a stroke could be identified and quantified by objective measurements.

The third methodological assumption was that a single-blind cluster randomised trial that falls within the quantitative research paradigm was the best approach to answer the primary research question of phase 2 of the study. Interpretation of the results of the single-blind cluster randomised trial completed during phase 2 of the study would enable the researcher to achieve the main aim of phase 2 of the study.

The fourth methodological assumption of phase 2 of the study was therefore that the effect of the intervention approaches on patients with central vestibular dysfunction following a stroke could be identified and objectively measured.

The fifth methodological assumption was that the tests and outcome measures used in the study were valid and reliable as reported by previous published studies. The tests and outcome measures that were selected for this study have been implemented on both national and international levels in the field of post-stroke rehabilitation.

The sixth methodological assumption was that the tests and outcome measures used in the study would provide an indication that the possible improvement on impairment level may attribute to restitution or may be the result of the compensation between the

impairment, functional activity and participation level that may have led to an observed improvement in the patients' participation level activities.

1.5. RESEARCH APPROACH

The study was conducted in two (2) phases. Phase 1 entailed a cross-sectional survey that was conducted to determine the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction and whether there is a relationship between the clinical features of central vestibular dysfunction and functional ability in patients who are in the sub-acute phase post-stroke. In phase 1 it was also determined which objective measures have to be used to identify the clinical features and activity limitations associated with central vestibular dysfunction in order to compile an assessment battery for the quantification of the clinical features and activity limitations associated with central vestibular dysfunction in patients who were in the sub-acute phase post-stroke. The cross-sectional survey was conducted on a population of sub-acute post-stroke patients.

Phase 2 entailed a single-blind cluster randomised controlled trial to determine the effect of the VRT integrated with task-specific activities on sensory re-weighting in the 'early reorganisation' phase post-stroke. The single-blind cluster randomised controlled trial was conducted on the same population as phase 1 of the study. The single-blind cluster randomised controlled trial was conducted to determine the effect of the intervention on the clinical features and activity and participation limitations associated with central vestibular dysfunction in patients in the sub-acute phase post-stroke.

1.6. IMPORTANCE AND BENEFITS OF THE CURRENT STUDY

This research may contribute to an evidence-based holistic understanding of the clinical features and activity limitations associated with central vestibular dysfunction that may present in patients in the 'early re-organisation' (sub-acute) phase following a stroke. The study may further contribute to the diagnosis and treatment strategies

that may be implemented during early rehabilitation of post-stroke patients. The results of phase 2 may contribute to the understanding of sensory re-weighting in the early reorganisation phase post-stroke to prevent development of maladaptive sensory strategies in the early months post-stroke. The study may further contribute to the diagnosis of vestibular-ocular interaction and treatment strategies such as facilitation of sensory reweighting that may be implemented in the rehabilitation of post-stroke patients who present with central vestibular dysfunction in the sub-acute phase post-stroke.

Lastly, the evidence from this study may contribute to an understanding of the clinical features of central vestibular dysfunction that may present in patients in the sub-acute phase post-stroke to optimise their sensorimotor control of balance, mobility and gait to ultimately improve patients' functional outcome post-stroke and contribute to the provision of evidence based post-stroke care.

1.7. COURSE OF THE STUDY

In Chapter 1, the differentiation between peripheral impairment versus central impairment, structural neural connectivity of the central vestibular system, model of disablement used in peripheral versus central vestibular dysfunction, the specific clinical features based on impairment on the level of body structure and function, as well as activity limitations on activity and participation level post-stroke, are discussed. Vestibular compensation, vestibular rehabilitation approach, the practical experience of the researcher, problem statement, research questions, aims and objectives of the study, research approach, importance and benefits of the proposed study are also discussed.

In Chapter 2 the existing research evidence that assessed the prevalence, assessment and interventions used to address central vestibular disorders in the post-stroke population, are reviewed.

In Chapter 3 a detailed account is given on how the research was performed. This account includes the research methodology for phase 1 and phase 2 of the study.

In Chapter 4 the results of the cross-sectional survey that was conducted during phase 1 of the study are discussed.

In Chapter 5 the results of the single-blind cluster randomised controlled trial that was conducted during phase 2 of the study, are discussed.

In Chapter 6 the results of the clinical trial are discussed in the context of the relevant literature.

In Chapter 7 the conclusion, limitations of the current study and suggestions for further studies are discussed.

CHAPTER 2

LITERATURE REVIEW

2.1. INTRODUCTION

In Chapter 1, the researcher indicated that central vestibular dysfunction in post-stroke patients may be identified by specific clinical features. The presence of these clinical features associated with central vestibular dysfunction may be categorised into impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level that includes; (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke (Section 1.1.3.1 to Section 1.1.3.2).

In Chapter 2 the existing research evidence that investigated the prevalence and management of these clinical features and activity limitations associated with central vestibular dysfunction on the level of body structure and function as well as activity and participation level of patients in the sub-acute phase post-stroke were reviewed and presented within the conceptual framework (ICF-model of disablement) (Lazaro *et al* 2013:187) presented in Chapter 1. The existing research evidence that investigated the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in the post-stroke population are discussed in Section 2.3. The existing research evidence that investigated the various objective measures used to identify and quantify the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients, are discussed in Section 2.4. Lastly, the various interventions used in the treatment of these clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients, are discussed in Section 2.5.

2.2. LITERATURE SEARCH STRATEGY

Throughout the literature review, the various literature searches that were performed followed by the critical analysis and limitations identified in the reviewed literature are presented to compile a concise understanding of the clinical features and activity limitations associated with central vestibular dysfunction based on impairment on the level of body structure and function, as well as activity and participation level in post-stroke patients. The literature search strategy of each clinical feature indicated at the beginning of each sub-section in this narrative literature review (Rother 2007:2).

2.2.1. Assessment of the quality of selected literature

The principal investigator performed all literature search strategies of each clinical feature associated with central vestibular dysfunction on the level of body structure and function, as well as activity and participation level in the post-stroke population. The principal investigator also critically reviewed and completed the assessment of the quality of evidence included in this narrative literature review (Rother 2007:2). To assess the quality of the studies selected, three literature appraisal tools relevant to the specific study designs were used to assess the quality of the literature. The 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement checklist was used to assess the quality of observational studies, including cohort, case-control and cross-sectional studies (Vandenbroucke, von Elm, Altman, Gøtzsche, Mulrow, Pocock, Poole, Schlesselman, Egger and STROBE Initiative 2007:805; von Elm, Altman, Egger, Pocock, Gøtzsche and Vandenbroucke 2007:573). The 'Consolidated Standards of Reporting Trials' (CONSORT) statement checklist was used to assess the quality of randomised controlled trials (RCTs) (Turner *et al* 2012:1465). The 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement' was used to assess the quality of systematic reviews (Moher *et al* 2015:1). The 'Standards for Reporting Qualitative Research' (SRQR) checklist was used to assess qualitative research (O'Brien, Harris, Beckman, Reed and Cook 2014:1245). The 'Consensus-based Clinical Case Reporting Guideline Development' (CARE) guidelines checklist was used to assess case reports (Gagnier, Kienle, Altman, Moher, Sox and Riley 2013:38). The 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) checklist was used to assess protocols of clinical trials (Chan *et al* 2013:200).

After appraisal of the quality of the studies using the STROBE, CONSORT, PRISMA, SRQR, CARE and SPIRIT statement checklists, levels of evidence were assigned to the consulted literature. The assignment of the levels of evidence was followed by the assignment of grades of recommendations of the literature appraised and reflects the overall strength of the evidence available. The criteria for the grades of recommendations of the literature appraised (Hall *et al* 2016:127) is presented in Table 2.1.

Table 2.1.: Criteria for the grades of recommendations of the literature appraised (Hall *et al* 2016:127).

Level of Evidence	
I	Evidence obtained from high-quality (≥50% critical appraisal score) diagnostic studies, prospective studies, or randomized controlled trials
II	Evidence obtained from lesser quality (<50% critical appraisal score) diagnostic studies, prospective studies, or randomized controlled trials
III	Case-controlled studies or retrospective studies
IV	Case study or case series
V	Expert opinion

The narrative review presented in Section 2.3 to Section 2.5 does not include grey literature such as theses and dissertations, research and committee reports, government reports and conference papers (Paez 2017:233).

Firstly, the existing research evidence that investigated the prevalence of clinical features associated with central vestibular dysfunction on the level of body structure and function, as well as activity and participation level in the post-stroke population, are discussed in Section 2.3.

2.3. PREVALENCE OF CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION

The presence of central vestibular dysfunction in patients post-stroke may be identified by the presence of specific clinical features. The presence of central vestibular dysfunction may be categorised by impairment on the level of body structure and function that includes impairment of; (1) oculomotor control; (2) reflexive control of

gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression. Central vestibular dysfunction may also be categorised by impairment on activity and participatory level that includes; (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke. The conceptual framework based on the ICF-model (Lazaro *et al* 2013:187) within which the existing research evidence that assessed the prevalence of clinical features and activity limitations associated with central vestibular disorders on the level of body structure and function as well, as activity and participation level in the post-stroke population, is presented in Table 2.2.

The prevalence of clinical features and activity limitations associated with central vestibular dysfunction are summarised in Table 2.2.

Table 2.2.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**	**Activity limitations associated with central vestibular dysfunction**		**Prevalence (%)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	5.0% (Rowe *et al* 2013:2) - 100.0% (Kikuchi and Yamasoba 2007:59)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	59.5% (De Haart *et al* 2004:886) - 100.0% (Wee and Hopman 2005:604; Brown et al 2006:76; Balci et al 2013:259)
	Saccadic eye movements	3.1% (Rowe *et al* 2013:2) - 77.1% (Herron 2016:72)		**Ability to modify gait in response to changing task demands**	None reported
	Static visual acuity	15.0% (Siong *et al* 2014:438) - 70.0% (Edwards *et al* 2006:45)			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	5.0% (Rowe *et al* 2013:2) - 100.0% (Chen *et al* 2014:83; Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279)	**FUNCTIONAL ABILITY**	**Functional ability**	None reported
	Dynamic visual acuity	60.0% (Niwa *et al* 2015:203)			

Table 2.2.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in the literature (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**		
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	28.9% (Kim *et al* 2016:2424) - 78.6% (Chen and Young 2003:990)		
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	26.7% (Kim *et al* 2016:2424) - 87.5% (Su and Young 2011:923)		
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	56.7% (Cate and Richards 2000:326) - 100.0% (Olk *et al* 2002:306; Kapoor *et al* 2004:1667)		
	Visual-perceptual function	19.1% (Ng *et al* 2005:2138) - 69.6% (Gottesman *et al* 2008:1439)		
	Cognition	38.7% (Påhlman *et al* 2011:1952)		
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	31.0% (Edwards *et al* 2006:45) - 53.0% (Ali *et al* 2013:133)		

Each of the clinical features and activity limitations associated with central vestibular dysfunction are discussed from Section 2.3.1. to Section 2.3.2. The first clinical feature of central vestibular dysfunction on the level of body structure and function to be discussed is oculomotor control in Section 2.3.1.

2.3.1. Level of body structure and function

2.3.1.1. Oculomotor control

When an individual moves or an object of interest moves relative to the environment, stabilising eye movements that include smooth pursuit and saccadic eye movements, optokinetic reflex and VOR, are required to ensure optimal visual acuity by limiting the retinal slip or movement of images on the retina (of the individual). The role of these visual fixation and stabilisation responses is to maintain optimal visual acuity while an individual's head is kept still, as well as during head motion when visual acuity dramatically decreases when retinal slip exceeds 4°/s (Hermann *et al* 2018:300). The first feature of oculomotor control to be discussed is smooth pursuit eye movement.

(i). Smooth pursuit eye movement

Smooth pursuit eye movement is the slow movement of the eyes (1°–30°/s) that serve to keep an image of a moving target steady on the fovea of the eye to ensure clear vision (optimal visual acuity) of the target. Performance of smooth pursuit eye movements requires focused attention to follow (track) a specific moving target (Kheradmand *et al* 2016:103-117). Smooth pursuit eye movements are also needed to stabilise the eye on a stationary target while an individual is moving, such as during locomotion. Smooth pursuit eye movements keep the image on the fovea of the eye despite relative motion of the background during functional activities, including walking and running (Sharpe 2008:241).

The generation of smooth pursuit eye movements is controlled by the visual cortex, medial temporal area (MT), MST, frontal eye fields (FEF), dorsolateral pontine nuclei, cerebellum (flocculus and oculomotor vermis), vestibular nuclei and oculomotor nuclei (Strupp *et al* 2014:542). The brain regions responsible for the generation of smooth

pursuit eye movements (Strupp *et al* 2014:542) is supported by findings by Jang *et al* (2018:727) that investigated the structural neural connectivity of the vestibular nuclei using DTT. Findings of the study demonstrated 100% connectivity between the vestibular nuclei and the cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus and reticular formation. These connected brain regions thus relate (100%) to the functions of the vestibular nuclei (Strupp *et al* 2014:542; Brandt and Dieterich 2017:352; Jang *et al* 2018:727) that includes the control of eye movements such as smooth pursuit eye movements. Impairment of smooth pursuit eye movements has been a well-described clinical sign of cerebral lesions since early in the last century (Sharpe 2008:241) and low gain smooth pursuit eye movement is a sensitive sign of chronic diffuse brain disease that may be useful in the detection of neurological disorders (Sharpe 2008:241). Previous studies demonstrated that smooth pursuit eye movement impairment endure weeks to months to years (long-term) beyond the acute lesion stage as a result of limited adaptation by redundant subcortical-pathways in the damaged hemisphere or the other intact hemispheric cortex (Sharpe 2008:241). Although the relationship between the presence of smooth pursuit eye movement impairment and neurological disorders are theoretically described in the literature (Sharpe 2008:241), limited evidence on the prevalence of oculomotor impairment, specifically smooth pursuit eye movements due to central vestibular dysfunction in post-stroke patients, has been described in the literature (Pollock *et al* 2011:2) (Section 1.1.3.1). The researcher therefore identified the need to investigate the prevalence of oculomotor impairment, specifically smooth pursuit eye movements due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to study the prevalence of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.1., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”, “oculomotor impairment”; “smooth pursuit eye movement”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of smooth pursuit eye movement impairment due to central vestibular

dysfunction in the sub-acute post-stroke population, were included in this section of the review.

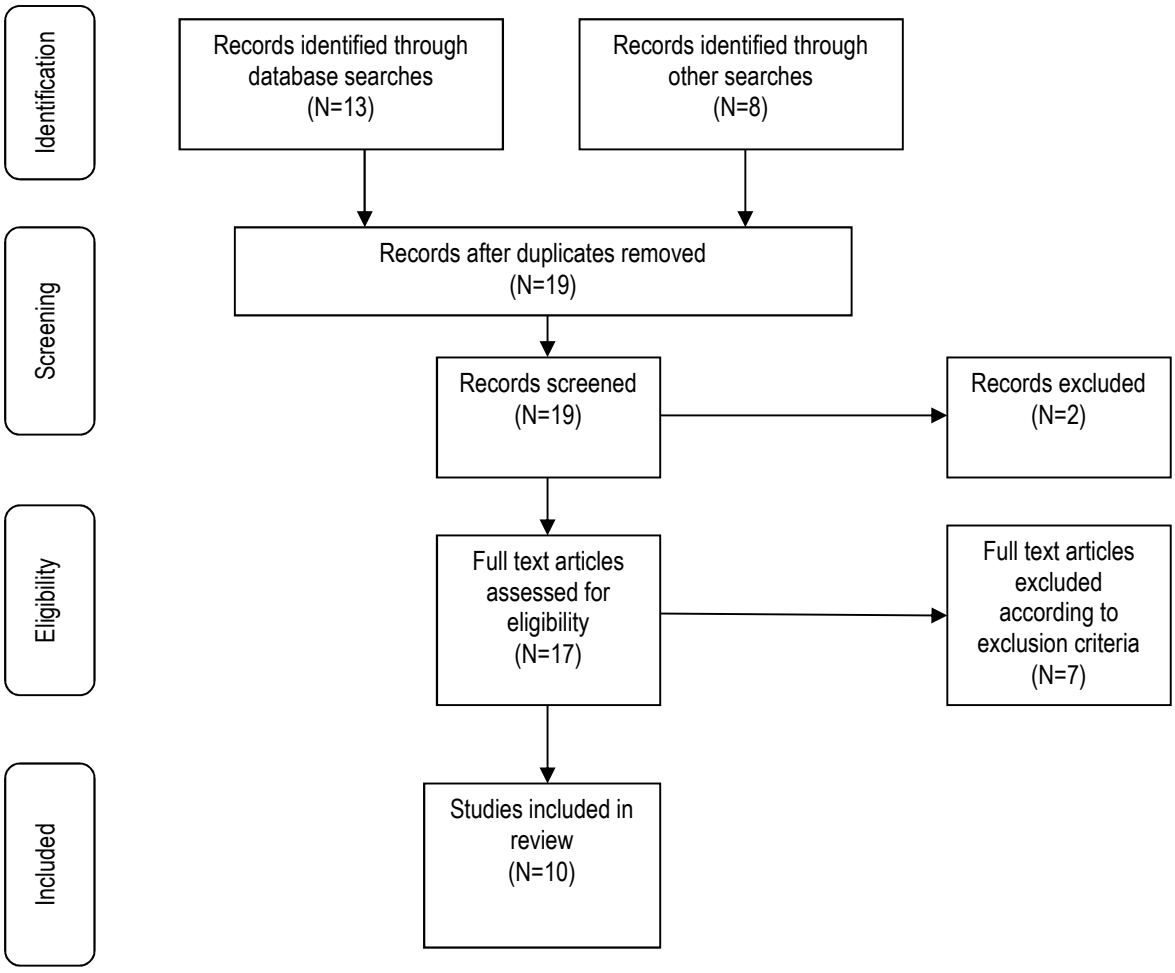


Figure 2.1.: Results of the literature search strategy on the prevalence of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Ten (10) articles were critically reviewed and an assessment of the quality of evidence was completed. Literature appraised included a systematic literature review, four (4) single-centre double blind RCTs, a prospective multi-centre observational study, three (3) retrospective studies and a case-control study. Articles appraised are presented in Table 2.3.

Table 2.3.: Appraised articles on the prevalence of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=10)				
Level of Evidence				
I (N=6)	**II**	**III** (N=4)	**IV**	**V**
Kerkhoff *et al* (2012:1164)		Baumann, Ziemus, Luerding, Schuierer, Bogdahn and Greenlee (2007:237)		
Kerkhoff *et al* (2013:789)		Ciuffreda, Kapoor, Rutner, Suchoff, Han and Craig (2007:155)		
Rowe *et al* (2013:2)		Kikuchi and Yamasoba (2007:59)		
Kerkhoff *et al* (2014:557)		Herron (2016:72)		
Hill, Coats, Halstead and Burke (2015:410)				
Carrick *et al* (2016:3)				

Based upon the articles appraised, the reported prevalence of smooth pursuit eye movements in post-stroke patients ranged between 5.0% (Rowe *et al* 2013:2) and 100.0% (Kikuchi and Yamasoba 2007:59). The difference in the reported prevalence of smooth pursuit eye movements in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (Kikuchi and Yamasoba 2007:59; Rowe *et al* 2013:1). The method of assessment of smooth pursuit eye movement used by Rowe *et al* (2013:1) was based upon observation only compared to Kikuchi and Yamasoba (2007:59) who quantified smooth pursuit eye movements using Electronystagmography (ENG). Both studies methodologies (Kikuchi and Yamasoba 2007:59; Rowe *et al* 2013:1) posed several limitations. Although the aim of the study by Rowe *et al* (2013:1) was to evaluate ocular gaze abnormalities in patients post-stroke, the absence of objective quantification of smooth pursuit eye movements may have resulted in limited accuracy in the identification and quantification of smooth pursuit eye movement impairment compared to detailed vestibular assessment using objective measures (videonystagmography [VNG]). Another limitation of the study by Rowe *et al* (2013:7) is that the study is not an

epidemiology study. The study sample only included stroke patients who were referred specifically for a vision assessment by an orthoptist when healthcare personnel suspected visual difficulty based on the presence of patient-reported visual symptoms, or the health care professional observed signs of visual impairment (Rowe *et al* 2013:2). Stroke patients with suspected visual difficulty were referred from in-patient wards, rehabilitation units, community services and outpatient clinics. Although the mean duration from onset of stroke to initial eye examination was 40.84±141.28 days (which falls within the sub-acute phase post-stroke), three (3) patients who sustained a stroke a number of years prior to the study, were also included in the study sample. The demographical data was therefore skewed because the study sample included patients both in the 'early reorganization' and 'later reorganization' phase post-stroke (Section 1.1.4.1). Findings of the study by Rowe *et al* (2013:3) demonstrated that post-stroke patients who present with smooth pursuit eye movement impairment, suffered either a haemorrhagic or ischaemic stroke in the frontal lobe (N=1), parietal lobe (N=8), temporal lobe (N=3), occipital lobe (N=8), periventricular (N=1), external capsule (N=1), internal capsule (N=1), thalamus (N=2), basal ganglia (N=1), lacunar area (N=1), brainstem (N=4) or cerebellum (N=6). Central vestibular dysfunction is diagnosed when lesions involve the (a) vestibular nuclei in the pontomedullary brainstem; (b) vestibular pathways that project from the vestibular nuclei to the vestibulocerebellum (via the cerebellar peduncles); (c) brainstem; (d) thalamus; and (e) multisensory vestibular cortex areas which include the PIVC and the MST of the visual cortex (Brandt and Dieterich 2017:352). Apart from the brain regions identified by Brandt and Dieterich (2017:352), findings of the study by Jang *et al* (2018:727) demonstrated 100% connectivity between the vestibular nuclei and the cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus and reticular formation. The vestibular nuclei also demonstrated high connectivity (over 70%) with the sensory-motor cortex (primary motor cortex (95.9%), primary somatosensory cortex (90.5%), premotor cortex (87.8%) and posterior parietal cortex (75.7%), hypothalamus (86.5%), lateral prefrontal cortex (70.3%), ventromedial prefrontal cortex (51.4%) and orbitofrontal cortex (40.5%). Although the association between central vestibular dysfunction and oculomotor impairment are well documented, Rowe *et al* (2013:7) did not mention the role of the central vestibular system involved in oculomotor impairment that specifically include smooth pursuit eye movement dysfunction post-stroke.

Alternatively, Kikuchi and Yamasoba (2007:59) demonstrated a 100% prevalence of smooth pursuit eye movement impairment using ENG. Electronystagmography (ENG) is a commonly used method for recording eye movements by applying the corneal-retinal potential variation principle during eye movements to record and quantify smooth pursuit eye movements (Ganança, Caovilla and Ganança 2010:400). Although the study by Kikuchi and Yamasoba (2007:59) demonstrated a 100% prevalence of impaired smooth pursuit eye movement post-stroke, the study sample was limited to only five (5) participants with very small (border zone) cerebellar infarcts (VSCIs) identified by magnetic resonance imaging (MRI). Despite these limitations, the study by Kikuchi and Yamasoba (2007:59) presented interesting findings: although cerebellar lesions may result in impaired smooth pursuit and saccadic eye movement dysfunction and decreased slow-phase velocity in optokinetic nystagmus (Figure 1.3), none of the participants demonstrated any abnormalities of saccadic eye movements or optokinetic nystagmus. Findings of the study demonstrated that impairment of saccadic eye movements and optokinetic nystagmus may not be evident until the cerebellar lesion has become more extensive. The symptoms and signs of VSCIs may mimic similar symptoms and signs observed in patients with benign peripheral vestibular disorders, except that smooth pursuit eye movement is impaired in patients with VSCIs. It is important to note that impaired smooth pursuit eye movement was the only abnormal ENG result identified in the study sample. Findings of the study by Kikuchi and Yamasoba (2007:59) indicate that central vestibular dysfunction in post-stroke patients may be identified by the presence of a specific clinical features which include impairment of oculomotor control, specifically smooth pursuit eye movement impairment. The second feature of oculomotor control to be discussed is saccadic eye movement.

(ii). Saccadic eye movement

When humans explore their surrounding environment, they form a clear and stable visual scene by automatically scanning their environment with accurate saccadic eye movements. The role of saccadic eye movements is to direct the fovea of the eye of an individual towards an object of interest. The image of an object of interest has to be brought within 0.5° from the fovea of the eye to ensure optimal visual acuity (Hermann *et al* 2018:300). Saccadic eye movements are fast eye movements (400°–600°/s) that shift the eyes from one target to another (looking from one object to

another) (Leigh and Zee 2006:5; Pollock *et al* 2011:2; Willard and Lueck 2014:75). The main function of saccadic eye movements is to bring objects of interest seen in the periphery, on to the fovea of the eye (Catz, Ron, Solzi and Korczyn 1997:175; Kheradmand *et al* 2016:103-117). Extensive research has been conducted to identify the different brain and eye mechanisms responsible for the generation of saccadic eye movements and the manner in which different pathologies affect these eye movements (Carrick *et al* 2016:3). The brain areas responsible for saccadic eye movements extend from the cortical structures, mainly the parietal and frontal cortices, through the basal ganglia and thalamus, to the superior colliculus, cerebellum and brainstem reticular formation (Munoz 2002:89). The basic pathways for saccadic eye movements from the cortical regions through the basal ganglia to the brainstem oculomotor nuclei, are well established (Tyler, Likova, Mineff and Nicholas 2015:173). The left and right oculomotor nuclei send signals directly to the medial rectus muscles for an inward eye movement. For outward eye movement, signals from left and right oculomotor nuclei, are sent via the descending pathway of the MLF to the paramedian pontine reticular formation (PPRF) and then to the adjacent abducens nuclei. The abducens nuclei also contain internuclear inhibitory neurons that project back up the MLF to the contralateral oculomotor nucleus, to inhibit the medial rectus muscles that is responsible for inward eye movement to allow for the maximum activation of the lateral rectus muscles for outward eye movement (Tyler *et al* 2015:173). The brain regions responsible for the generation of saccadic eye movements described by Munoz (2002:89), is supported by findings by Jang *et al* (2018:727) who investigated the structural neural connectivity of the vestibular nuclei using DTT. Findings of the study demonstrated 100% connectivity between the vestibular nuclei and the oculomotor nucleus, trochlear nucleus, abducens nucleus, thalamus, reticular formation and cerebellum. These connected brain regions thus relate (100%) to the functions of the vestibular nuclei (Munoz 2002:89; Tyler *et al* 2015:173; Brandt and Dieterich 2017:352; Jang *et al* 2018:727) that include the control of eye movements, such as saccadic eye movements. Although previous studies have described the relationship between saccadic eye movement impairment and stroke (Dong *et al* 2013:337; Carrick *et al* 2016:3), limited evidence on the prevalence of oculomotor impairment, specifically saccadic eye movements due to central vestibular dysfunction in post-stroke patients, have been described in the literature (Pollock *et al* 2011:2) (Section 1.1.3.1). The researcher therefore identified the need to investigate the

prevalence of oculomotor impairment, specifically saccadic eye movements due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to study the prevalence of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.2 was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”, “oculomotor impairment”; “saccadic eye movement”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

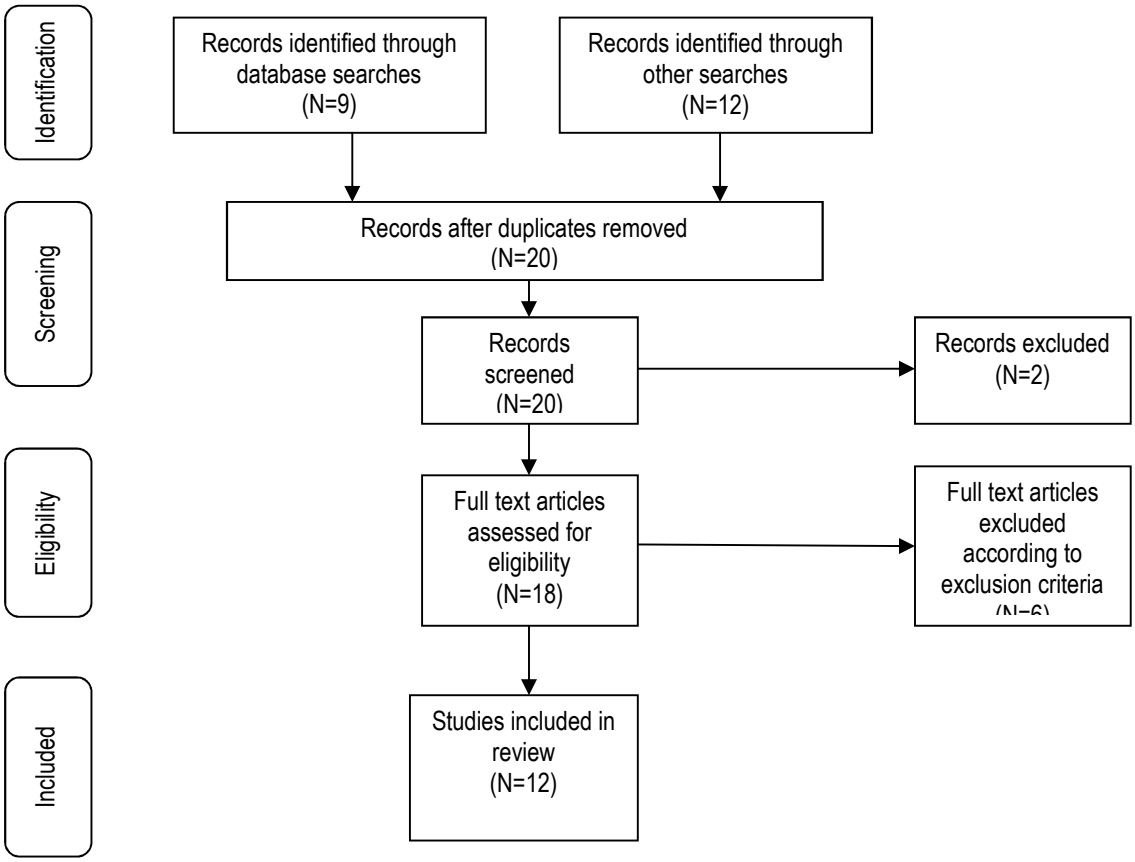


Figure 2.2.: Results of the literature search strategy on the prevalence of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Twelve (12) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a single-centre double blind RCT, four (4) prospective multi-centre observational studies, three (3) retrospective studies, three (3) case-control studies and a review (expert opinion). Articles appraised are presented in Table 2.4.

Table 2.4.: Appraised articles on the prevalence of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=12)				
Level of Evidence				
I (N=5)	**II**	**III** (N=6)	**IV**	**V** (N=1)
Rowe *et al* (2009:188)		Catz *et al* (1997:175)		Willard and Lueck (2014:75)
Rowe *et al* (2011:406)		Ciuffreda *et al* (2007:155)		
Rowe *et al* (2013:2)		Ciuffreda, Rutner, Kapoor, Suchoff, Craig and Han (2008:18)		
Siong *et al* (2014:438)		Dong *et al* (2013:337)		
Carrick *et al* (2016:3)		Herron (2016:72)		
		Rizzo *et al* (2017:12)		

Based upon the articles appraised, the reported prevalence of saccadic eye movements in post-stroke patients ranged between 3.1% (Rowe *et al* 2013:2) and 77.1% (Herron 2016:72). The difference in the reported prevalence of saccadic eye movements in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (Rowe *et al* 2013:2; Herron 2016:69). The method of assessment of saccadic eye movement used by Rowe *et al* (2013:2) was based upon observation only compared to Herron (2016:69) who identified saccadic eye movement impairment using an occupational therapy vision screening tool developed by an interdisciplinary team that included occupational therapists and an optometrist. Both studies (Rowe *et al* 2013:7; Herron, 2016:73) posed several limitations. Although the aim of the study by Rowe *et al* (2013:2) was to evaluate ocular gaze abnormalities

in patients post-stroke, the absence of objective quantification of saccadic eye movements may result in limited accuracy in the identification and quantification of saccadic eye movement impairment compared to detailed vestibular assessment using objective measures such as VNG to determine the prevalence of impaired saccadic eye movement in patients post-stroke. As previously discussed, the study by Rowe *et al* (2013:7) was not an epidemiological study. The study sample only included stroke patients who were referred specifically for a vision assessment by an orthoptist when healthcare personnel suspected visual difficulty based on the presence of patient-reported visual symptoms or the health care professional observed signs of visual impairment (Rowe *et al* 2013:2). The demographical data specifically the date of sustaining a stroke was skewed due to the inclusion of three (3) patients who were a number of years post-stroke. The study sample therefore included patients both in the 'early reorganization' and 'later reorganization' phase post-stroke (Section 1.1.4.1). Findings of the study by Rowe *et al* (2013:3) demonstrated that post-stroke patients who present with saccadic eye movement impairment suffered either a haemorrhagic or ischaemic stroke in the following brain areas, namely parietal lobe (N=3), occipital lobe (N=2), intraventricular (N=1), periventricular (N=1), internal capsule (N=1), thalamus (N=3), basal ganglia (N=2), lacunar area (N=2), brainstem (N=1) and cerebellum (N=2). Central vestibular dysfunction is diagnosed when lesions involve the (a) the vestibular nuclei in the pontomedullary brainstem; (b) the vestibular pathways that project from the vestibular nuclei to the vestibulocerebellum (via the cerebellar peduncles); (c) brainstem; (d) thalamus; and (e) multisensory vestibular cortex areas (Brandt and Dieterich 2017:352). Apart from the brain regions identified by Brandt and Dieterich (2017:352), findings of the study by Jang *et al* (2018:727) demonstrated 100% connectivity between the vestibular nuclei and the oculomotor nucleus, trochlear nucleus, abducens nucleus, thalamus, reticular formation and cerebellum. The vestibular nuclei also demonstrated high connectivity (over 70%) with the sensory-motor cortex (primary motor cortex (95.9%), primary somatosensory cortex (90.5%), premotor cortex (87.8%) and posterior parietal cortex (75.7%), hypothalamus (86.5%), lateral prefrontal cortex (70.3%), ventromedial prefrontal cortex (51.4%) and orbitofrontal cortex (40.5%). Though the association between central vestibular dysfunction and oculomotor impairment are well documented, Rowe *et al* (2013:7) did not mention the role of the central vestibular system involved in

oculomotor impairment that specifically include saccadic eye movement dysfunction post-stroke.

During the study by Herron (2016:69), an occupational therapist identified saccadic eye movement impairment in post-stroke patients by using an occupational therapy vision screening tool. Although Herron (2016:73) stated that the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study, the psychometric properties of the vision screening tool were not determined prior to the study. Another limitation of the study is that although Herron (2016:73) acknowledged that lesions in the parietal, frontal and occipital lobes, thalamus, brainstem and cerebellum results in oculomotor impairment, the author did not mention the role of the central vestibular system involved in oculomotor impairment that specifically include saccadic eye movement impairment post-stroke. Brandt and Dieterich (2017:352) and Jang *et al* (2018:727) have demonstrated that the central vestibular system relates (100%) to the areas of the brain that are responsible for the control of eye movements, including saccadic eye movements (Herron 2016:67).

A stroke may not only result in impaired eye movements which include impairment of smooth pursuit eye movement and saccadic eye movement, it may also affect the visual pathways in a patient's brain (Moodley 2016:61). The third feature of oculomotor control to be discussed is static visual acuity.

(iii). Static visual acuity

A person's visual pathways include the optic nerve, optic chiasm, optic tract, optic radiation and the visual cortex in the occipital lobes. The visual pathway is presented in Figure 2.3. (Coren, Ward and Enns 2003:608).

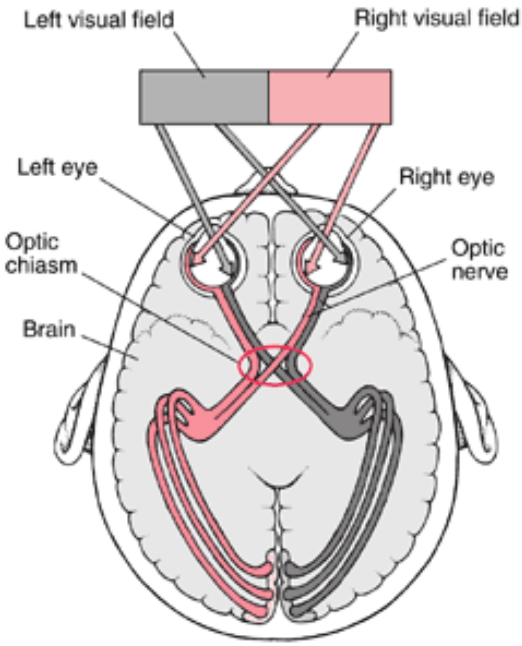


Figure 2.3.: Visual pathway (Coren *et al* 2003:608).

Visual information travel from the retina of the eye via the optic nerve to the optic chiasm. In the optic chiasm, visual information crosses over so that images which fall on the right visual field of each eye travel via the optic tract and the optic radiation to the left visual cortex. Visual information from the left visual field in each eye travel via the optic tract and the optic radiation to the right visual cortex (Coren *et al* 2003:608) (Figure 2.3). Although a stroke may result in damage to the visual pathways that may lead to loss of static visual acuity, it is also important to highlight the relationship between oculomotor impairment, specifically reduced static visual acuity and central vestibular dysfunction, in patients post-stroke. Becker-Bense *et al* (2013:1103) demonstrated a significant hyper-metabolism in the contralateral medulla (probably comprising the contralateral vestibular nucleus), the contralateral middle and inferior cerebellar peduncles, vermal structures (predominantly the pyramid and tonsil) and both cerebellar hemispheres in twelve (N=12) patients with acute unilateral lesions of the vestibular nucleus following a resting-state fluorodeoxyglucose (FDG)-PET scan on mean day 8 (range 4–12 days post-infarct) after onset of a medullary infarct. Findings of the study by Becker-Bense *et al* (2013:1103) suggest that a central vestibular lesion affects the vestibular nucleus of one side and effect acute damage by interrupting the ascending vestibulo-thalamo-cortical pathways to the thalamus and

cortex on the ipsilateral side of the lesion, as well as vestibular projections to the contralateral vestibular nucleus and the ipsilateral vestibular-cerebellar structures (vestibulocerebellar tract). An error signal to the cortex results in downregulation in parts of both cortical sensory systems with the visual areas more downregulated than the multisensory vestibular areas. The primary visual and motion-sensitive visual cortical areas were downregulated in both cortical hemispheres to suppress blurred vision as result of oscillopsia caused by spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction as result of a lateral medullary stroke (Becker-Bense *et al* 2013:1103).

Although previous studies have described the relationship between reduced static visual acuity and stroke (Rowe *et al* 2011:408), limited evidence on the prevalence of reduced static visual acuity due to central vestibular dysfunction in post-stroke patients, has been described in the literature (Willis *et al* 2013:1049). The researcher therefore identified the need to investigate the prevalence of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.4., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”, “oculomotor impairment”; “static visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population were included in this section of the review.

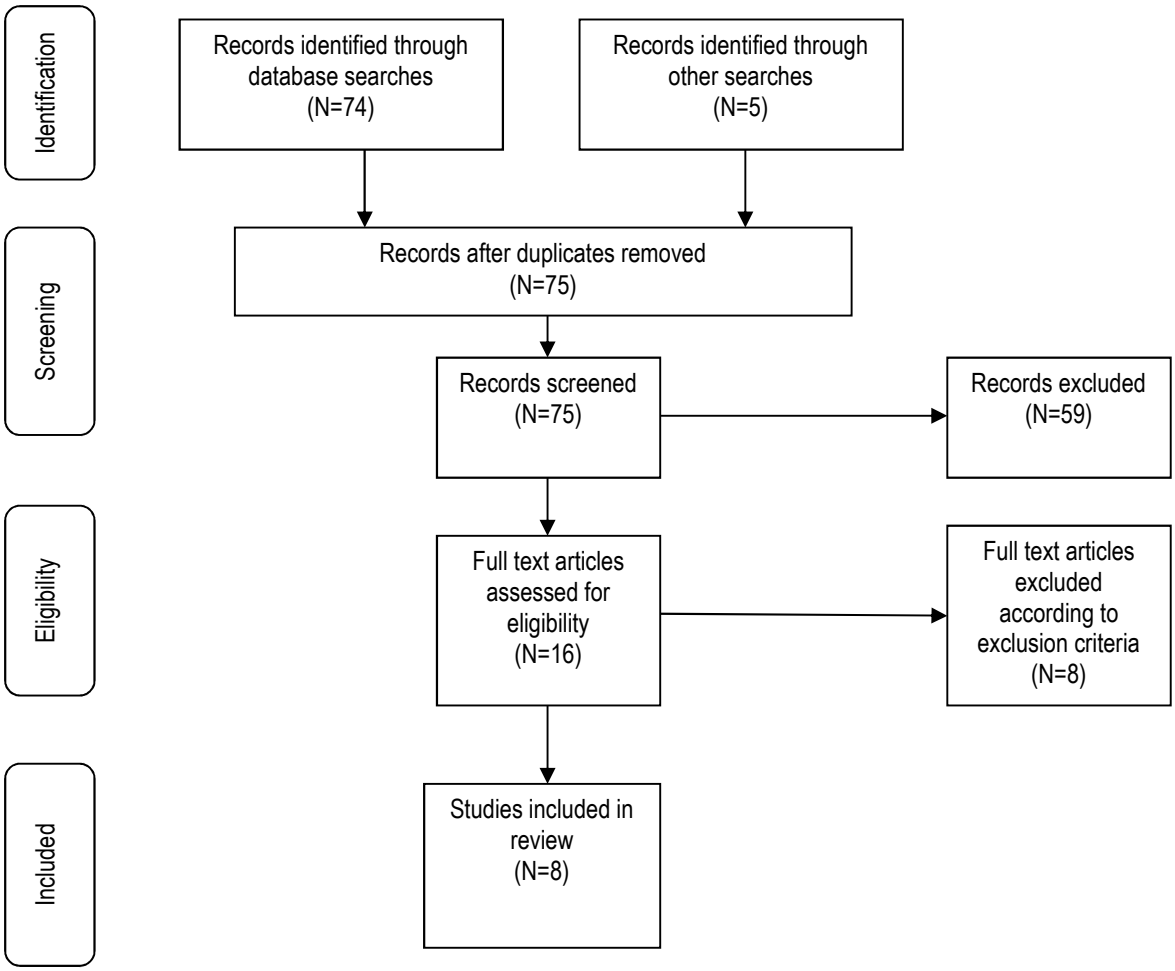


Figure 2.4.: Results of the literature search strategy on the prevalence of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Eight (8) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included seven (7) prospective observational studies and a systematic literature review. Articles appraised are presented in Table 2.5.

Table 2.5.: Appraised articles on the prevalence of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=8)				
Level of Evidence				
I (N=8)	**II**	**III**	**IV**	**V**
Lotery *et al* (2000:221)				
Edwards *et al* (2006:45)				
Rowe *et al* (2009:188)				
Rowe *et al* (2011:406)				
Naeem (2012:55)				
Shrestha *et al* (2012:46)				
Siong *et al* (2014:438)				
Hepworth *et al* (2015:146)				

Based upon the articles appraised, the reported prevalence of reduced static visual acuity in post-stroke patients ranged between 15.0% (Siong *et al* 2014:438) and 70.0% (Edwards *et al* 2006:45). The difference in the reported prevalence of reduced static visual acuity in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (Siong *et al* 2014:438; Edwards *et al* 2006:45). The method of assessment of reduced static visual acuity used by Siong *et al* (2014:438) was the LogMAR chart compared to Edwards *et al* (2006:45) who used the MIS Pocket Vision Guide (Edwards *et al* 2006:45). The LogMar chart is regarded as the gold standard for the assessment of visual acuity (Noushad, Thomas and Amin 2012:87; Van Wyk *et al* 2016:140). Although static visual acuity was assessed using the LogMar chart (gold standard), the period from the onset of stroke to visual assessment ranged between ten (10) days to 26 years. The study sample therefore included patients both in the 'early reorganization' and 'later reorganization' phase post-stroke (Section 1.1.4.1). The study sample included patients who suffered either a haemorrhagic or ischaemic stroke in the following brain areas: the frontal lobe (N=40), parietal lobe (N=8), temporal lobe (N=4), occipital lobe (N=8), external and internal capsule (N=40), intraventricular & periventricular areas (N=14), thalamus,

basal ganglia and lacunar areas (N=68). Although central vestibular dysfunction is diagnosed when lesions involve the cerebellum, brainstem, thalamus and multisensory vestibular cortex areas (Brandt and Dieterich 2017:352), Siong *et al* (2014:438) did not mention the role of the central vestibular system involved in oculomotor impairment that specifically include reduced visual acuity post-stroke.

Findings of the study by Edwards *et al* (2006:45) indicated that the mean time from stroke onset to visual acuity assessment was 4.3 ±2.9 days. Thus, only patients in the 'early reorganization' (sub-acute phase post-stroke) were included in the study. Edwards *et al* (2006:45) opined that although all of the measures used in the study that included the MIS Pocket Vision Guide presented with well-documented reliability and validity, results of the study may have reflected the sensitivity of the measures used that led to the possibility of increased false positives (type I error) that resulted in an inflated level of impairment such as increased prevalence of reduced static visual acuity observed in the study sample.

In summary, central vestibular dysfunction may be categorised by impairment on the level of body structure and function that includes oculomotor impairment (Section 2.3.1.1). Central vestibular dysfunction may also be categorised by the impairment of reflexive control of gaze. The second clinical feature of central vestibular dysfunction on the level of body structure and function to be discussed in Section 2.3.1.2, is reflexive control of gaze.

2.3.1.2. Reflexive control of gaze

Impairment of reflexive control of gaze may include deficits of the VOR-gain and dynamic visual acuity. The first feature of reflexive control of gaze to be discussed is VOR-gain.

(i). Vestibular-ocular reflex gain

The VOR is an involuntary eye movement with a short latency that responds to changes in head acceleration to maintain gaze and stabilize vision during head movements (Ranjbaran, Katsarkas and Galiana 2016:26). The neural pathway for the

VOR consists of three main components that include the vestibular apparatus (the semicircular canals and the otolith organs), central processing and the oculomotor system (Ranjbaran *et al* 2016:26). Angular and linear head movements are detected by the semicircular canals and the otoliths (saccule and utricle) located in the inner ear. From the vestibular apparatus, sensory (afferent) information is relayed through the vestibular afferents to the brainstem centres, which includes the vestibular nuclei and the Prepositus-Hypoglossi (PH). In response to the received sensory information, the vestibular nuclei and the Prepositus-Hypoglossi (brainstem centres) combine the sensory and motor information to drive the extraocular muscles to generate involuntary eye movements that match the velocity of the head movement by moving the eyeballs in the appropriate direction by means of the VOR (Hain and Helminski 2007:2; Ranjbaran *et al* 2016:26). By generating involuntary compensatory eye movements in response to the sensory information received from the vestibular apparatus, the VOR ensures that the eye remains still in space during head movement and thus ensures clear vision during angular and linear head movements (Hain and Helminski 2007:2). The VOR-gain is defined as the ratio of the corrective eye movement response to a passive head movement stimulus. The perfect VOR-gain is 1.0 which is indicative that the corrective eye movement is exactly equal and opposite of the head movement and that the retinal image remains stable during the head movement (MacDougall and Curthoys 2012:1).

The neural structure of the VOR is bilateral and symmetric with commissural connections between the two sides of the brainstem. The VOR relies on balanced reciprocal stimulation of vestibular sensors on both sides to ensure normal functioning of the VOR. A stroke may cause partial or complete loss of sensory (afferent) input to the central vestibular system which includes the brainstem circuit that may result in an asymmetry in the VOR pathway. Although the relationship between VOR-gain dysfunction and stroke is described in the literature (Park *et al* 2013:1576; Chen *et al* 2014:83; Baek *et al* 2015:279; Choi *et al* 2018:90), limited evidence on the prevalence of impaired reflexive control of gaze, specifically VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired reflexive control of gaze, specifically VOR-gain dysfunction due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to

study the prevalence of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.5., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”, “vestibulo-ocular reflex”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

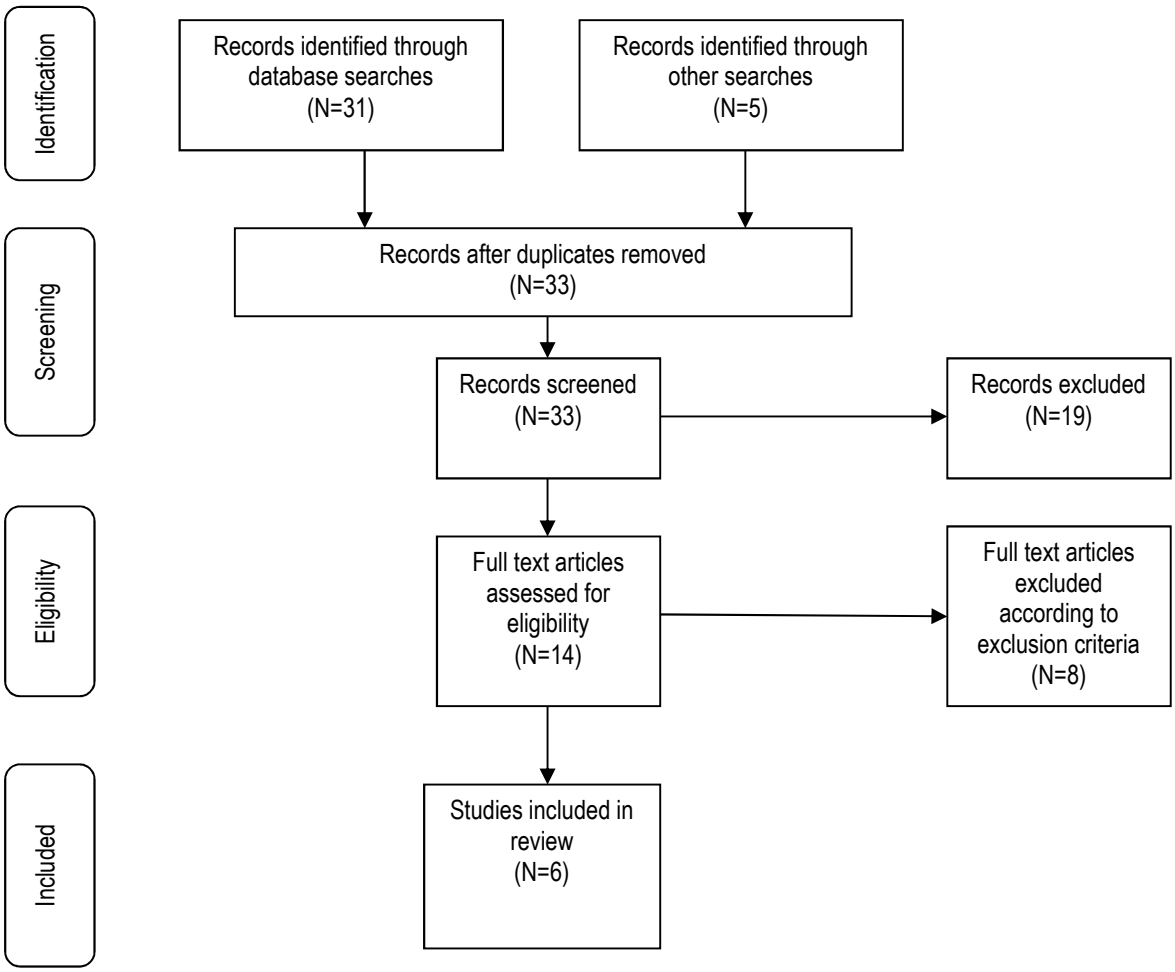


Figure 2.5.: Results of the literature search strategy on the prevalence of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Six (6) articles were critically reviewed and an assessment of the quality of evidence was completed. Of the six (6) articles appraised, three (3) were prospective observational studies and three (3) were case studies. Articles appraised are presented in Table 2.6.

Table 2.6.: Appraised articles on the prevalence of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=6)				
Level of Evidence				
I (N=3)	**II**	**III**	**IV** (N=3)	**V**
Chen *et al* (2014:83)			Park *et al* (2013:1576)	
Rowe *et al* (2013:2)			Kim *et al* (2014:121)	
Mitsutake, Sakamoto, Ueta, Oka and Horikawa (2017:745)			Baek *et al* (2015:279)	

Based upon the articles appraised, the reported prevalence of impaired reflexive control of gaze, specifically VOR-gain dysfunction in post-stroke patients, ranged between 5.0% (Rowe *et al* 2013:2) and 100.0% (Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279). The difference in the reported that prevalence of impaired reflexive control of gaze, specifically VOR-gain dysfunction in post-stroke patients, may be attributed to the respective assessment methods used in the four (4) studies (Park *et al* 2013:1576; Rowe *et al* 2013:2; Kim *et al* 2014:121; Baek *et al* 2015:279). The method of assessment of 'impaired gaze holding' used by Rowe *et al* (2013:2), was based upon observation only. In comparison to Rowe *et al* (2013:2), Park *et al* (2013:1576) and Kim *et al* (2014:121) implemented the head impulse test (HIT) using the search coil system and Baek *et al* (2015:279) performed a bedside HIT to quantify VOR-gain dysfunction in the respective study samples.

All four (4) studies (Park *et al* 2013:1576; Rowe *et al* 2013:7; Kim *et al* 2014:121; Baek *et al* 2015:279) posed several limitations. Although the aim of the study by Rowe *et al* (2013:2) was to evaluate ocular gaze abnormalities in patients post-stroke, the

absence of objective quantification of the VOR of post-stroke patients may result in limited accuracy in the quantification of the VOR-gain compared to the detailed assessment of the VOR using objective measures such as the vHIT (Section 2.4.1.2) to determine the prevalence of VOR-gain dysfunction in patients post-stroke. Another limitation of the study by Rowe *et al* (2013:7) is that the study is not an epidemiological study. The study sample only included stroke patients who were referred specifically for a vision assessment by an orthoptist when healthcare personnel suspected visual difficulty based on the presence of patient-reported visual symptoms, or the health care person observed signs of visual impairment (Rowe *et al* 2013:2). Stroke patients with suspected visual difficulty were referred from in-patient wards, rehabilitation units, community services and outpatient clinics.

Although the three (3) case studies (Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279) indicated a 100% of VOR-gain dysfunction in patients post-stroke, the study samples of these case studies were limited to only four (4) participants with lesions within the cerebellum which included one (1) patient who experienced a unilateral flocculus and anterior paraflocculus ischaemic stroke (Park *et al* 2013:1576), one (1) patient with anterior inferior cerebellar artery (AICA) territory stroke (Kim *et al* 2014:121), one (1) patient with posterior inferior cerebellar artery (PICA) territory stroke (Kim *et al* 2014:121) and one (1) patient who suffered a stroke in the biventor lobule adjacent to the flocculus, tonsil and inferior cerebellar peduncle (Baek *et al* 2015:279). The results of the studies by Park *et al* (2013:1576), Kim *et al* (2014:121) and Baek *et al* (2015:279) limit the generalizability of the findings to patients who suffered either hemispheric, subcortical or brainstem strokes.

Mitsutake *et al* (2017:745) investigated the relationship between VOR function and gait performance in post-stroke patients (N=75). Vestibular function testing included the assessment of the horizontal semi-circular canal VOR using the GST. Lower extremity function was assessed using the Fugl-Meyer Assessment (FMA-LE). Gait performance was evaluated using the Ten-Meter Walk Test (10MWT), the Timed “Up and Go” (TUG) test and the Dynamic Gait Index (DGI). Findings of the study by Mitsutake et al (2017:745) indicated that the 10MWT ($P<0.001$; $P<0.001$), TUG ($P<0.001$; $P<0.05$) and DGI ($P<0.001$; $P<0.001$) were significantly correlated to the FMA-LE *and* GST respectively. Based upon stepwise multiple regression analysis, the GST also remained a significant predictor ($P<0.001$) of the DGI. Results of the study

demonstrated that decreased VOR function contributes to impaired gait performance that includes the ability to modify gait in response to changing task demands in post-stroke patients (Mitsutake *et al* 2017:745) (Section 2.3.2.1).

The second feature of reflexive control of gaze to be considered is dynamic visual acuity.

(ii). Dynamic visual acuity

The role of the VOR is to enable gaze stabilization by moving the eyes contrary to the head to prevent retinal slip during both linear and angular head motion (Li, Beaumont, Rine, Slotkin and Schubert 2014:1). Impairment of the VOR may result in poor visual acuity (decreased dynamic visual acuity) during head motion due to an individual's decreased ability to maintain gaze during head rotation. Clinical observations of patients who present with impaired dynamic visual acuity (DVA) due to VOR dysfunction may include subjective complaints of visual blurring with head movement (oscillopsia). Symptoms of oscillopsia and impaired visual acuity during head motion may have a severe impact on the quality of life of patients. Although previous studies have demonstrated that the quantification of DVA effectively evaluates the ability to see clearly during head rotation (Li *et al* 2014:1), many studies have restricted the study population to patients who presented with vestibular dysfunction as a result of meningitis, Ménière's disease, radiotherapy, idiopathic in origin, congenital (Lambert, Sigrist, Delaspre, Pelizzone and Guyot 2010:820; Meldrum *et al* 2015:1322), labyrinthectomy, vestibular neurectomy (Herdman, Schubert, Das and Tusa 2003:819; Vital *et al* 2010:686; Meldrum *et al* 2015:1322), vestibular neuritis, acoustic neuroma, cochlear implant (Herdman, Schubert and Tusa 2001:1205; Herdman *et al* 2003:819; Meldrum *et al* 2015:1322), neurosarcoidosis (Herdman *et al* 2001:1205), vestibular schwannoma, Ramsay Hunt syndrome (Meldrum *et al* 2015:1322), and patients with a history of concussion or traumatic brain injury (TBI) (Kelley, Ranes, Estrada and Grandizio 2015:11). Limited evidence on the prevalence of impaired reflexive control of gaze, specifically reduced DVA due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired reflexive control of gaze, specifically reduced DVA due to central vestibular dysfunction, in the sub-

acute post-stroke. In order to study the prevalence of reduced DVA due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.6., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”, “dynamic visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of reduced DVA due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

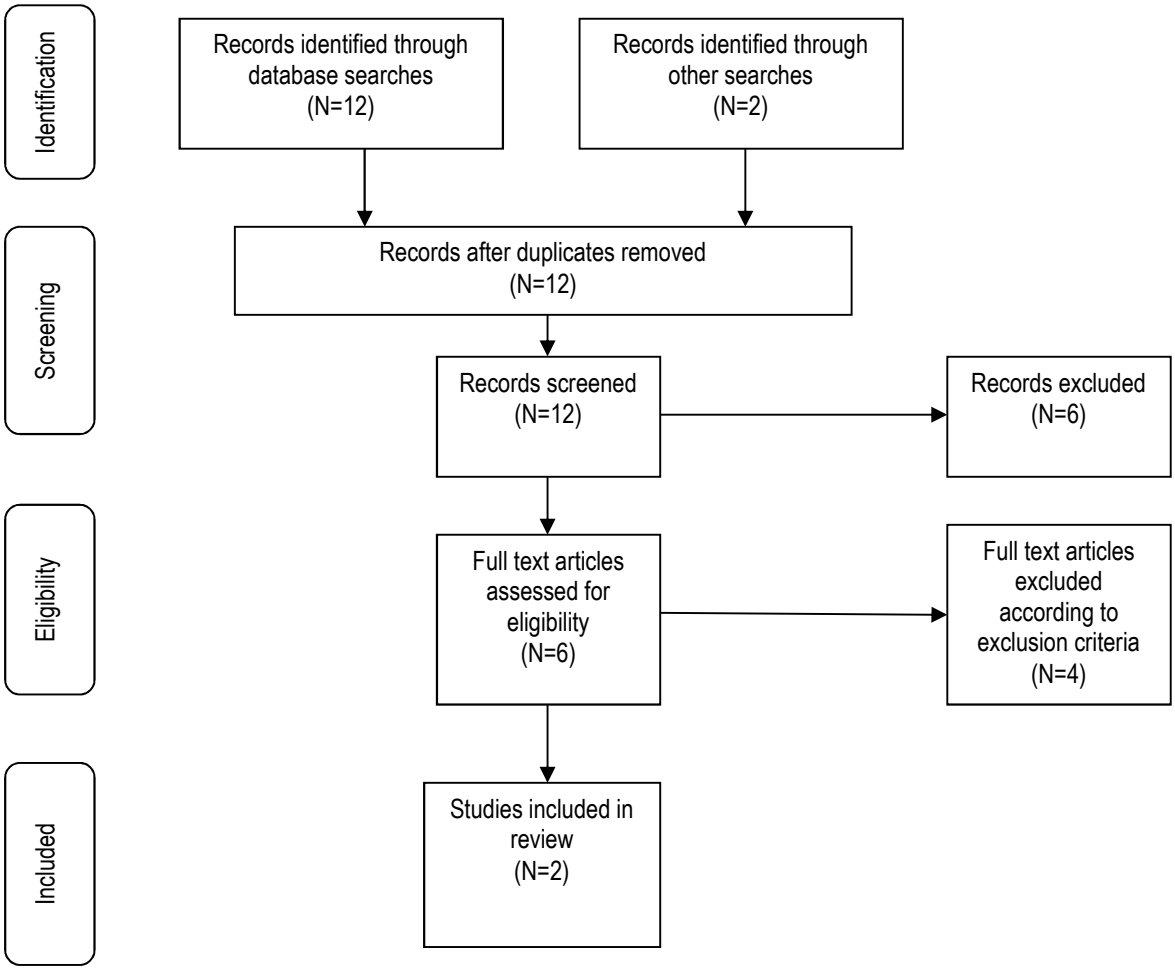


Figure 2.6.: Results of the literature search strategy on the prevalence of reduced dynamic visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Two (2) articles were critically reviewed and an assessment of the quality of evidence was completed. Of the two (2) articles appraised, one (1) was a prospective observational study (Mitsutake *et al* 2017:745) and the other article a non-randomised case control study (Niwa *et al* 2015:203). Articles appraised are presented in Table 2.7.

Table 2.7.: Appraised articles on the prevalence of reduced dynamic visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=2)				
Level of Evidence				
I (N=1)	**II**	**III** (N=1)	**IV**	**V**
Mitsutake *et al* (2017:745)		Niwa *et al* (2015:203)		

Based upon the articles appraised, the reported prevalence of reduced DVA in post-stroke patients is 60.0% (Niwa *et al* 2015:203). The study sample included forty (40) patients who sustained a stroke and 321 control subjects. Although the forty (40) post-stroke patients were in-patients between 39 years and 86 years old, the time since onset of the stroke to assessment of DVA ranged between 28 days to 7070 days. The study sample therefore included patients both in the 'early reorganization' and 'later reorganization' phase post-stroke (Section 1.1.4.1). The study sample included patients who suffered either a haemorrhagic or ischaemic stroke of the middle cerebral artery (MCA) (N=4), anterior cerebral artery (N=2), frontal–parietal lobe (N=1), frontal lobe (N=1), cortex (N=1), putamen (N=13), putamen–corona radiata (N=3), internal capsule–corona radiate (N=1), corona radiata (N=4), caudate nucleus (N=1), thalamus (N=4), midbrain (N=1), midbrain–pontile (N=1) and cerebellum (N=3). Although central vestibular dysfunction is diagnosed when lesions involve the cerebellum, brainstem, thalamus and multisensory vestibular cortex areas (Brandt and Dieterich 2017:352), Niwa *et al* (2015:203) did not mention the role of the central vestibular system involved in the reflexive control of gaze that specifically include reduced DVA post-stroke. It is also important to highlight that the study sample included four (4) patients who suffered a MCA-stroke. The MCA is responsible for the vascular supply to a portion of the

frontal lobe, lateral surface of the temporal lobe, parietal lobe, integrative associative areas and a variety of other critical loci of cerebral function that extends from the frontal lobe, over the lateral convexity of the brain to the occipital lobe (Yeo, Jang and Kwon 2017:1). The MCA also supplies blood to the Sylvian triangle in the insular region which is a main region of the PIVC. The PIVC is a core region of vestibular input into the cortical brain areas in the central vestibular system and is responsible for the processing of the perception of self-motion and visual motion, as well as the estimation of verticality (Yeo *et al* 2017:1). Findings of the study by Yeo *et al* (2017:1) indicated that patients with MCA territory infarction may present with decreased tract volume of the vestibular pathway observed on diffusion tensor imaging (DTI). Yeo *et al* (2017:1) thus support findings from previous studies that central vestibular dysfunction is relatively common after MCA territory infarction. The third clinical feature of central vestibular dysfunction on the level of body structure and function is saccule and inferior vestibular nerve function, discussed in Section 2.3.1.3.

2.3.1.3. Saccule and inferior vestibular nerve function

The vestibular end-organ consists of the otolith organs that include the saccule and utricle which transduce linear acceleration and the semicircular canals which transduce angular acceleration. Impulses travel from the semicircular canals, saccule and utricle to the vestibular nerve, the brainstem and cerebellar circuits, vestibular thalamic pathways, vestibulospinal tracts and to the vestibular cortical network (Cronin *et al* 2017:538). Cervical vestibular-evoked myogenic potential (cVEMP) is a recently developed clinical test of vestibular function that is used to assess the cVEMP response that originates from the saccule and its afferent nerve (inferior vestibular nerve) to evaluate the inferior vestibular function of an individual (Ahn, Kim, Yi, Oh and Lee 2011:114). Although the relationship between the saccule and inferior vestibular nerve function impairment and stroke is described in the literature (Miller, Klein, Suresh and Rymer 2014:2070), limited evidence on the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to study the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in

the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.7., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “saccule”; “inferior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

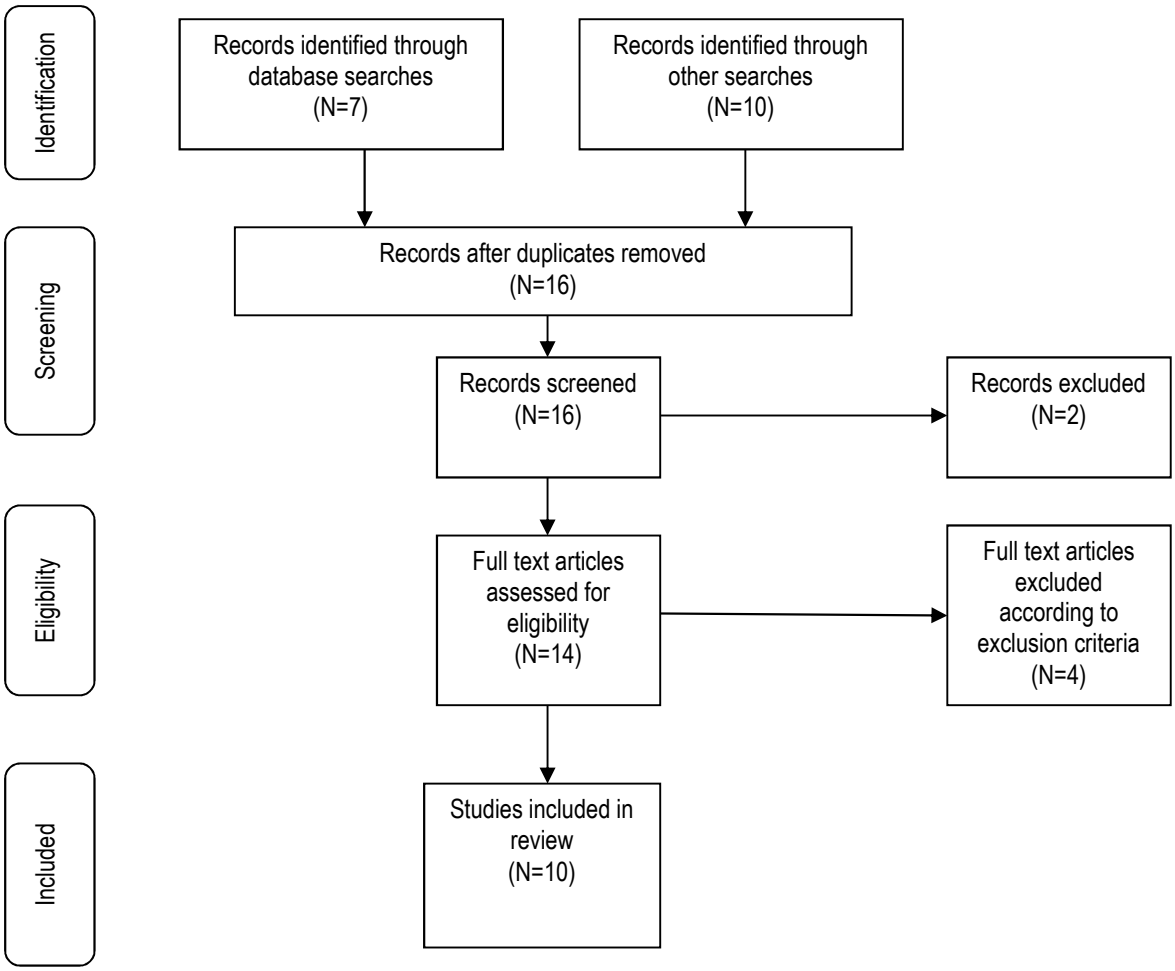


Figure 2.7.: Results of the literature search strategy on the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Ten (10) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included nine (9) prospective observational studies and a case study. Articles appraised are presented in Table 2.8.

Table 2.8.: Appraised articles on the prevalence of impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=10)				
Level of Evidence				
I (N=9)	**II**	**III**	**IV** (N=1)	**V**
Chen and Young (2003:990)			Tseng and Young (2010:267)	
Pollak, Kushnir and Stryjer (2006:227)				
Heide, Luft, Franke, Schmidt, Witte and Axer (2010:1102)				
Kim, Lee and Kim (2010:825)				
Ahn *et al* (2011:114)				
Kim, Kim and Kim (2011:1)				
Su and Young (2011:923)				
Choi *et al* (2014:362)				
Kim *et al* (2016:2424)				

Based upon the articles critically reviewed and assessment of the quality of evidence completed, the reported prevalence of saccule and inferior vestibular nerve function impairment in post-stroke patients ranged between 28.9% (Kim *et al* 2016:2424) and 78.6% (Chen and Young 2003:990). The difference in the reported prevalence of impaired saccule and inferior vestibular nerve function in post-stroke patients by Kim *et al* (2016:2424) and Chen and Young (2003:990), may be attributed to the patients included in the study sample. The study sample of Kim *et al* (2016:2424) was restricted to forty-five (N=45) patients with lateral medullary infarction. The study sample of Chen and Young (2003:990) included seven (7) patients with brainstem stroke, of which three (3) of the seven (7) patients were categorised as a brainstem stroke compared to four (4) patients who were categorised as a pontine stroke. None of the study

samples included patients who sustained a hemispheric, subcortical or cerebellar stroke (Kim *et al* 2016:2424; Chen and Young 2003:990).

The fourth clinical feature of central vestibular dysfunction on the level of body structure and function is the utricle and superior vestibular nerve function, discussed in Section 2.3.1.4.

2.3.1.4. Utricle and superior vestibular nerve function

As previously discussed in Section 2.3.1.3., the utricle is one of the otoliths that respond to linear accelerations and decelerations (Oh *et al* 2013:770). The ocular vestibular-evoked myogenic potential (oVEMP) test assesses the utricle and superior vestibular nerve function (Curthoys, Vulovic and Manzari 2012:41). Although the relationship between utricle and superior vestibular nerve function impairment and stroke is described in the literature (Su and Young 2011:923; Oh *et al* 2013:770; Park *et al* 2013:1576; Choi *et al* 2014:362; Kim, Lee and Kim, 2014:1042; Kim *et al* 2014:121; Kim *et al* 2016:2424), limited evidence on the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.8., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “utricle”; “superior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

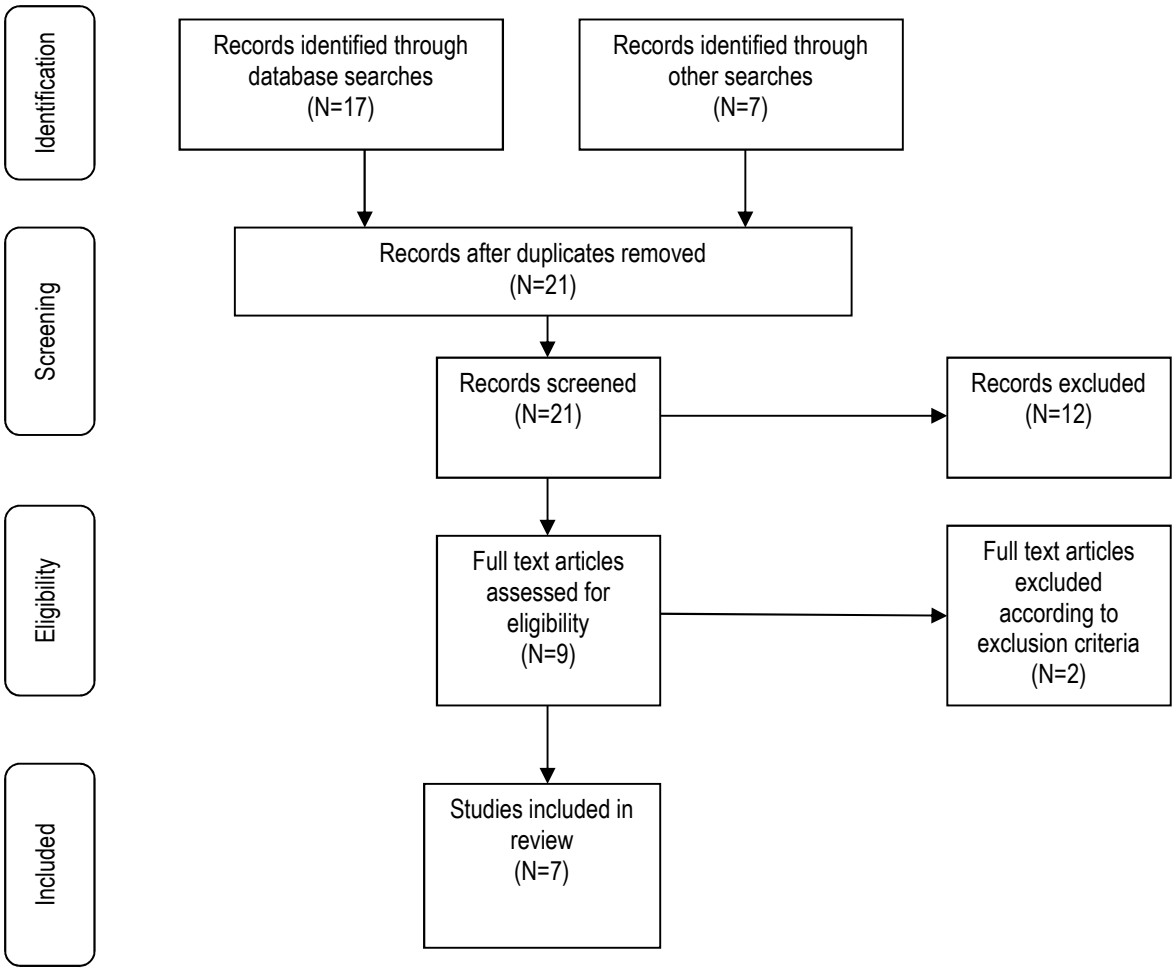


Figure 2.8.: Results of the literature search strategy on the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Seven (7) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included five (5) prospective observational studies and two (2) case studies. Articles appraised are presented in Table 2.9.

Table 2.9.: Appraised articles on the prevalence of impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=7)				
Level of Evidence				
I (N=5)	**II**	**III**	**IV** (N=2)	**V**
Su and Young (2011:923)			Park *et al* (2013:1576)	
Oh *et al* (2013:770)			Kim *et al* (2014:121)	
Choi *et al* (2014:362)				
Kim *et al* (2014:1042)				
Kim *et al* (2016:2424)				

Based upon the articles critically reviewed and assessment of the quality of evidence completed, the reported prevalence of utricle and superior vestibular nerve function impairment in post-stroke patients ranged between 26.7% (Kim *et al* 2016:2424) and 87.5% (Su and Young 2011:923). The difference in the reported prevalence of impaired utricle and superior vestibular nerve function in post-stroke patients by Kim *et al* (2016:2424) and Su and Young (2011:923), may be attributed to the patients included in the study sample. The study sample of Kim *et al* (2016:2424) was restricted to forty-five (N=45) patients with lateral medullary infarction. The study sample of Su and Young (2011:923) included twelve (12) patients with cerebellar disorder confirmed by MRI, of which eight (8) patients presented with extended cerebellar lesions that involved the brainstem, compared to four (4) patients with localized cerebellar lesions that excluded the brainstem. Of these twelve (12) patients, five (5) patients presented with cerebellar stroke and seven (7) patients presented with cerebellar tumour. None of the study samples included patients who sustained either a hemispheric or subcortical stroke.

The fifth clinical feature of central vestibular dysfunction on the level of body structure and function to consider is higher vestibular function, discussed in Section 2.3.1.5.

2.3.1.5. Higher vestibular function

Higher vestibular function results from the integration of the vestibular network at the cortical level and within the hippocampal and limbic system that are responsible for perceptual and cognitive functions. Perceptual and cognitive functions include the internal representation of the body schema of an individual, internal model of the environment surrounding the individual, multisensory perception of motion, attention, spatial memory and navigation (Brandt, Strupp and Dieterich 2014:47). Patients with impaired higher vestibular function may present with complex perceptual, sensorimotor and behavioural dysfunction in addition to impairments related to (1) oculomotor function (Section 2.3.1.1); (2) reflexive control of gaze (Section 2.3.1.2); (3) saccule and inferior vestibular nerve function (Section 2.3.1.3); and (4) utricle and superior vestibular nerve function (Section 2.3.1.4) (Brandt *et al* 2014:47). In the current study, the management of impaired higher vestibular function are limited to the residual oculomotor visual performance, visual-perceptual function and cognitive function. The first feature of higher vestibular function to be discussed is residual oculomotor visual performance.

(i). Residual oculomotor visual performance

Karnath and Dieterich (2006:293) suggest that impaired higher vestibular function, specifically visual-perceptual dysfunction, may be a result from damage to the multisensory cortex where visual, vestibular, auditory and proprioceptive information are combined. After the multisensory integration occurred within the multisensory cortex, higher order spatial representations of the individual's body position in relation to the environment, are established (Kerkhoff and Schenk 2012:1072). The primary visual processes include oculomotor function and visual acuity. In this section, the association between impaired higher vestibular function, specifically residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population, is discussed. It is of importance to differentiate between residual oculomotor visual performance and visual-perceptual dysfunction following a stroke (Chaikin 2013:867). Although the relationship between impaired higher vestibular function, specifically residual oculomotor visual performance and stroke, is described in the literature (Kapoor *et al* 2004:1667), limited evidence on the prevalence of residual oculomotor visual performance due to central vestibular

dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired higher vestibular function, specifically residual oculomotor visual performance due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to study the prevalence of impaired higher vestibular function, specifically residual oculomotor visual performance due to central vestibular dysfunction, in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.9., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “impaired higher vestibular function”; “residual oculomotor visual performance”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired higher vestibular function, specifically residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

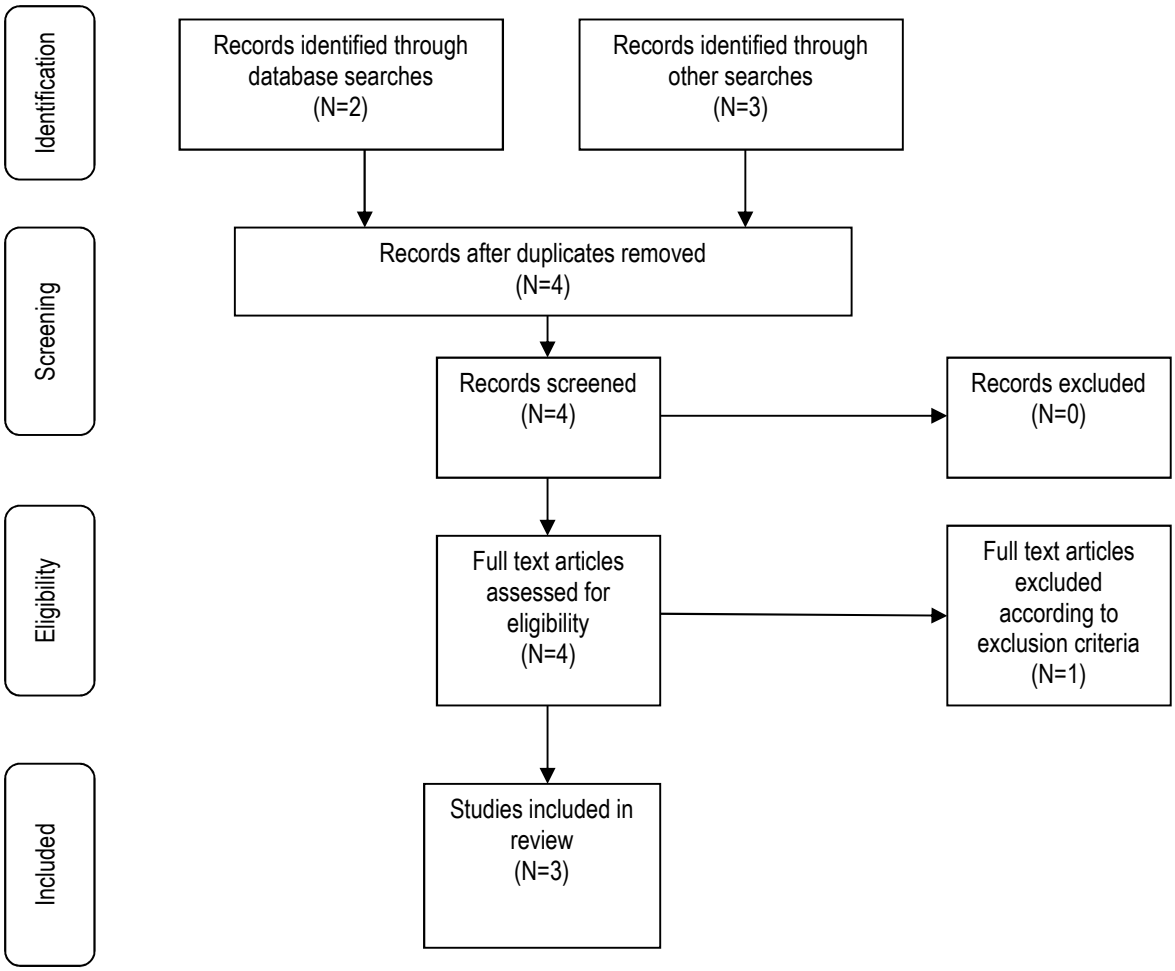


Figure 2.9.: Results of the literature search strategy on the prevalence of impaired higher vestibular function specifically residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Only three (3) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a case control study and two (2) case studies. Articles appraised is presented in Table 2.10.

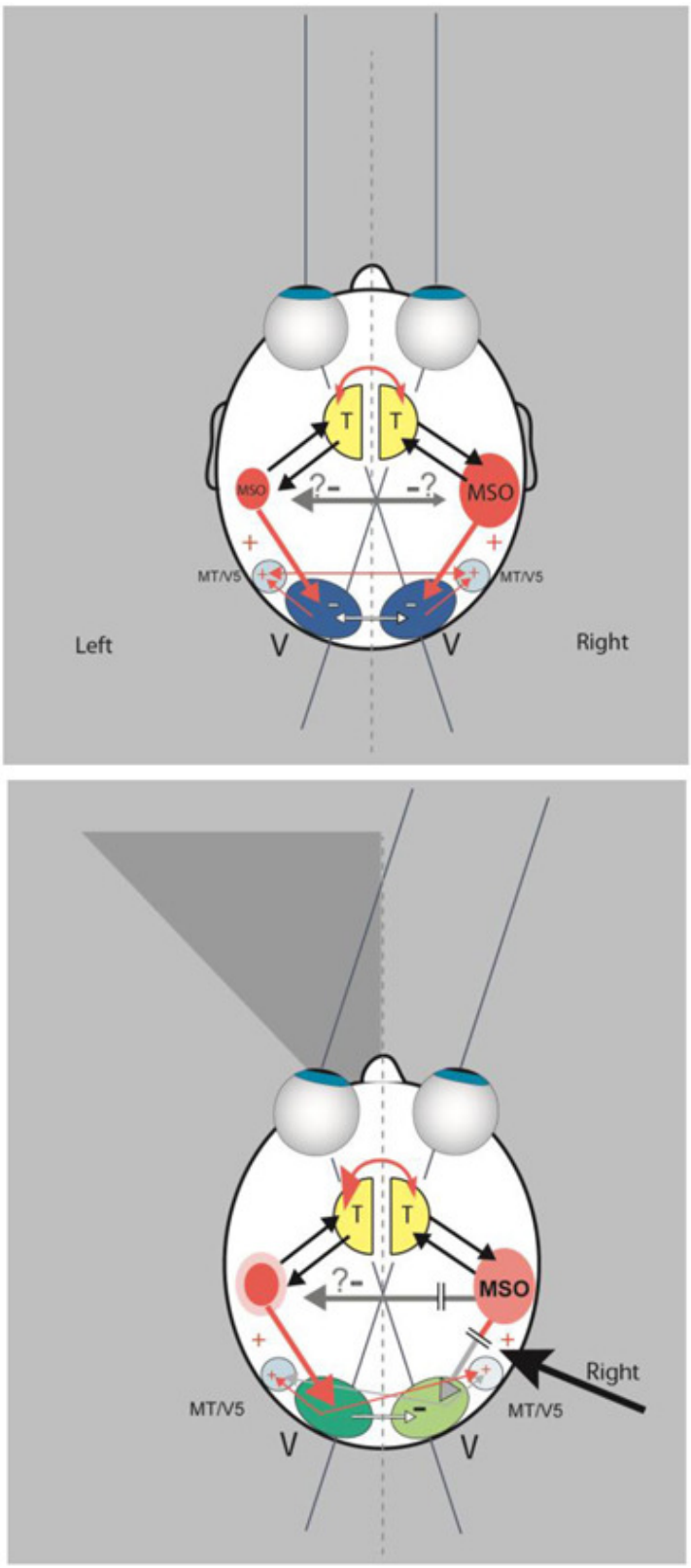
Table 2.10.: Appraised articles on the prevalence of residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=3)				
Level of Evidence				
I	**II**	**III** (N=1)	**IV** (N=2)	**V**
		Cate and Richards (2000:326)	Olk *et al* (2002:306)	
			Kapoor *et al* (2004:1667)	

Based upon the articles appraised, the reported prevalence of residual oculomotor visual performance impairment in post-stroke patients ranged between 56.7% (Cate and Richards 2000:326) and 100.0% (Olk *et al* 2002:306; Kapoor *et al* 2004:1667). The difference in the reported prevalence of residual oculomotor visual performance impairment in post-stroke patients may be attributed to the respective assessment methods used in the three (3) studies (Cate and Richards 2000:326; Olk *et al* 2002:306; Kapoor *et al* 2004:1667) and the selection of patients included in the study samples (Olk *et al* 2002:306; Kapoor *et al* 2004:1667). The method of assessment of residual oculomotor visual performance used by Cate and Richards (2000:326) consisted of a 'basic visual skills screening battery' compared to Olk *et al* (2002:306) who used a computerised visual search task and an eye tracker that assessed reaction time, latencies and amplitudes of eye movements. Kapoor *et al* (2004:1667) used a goggle-mounted, infrared limbal reflection eye movement system to assess both basic and reading eye movement parameters, as well as a subjective reading-related questionnaire. Both case studies included only one (1) patient in their study samples. Olk *et al* (2002:306) included one (1) patient with a right thalamus haemorrhagic stroke and Kapoor *et al* (2004:1667) included one (1) patient with a left occipital lobe stroke. The second feature of higher vestibular function to be discussed is visual-perceptual function.

(ii). Visual-perceptual function

The major anatomical structures and their functional connections of underlying mechanisms of higher vestibular function are presented in Figure 2.10. (Brandt *et al* 2014:47).



(*MSO = multisensory orientation; T = thalamus; V = visual cortex; MT/V5 = motion-sensitive areas)

Figure 2.10.: Major anatomical structures and the functional connections of underlying mechanisms of higher vestibular function (Brandt *et al* 2014:47).

In Figure 2.10., the bilateral multisensory orientation (MSO) centers in both (a) and (b), are illustrated. The MSO receives vestibular and somatosensory information from the thalamus (T) and directs visual attention by excitatory connections to the ipsilateral and contralateral visual cortex (V). Figure 2.10., (a) also indicates the transcallosal connections between the visual cortices. Of the transcallosal connections between the visual cortices, the inhibitory connections are indicated by white arrows and the excitatory connections (to a lesser extent) by thin red arrows. Interhemispheric transcallosal connections are responsible for bilateral activation of the motion-sensitive areas MT/V5 (Brandt *et al* 2014:47). Figure 2.10., (b) demonstrates a lesion of the dominant MSO in the right hemisphere (indicated by a large black arrow). The lesion of the right MSO results in a left-sided visual-spatial neglect (visual-perceptual dysfunction) due to decreased excitation ("deactivation") of the ipsilateral visual cortex that is also further suppressed by increased inhibition from the contralateral visual cortex. The motion-sensitive area MT/V5 receives decreased input from the ipsilateral visual cortex but continues to receive excitatory input from the contralesional MT/V5. Increased visual-spatial attention within the right visual field (Figure 2.10.(b)) may be observed due to the increased activation from the non-dominant MSO in the left hemisphere and decreased inhibition from the ipsilateral right visual cortex (Brandt *et al* 2014:47).

This hypothetic model by Brandt *et al* (2014:47) is supported by findings of Becker-Bense *et al* (2013:1103). Findings of the study by Becker-Bense *et al* (2013:1103) indicated that the primary visual and motion-sensitive visual cortical areas were downregulated in both cortical hemispheres to suppress blurred vision as result of oscillopsia caused by spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction as result of a lateral medullary stroke (Becker-Bense *et al* 2013:1103). Brandt *et al* (2014:47) and Karnath and Dieterich (2006:293) thus hypothesise that a vestibular tone imbalance may be one of the underlying mechanisms of higher vestibular function, specifically visual-perceptual dysfunction. Although visual fields may have been preserved, patients spontaneously direct their eye movements, head movements and spatial attention to the ipsilesional visual field. Increased spatial attention to the ipsilesional visual field results in a visual-spatial neglect of stimuli in the contralateral visual field, which further contributes to impaired

higher vestibular function, specifically visual-perceptual dysfunction (Brandt *et al* 2014:47).

Although the relationship between impaired higher vestibular function, specifically visual-perceptual dysfunction and stroke, is described in the literature (Cate and Richards 2000:326), limited evidence on the prevalence of impaired higher vestibular function, specifically visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired higher vestibular function, specifically visual-perceptual dysfunction due to central vestibular dysfunction, in the sub-acute post-stroke population. In order to study the prevalence of impaired higher vestibular function, specifically visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.11., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “impaired higher vestibular function”; “visual-perceptual dysfunction”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired higher vestibular function, specifically visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

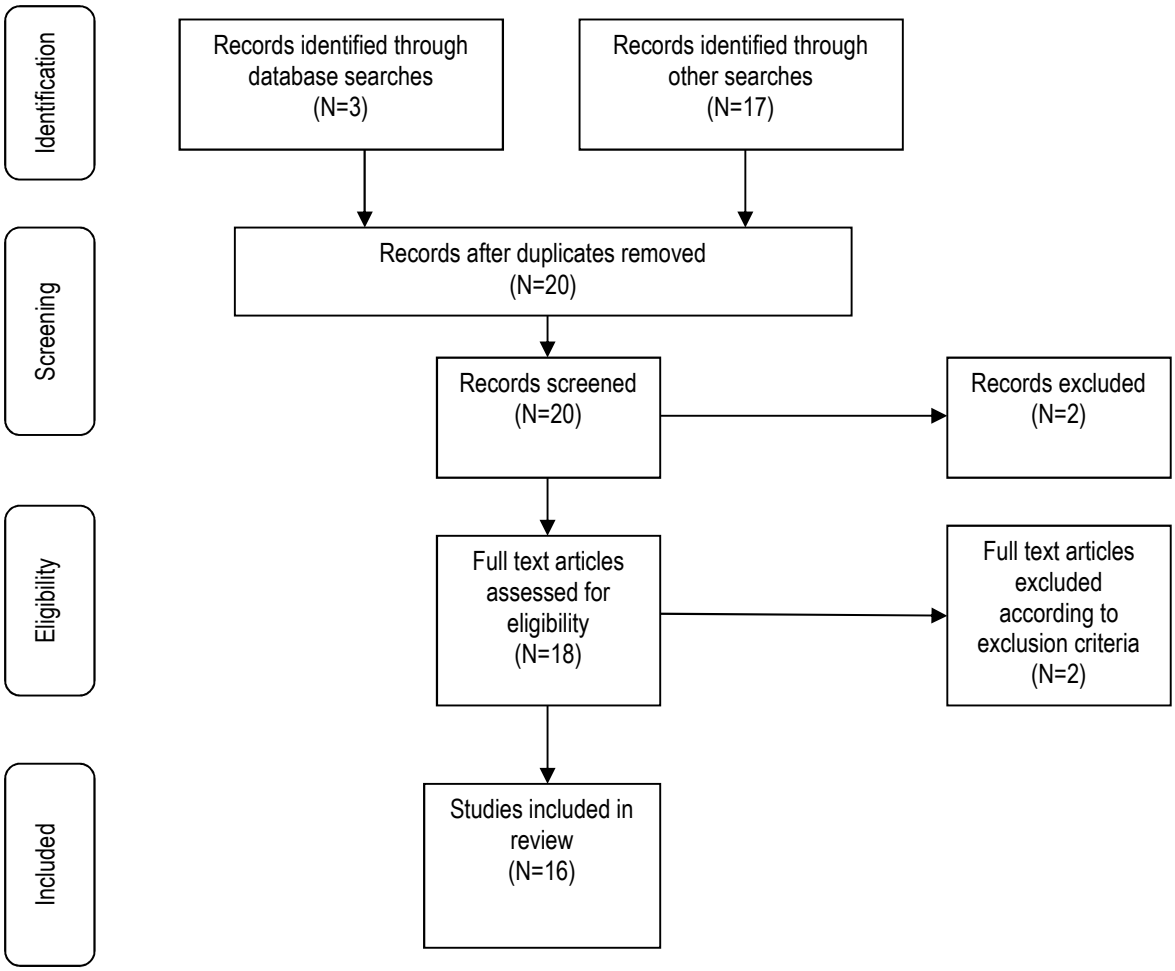


Figure 2.11.: Results of the literature search strategy on the prevalence of visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Sixteen (16) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a single-centre double blind matched-pair RCT, five (5) prospective observational studies, seven (7) case control studies, a retrospective study and two (2) case studies. Articles appraised are presented in Table 2.11.

Table 2.11.: Appraised articles on the prevalence of visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=16)				
Level of Evidence				
I (N=6)	**II**	**III** (N=8)	**IV** (N=2)	**V**
Kizony and Katz (2002:82)		Behrmann, Watt, Black and Barton (1997:1445)	Olk *et al* (2002:306)	
Gottesman *et al* (2008:1439)		Karnath, Niemeier and Dichgans (1998:2357)	Kapoor *et al* (2004:1667)	
Van Nes *et al* (2009:819)		Bailey, Riddoch and Crome (2000:139)		
Nijboer, Kollen and Kwakkel (2013:2021)		Cate and Richards (2000:326)		
Vossel, Weiss, Eschenbeck and Fink (2013:1782)		Fruhmann-Berger and Karnath (2005:1194)		
Van Wyk *et al* (2014:856)		Ng *et al* (2005:2138)		
		Van Kessel, van Nes, Brouwer, Geurts and Fasotti (2010:603)		
		Kettunen *et al* (2012:359)		

Based upon the articles appraised, the reported prevalence of visual-perceptual dysfunction impairment in post-stroke patients ranged between 19.1% (Ng *et al* 2005:2138) and 69.6% (Gottesman *et al* 2008:1439). The difference in the reported prevalence of visual-perceptual dysfunction in post-stroke patients may be attributed to the patients included in the study samples and the respective assessment methods used in the two (2) studies (Ng *et al* 2005:2138; Gottesman *et al* 2008:1439). The retrospective study sample by Ng *et al* (2005:2138) was limited to patients with posterior cerebral artery (PCA) stroke admitted to a rehabilitation hospital over an 8-year period. The low prevalence reported by Ng *et al* (2005:2138) was based on information obtained from a stroke registry over an eight (8)-year period. The absence of objective quantification of visual-perceptual dysfunction may have contributed to the limited accuracy in the identification of visual-perceptual dysfunction in the study

sample. Although the method of assessment of visual-perceptual dysfunction used by Gottesman *et al* (2008:1439) consisted of a battery of tests that included Line Bisection Test, Copying, Line Cancellation Test, visual & tactile extinction and oral reading, the study sample was limited to patients with only right hemispheric stroke (N=204). Lastly, neither authors (Ng *et al* 2005:2138; Gottesman *et al* 2008:1439) mentioned the role of the central vestibular system involved in impaired higher vestibular function, specifically visual-perceptual dysfunction post-stroke, based on findings by Brandt *et al* (2014:47) and Brandt and Dieterich (2017:352). The third feature of higher vestibular function to be discussed is cognitive function.

(iii). Cognitive function

The presence of cognitive dysfunction in addition to motor impairment may result in extensive functional, social and vocational impairments that may further increase the disability risk in patients who have suffered a stroke (Song *et al* 2015:142). Hitier *et al* (2014:59) suggest that four (4) different pathways are responsible for the transmission of vestibular information to cortical areas involved in higher vestibular function, namely: (1) the vestibulo-thalamo-cortical pathway; (2) a pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex; (3) a pathway via the nucleus reticularis pontis oralis, the supramammillary nucleus and the medial septum to the hippocampus; and (4) a possible pathway via the cerebellum and the ventral lateral nucleus of the thalamus (to the parietal cortex). The conceptual model by Bigelow and Agrawal (2015:83) (Figure 1.4) supports the findings by Hitier *et al* (2014:59) that central vestibular dysfunction may result in atrophy of areas within the cortical vestibular network that may include the hippocampus which is responsible for higher vestibular function of memory and visuospatial ability (Bigelow and Agrawal 2015:83). Limited evidence on the prevalence of impaired higher vestibular function, specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired higher vestibular function, specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of impaired higher vestibular function, specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure

2.12., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “impaired higher vestibular function”; “cognitive impairment”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired higher vestibular function, specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

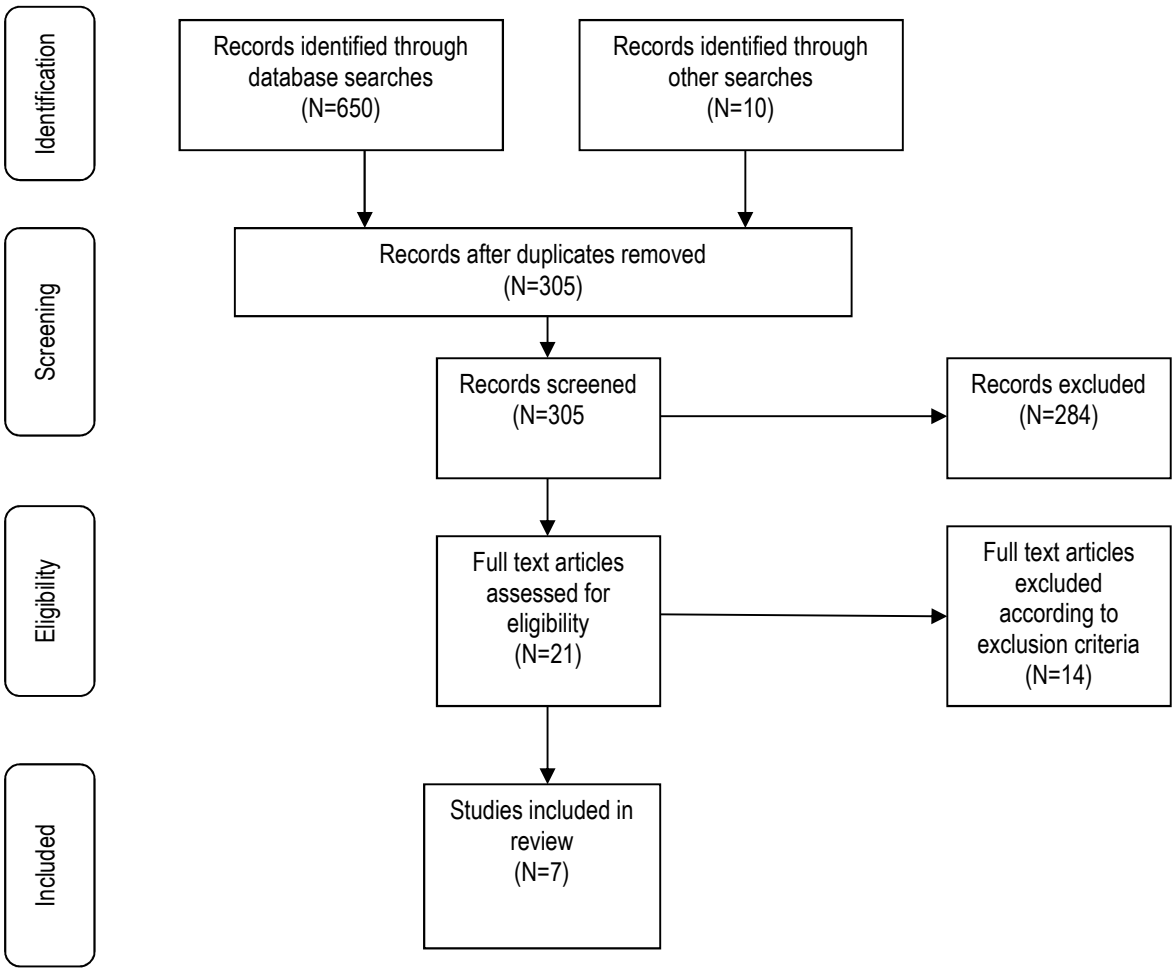


Figure 2.12.: Results of the literature search strategy on the prevalence of impaired higher vestibular function specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Seven (7) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included three (3) prospective observational studies, a case control study, retrospective study, review (expert opinion) and an editorial commentary. Articles appraised are presented in Table 2.12.

Table 2.12.: Appraised articles on the prevalence of impaired higher vestibular function specifically cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=7)				
Level of Evidence				
I (N=3)	**II**	**III** (N=2)	**IV**	**V** (N=2)
Kizony and Katz (2002:82)		Ng *et al* (2005:2138)		Anderson (2013:242)
Påhlman *et al* (2011:1952)		Dong *et al* (2013:337)		Willard and Lueck (2014:75)
Nijboer *et al* (2013:2021)				

Although seven (7) articles were critically reviewed, only one (1) article indicated the prevalence of impaired higher vestibular function, specifically cognitive impairment, in patients post-stroke. Påhlman *et al* (2011:1952) indicated that 38.7% of stroke patients present with cognitive impairment post-stroke. Påhlman *et al* (2011:1952) measured cognitive impairment using the Mini-Mental State Examination (MMSE). The MMSE presents with significant correlates with the Barthel Index (Mahoney and Barthel 1965:61), assessing activities of daily living, the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979:382) and the Zung Depression Scale (Zung 1965:63; Agrell and Dehlin, 2000:439). The internal consistency of the MMSE ranged from alpha=0.54–0.96 (Tombaugh and McIntyre 1992:922). McDowell, Kristjansson, Hill and Hebert (1997:377) reported that the internal consistency of the MMSE was adequate (alpha=0.78). Twenty-four (24) studies reported test–retest reliability (r>0.75) for the MMSE (Tombaugh and McIntyre 1992:922). The other articles reviewed did not report on the prevalence (%) of cognitive impairment post-stroke and only indicated the level of cognitive function of patients included in the study samples based on the mean and standard deviation score. It is important to highlight that although the association between cognitive function and vestibular dysfunction

post-stroke are established in the literature (Smith 2017:84), none of the articles reviewed mentioned the role of the central vestibular system involved in impaired higher vestibular function, specifically cognitive impairment post-stroke.

The sixth and final clinical feature of central vestibular dysfunction on the level of body structure and function to consider, is the presence of anxiety and/or depression in the sub-acute phase post-stroke. The level of anxiety and/or depression in post-stroke patients are discussed in Section 2.3.1.6.

2.3.1.6. Level of anxiety and/ or depression post-stroke

The concurrent symptoms of vestibular dysfunction and anxiety may be explained by overlapping and interacting brainstem pathways of both the vestibular system and the centre that controls psychopathology (Nagaratnam *et al* 2005:253). The neuroanatomical link between the vestibular system and the centre that controls psychopathology, includes the parabrachial nucleus network in the brainstem. The parabrachial nucleus network is under the control of the higher cortical centres that receive inputs from the vestibular nuclei via the thalamo-cortical projections. The parabrachial nucleus is also connected to the central amygdaloid nucleus, infralimbic cortex and hypothalamus which are the regions involved in avoidance conditioning, anxiety and conditioned fear. The parabrachial nucleus is further connected to brainstem respiratory centre and other regions that control the parasympathetic and sympathetic connections that are involved in the control of expression of emotions and the behavioural manifestation of anxiety disorder (Nagaratnam *et al* 2005:253).

It is important to highlight that the vestibulo-thalamo-cortical pathway is not only involved in the concurrent symptoms of vestibular dysfunction and anxiety, but is also a pathway for the transmission of vestibular information to cortical areas involved in higher vestibular function, namely visual-perceptual function and cognition. Findings of the study by Becker-Bense *et al* (2013:1103) also highlighted the involvement of the vestibulo-thalamo-cortical pathways and specifically visual acuity in patients with central vestibular dysfunction following a lateral medullary stroke. A central vestibular lesion may affect the vestibular nucleus of one side and effect acute damage by interrupting the ascending vestibulo-thalamo-cortical pathways to the thalamus and cortex on the ipsilateral side. A central vestibular lesion may also result in an interruption of the vestibular projections to the contralateral vestibular nucleus and the

ipsilateral vestibular-cerebellar structures (vestibulocerebellar tract). An error signal to the cortex results in downregulation in parts of both cortical sensory systems, with the visual areas more downregulated than the multisensory vestibular areas. The primary visual and motion-sensitive visual cortical areas are downregulated in both cortical hemispheres to suppress blurred vision as result of oscillopsia caused by spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction as result of a lateral medullary stroke (Becker-Bense *et al* 2013:1103).

Although the relationship between anxiety, depression and vestibular dysfunction is described in the literature (Bigelow and Agrawal 2015:83; Bigelow *et al* 2016:367), studies that have assessed the association between vestibular dysfunction and patients' level of anxiety and depression, have restricted the study populations to mainly patients with peripheral vestibular impairment which included vestibular neuritis, sudden deafness and vertigo, unilateral Ménière's disease and bilateral Ménière's disease (Sakagami *et al* 2016:632). Limited evidence on the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.13., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "prevalence"; "anxiety"; "depression"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

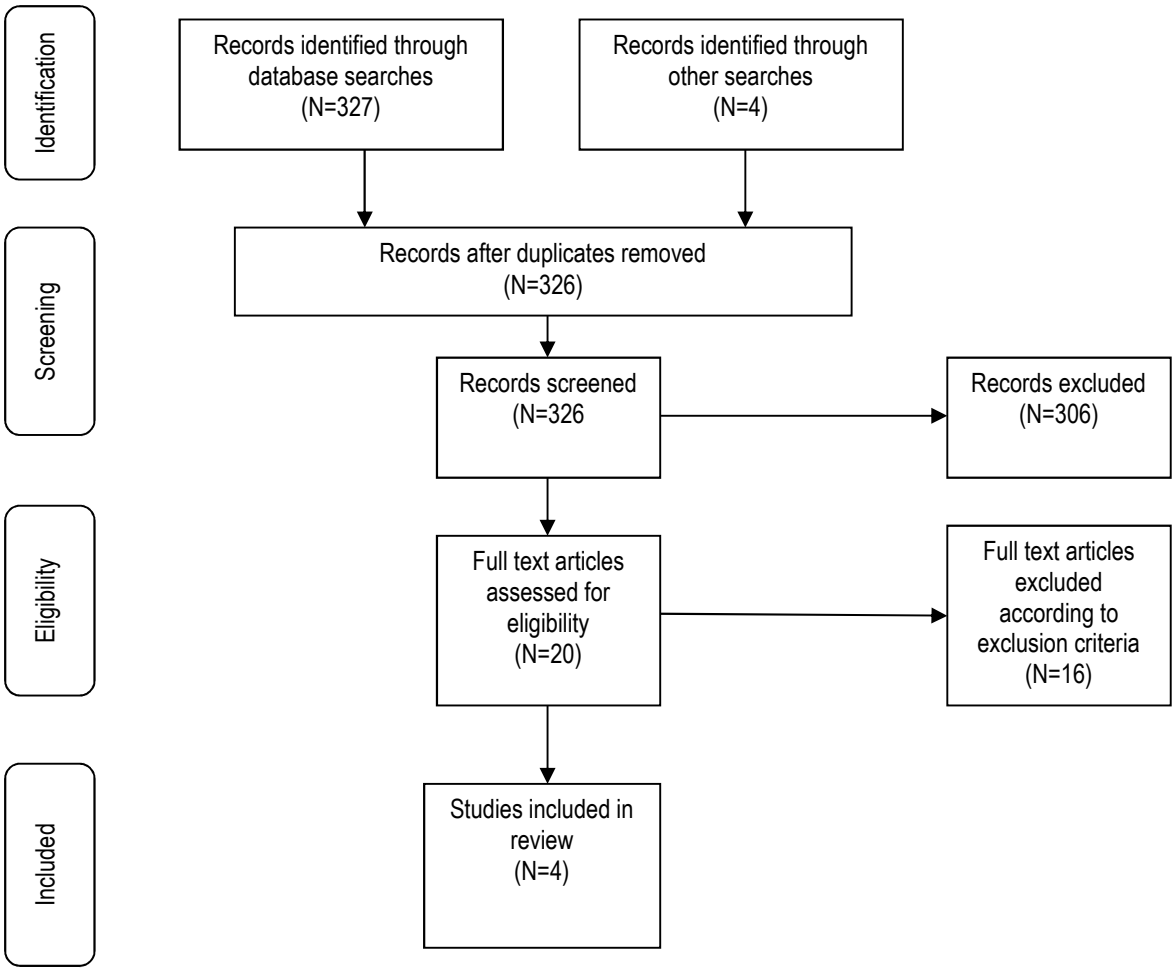


Figure 2.13.: Results of the literature search strategy on the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Four (4) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a RCT, a prospective observational study, a retrospective study and a case-study. Articles appraised are presented in Table 2.13.

Table 2.13.: Appraised articles on the prevalence of anxiety and depression due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=4)				
Level of Evidence				
I (N=1)	**II** (N=1)	**III** (N=1)	**IV** (N=1)	**V**
Edwards *et al* (2006:45)	Meli *et al* (2007:185)	Ali *et al* (2013:133)	Nagaratnam *et al* (2005:253)	

Based upon the articles critically reviewed and assessment of the quality of evidence completed, the reported prevalence of anxiety and depression in post-stroke patients ranged between 31.0% (Edwards *et al* 2006:45) and 53.0% (Ali *et al* 2013:133). The difference in the reported prevalence of anxiety and depression in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (Edwards *et al* 2006:45; Ali *et al* 2013:133). The method of assessment of level of anxiety and depression used by Edwards *et al* (2006:45), was the Geriatric Depression Scale–Short Form compared to Ali *et al* (2013:133) who used the European Quality of Life Score (EQ-5D). The EQ-5D is a visual analogue scale that enable patients to assess their own level of mobility, self-care, 'usual' activities, anxiety/depression and pain/discomfort. The EQ-5D is thus a scale that quantifies patients' general perceived quality of life and is therefore not a true reflection of only their perceived level of anxiety and depression post-stroke. The retrospective study by Ali *et al* (2013:133) used anonymised stroke trial data from the acute ischemic, intracerebral haemorrhage and rehabilitation sections of the Virtual International Stroke Trials Archive (VISTA).

Central vestibular dysfunction is also categorised by impairment on activity and participation level that includes; (1) impaired sensorimotor control of balance, mobility and gait; and (2) functional ability. The first activity limitation on activity and participation level to be discussed in Section 2.3.2., is sensorimotor control of balance, mobility and gait.

2.3.2. Activity and participation level

2.3.2.1. Sensorimotor balance, mobility and gait

As discussed in Section 1.1.3.2., the vestibulospinal pathways are intimately involved in postural control and balance (Keshner 2007:65). The medial vestibulospinal tract (MVST) and the lateral vestibulospinal tract (LVST) originates from the vestibular nuclei and provide input to the spinal cord segments containing motor neurons in the limbs (McCall, Miller and Yates 2017:1). Projections from the MVST provide input to the neck muscles and to segments that contain upper limb motor neurons (McCall *et al* 2017:1). The LVST extends the entire length of the spinal cord and provides extensive inputs to spinal cord segments containing motor neurons that innervate both upper- and lower limb muscles (McCall *et al* 2017:1). The LVST provides more extensive inputs to the spinal cord segments that contains upper- and lower limb motor neurons, compared to the MVST. McCall *et al* (2017:1) hypothesise that the LVST, therefore, plays a predominant role in the control of postural responses of the limbs to generate antigravity postural motor activity and protective extension, primarily in the lower extremities, in response to changes of the head position. Impairment of sensorimotor balance, mobility and gait may include deficits in functional balance and the ability to modify gait in response to changing task demands. The first activity limitation of sensorimotor balance, mobility and gait to be discussed is functional balance.

(i). Functional balance

The vestibulospinal tract (VST) is an extrapyramidal motor pathway involved in balance control and gait function (Jang *et al* 2018:727). Recently, Jang *et al* (2018:727) investigated the anatomical three-dimensional characteristics of the medial and lateral VST in the human brain using DTT. The VST consists of two (2) pathways, namely the medial and lateral VST. The medial VST originates from the medial vestibular nuclei at the level of lower pons, where after it descends through the posteromedial region of the medulla oblongata and terminates at the anterior funiculus of the cervical spinal cord. The lateral VST originates from the lateral vestibular nuclei in the lower pons, where after it descends through the antero-lateral region of the medulla oblongata and terminates at the lateral funiculus through total length of the spinal cord (Jang *et al* 2018:727). The lateral VST receives the majority of input from

the otoliths and cerebellum. The role of the lateral VST is to generate antigravity postural motor activity and protective extension primarily in the lower extremities in response to changes of the head position that occur as a result of gravity (Hain and Helminski 2007:11). The role of the medial VST is to activate the cervical axial musculature to mediate on-going postural changes or head righting in response to the sensory input (angular head motion) from the semicircular canals. The third white matter pathway to highlight is the reticulospinal tract. The reticulospinal tract receives sensory input from all the vestibular nuclei, as well as from all the other sensory and motor systems involved with maintaining balance (Hain and Helminski 2007:11). Although the entire extent of the reticulospinal tract through the spinal cord is poorly defined, it is accepted that the reticulospinal tract is probably involved in most reflex balance motor responses, including postural adjustments made as a result of extravestibular sensory input from visual, tactile and auditory stimuli (Hain and Helminski 2007:11).

Although the relationship between impaired functional balance and stroke is described in the literature (Bonan *et al* 2004:268), limited evidence on the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature (Marsden *et al* 2005:677). The researcher therefore identified the need to investigate the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.14., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “functional balance”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

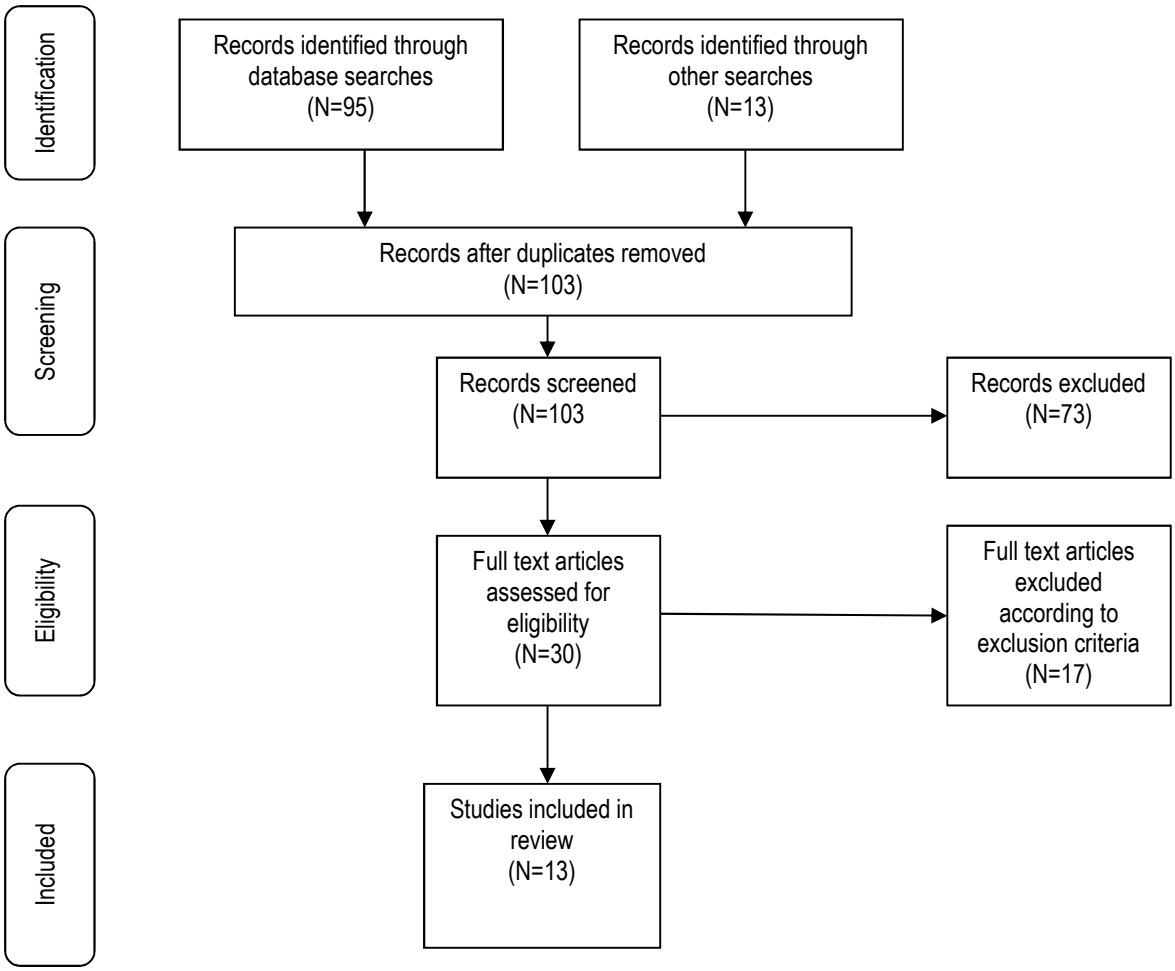


Figure 2.14.: Results of the literature search strategy on the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Thirteen (13) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a RCT, four (4) prospective observational studies, five (5) case control studies and three (3) case series studies. Articles appraised are presented in Table 2.14.

Table 2.14.: Appraised articles on the prevalence of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=13)				
Level of Evidence				
I (N=5)	**II**	**III** (N=5)	**IV** (N=3)	**V**
Stapleton, Ashburn and Stack (2001:437)		Marsden *et al* (2005:677)	De Haart *et al* (2004:886)	
Bonan *et al* (2004:268)		Manor *et al* (2010:458)	Brown *et al* (2006:76)	
Bonan *et al* (2004:274)		Oliveira *et al* (2011:2043)	Schow *et al* (2016:333)	
Wee and Hopman (2005:604)		Bonan *et al* (2013:713)		
Van Nes *et al* (2009:819)		Bonan *et al* (2015:521)		

Based upon the articles critically reviewed and assessment of the quality of evidence completed, the reported prevalence of impaired functional balance in post-stroke patients ranged between 59.5% (De Haart *et al* 2004:886) and 100.0% (Wee and Hopman 2005:604). The difference in the reported prevalence of impaired functional balance in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (De Haart *et al* 2004:886; Wee and Hopman 2005:604). The method of assessment of impaired functional balance used by De Haart *et al* (2004:886) was based on a trunk control score determined by the sitting balance item of the Trunk Control Test. A patient's trunk control was categorised as "disturbed" if a patient was unable to maintain balance in sitting while seated over the edge of a bed with feet lifted off the ground for a period of 30 seconds. Wee and Hopman (2005:604) quantified patients' functional balance (N=313) using the Berg Balance Scale (BBS). The study samples of both studies were limited to patients in the 'early reorganization' only (sub-acute phase post-stroke). The time post-stroke ranged from 3.3 weeks to 24.1 weeks (De Haart *et al* 2004:886), compared to 0.0 weeks to 24.0 weeks (Wee and Hopman 2005:604).

The second activity limitation of sensorimotor balance, mobility and gait to be discussed is the ability to modify gait in response to changing task demands.

(ii). Ability to modify gait in response to changing task demands

Apart from the vestibulo-spinal reflex (VSR) that contributes to postural control and functional balance, the vestibular system also contributes to visual stabilisation and gaze stability through the vestibulo-ocular reflex (VOR) (Section 1.1.3.1. and Section 2.3.1.2). The VOR generates eye movements of equal speed and opposite direction in response to head movement to stabilise gaze (eye position in space) to ensure adequate visual acuity (clear vision) during head movement (Hain and Helminski 2007:2; Goldberg and Cullen, 2011:331; Pimenta, Correia, Alves and Virella 2017:69). Gaze stability is essential to coordinate the movements of the head, trunk and pelvis during locomotion (Pimenta *et al* 2017:69). Turning during locomotion is usually initiated by a horizontal gaze and head reorientation in the direction of the turn, which is then followed by the trunk (Lamontagne and Fung 2009:256). Thereafter, the head and trunk are also tilted toward the shortened lateral side of the trunk in preparation of the turn. Orientation of the gaze and head is anticipatory components of postural control that occurs before the turn is reached, preceding the changes of the direction of the walking trajectory (Lamontagne and Fung 2009:256). The anticipatory components of gaze and head orientating behaviour are essential for visual scanning of the following travel path and to establish a stable frame of reference for future sensory and motor events associated with the control of body reorientation (Lamontagne and Fung 2009:256).

Stroke patients may present with impaired coordination of axial segments such as pelvic rotations during head rotation, which may contribute to impaired balance during gait (Pimenta *et al* 2017:69) and the ability to modify gait in response to changing task demands. Although the relationship between impaired ability to modify gait in response to changing task demands in post-stroke patients is described in the literature (Brown *et al* 2006:76; Balci *et al* 2013:259), limited evidence on the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke, population has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population, the

literature search strategy indicated in Figure 2.15., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “ability to modify gait in response to changing task demands”; “gait modification”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

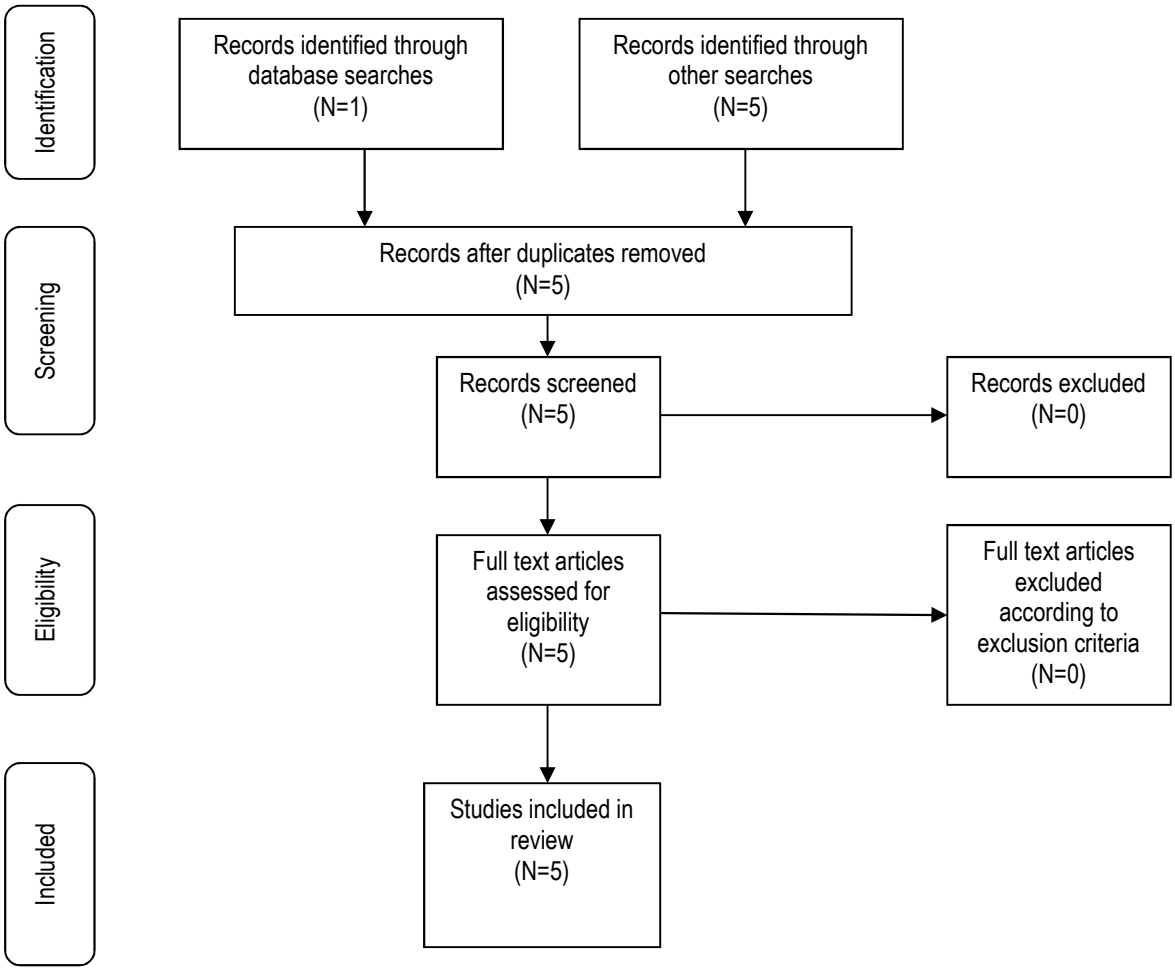


Figure 2.15.: Results of the literature search strategy on the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Five (5) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, a case control study and a case series study. Articles appraised are presented in Table 2.15.

Table 2.15.: Appraised articles on the prevalence of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=5)				
Level of Evidence				
I (N=3)	**II**	**III** (N=1)	**IV** (N=1)	**V**
Bonan *et al* (2004:274)		Lamontagne and Fung (2009:256)	Brown *et al* (2006:76)	
Balci *et al* (2013:259)				
Mitsutake *et al* (2017:745)				

None of the articles critically reviewed indicated a reported prevalence of impaired ability to modify gait in response to changing task demands. Outcome measures used by the articles reviewed included the Dynamic Gait Index (DGI) (Mitsutake *et al* 2017:745), a motion capture system & eye tracker (Lamontagne and Fung 2009:256) and self-assessment of ease of gait (Bonan *et al* 2004:274). The DGI was developed by Shumway-Cook, Baldwin, Polissar and Gruber (1997:812) to assess a patient's ability to modify gait in response to changing task demands in ambulatory patients with balance impairments. The outcome measure has been used to; (i) measure mobility in older adults with a score below nineteen (<19) as an indicator of increased fall risk (Brown *et al* 2006:76; Shumway-Cook and Woollacott 2007:396); and (ii) predict fall risk in patients with vestibular dysfunction (Whitney, Hudak and Marchetti 2000:99). Although Brown *et al* (2006:76) and Balci *et al* (2013:259) utilised the DGI to quantify patients' ability to modify gait in response to changing task demands, Brown *et al* (2006:76) indicated only the DGI mean score (13/24) of ten (10) post-stroke patients. Balci *et al* (2013:259) indicated the DGI median (50%) and interquartile range (IQR) (25%-75%) (1.0 [0.3–3.5]) of twenty-five (25) stroke patients. Neither Brown *et al* (2006:76) nor Balci *et al* (2013:259) mentioned the role of the central vestibular system

involved in impaired ability to modify gait in response to changing task demands post-stroke.

Mitsutake *et al* (2017:745) investigated the relationship between VOR function and gait performance in post-stroke patients (N=75). The horizontal semi-circular canal VOR was assessed using the GST. Lower extremity function was assessed using the FMA-LE and gait performance was evaluated using the DGI, 10MWT and TUG test. Findings of the study by Mitsutake *et al* (2017:745) indicated that the DGI were significantly correlated (P<0.001) to the FMA-LE *and* GST. Based upon stepwise multiple regression analysis, the GST also remained a significant predictor (P<0.001) of the DGI. Results of the study demonstrated that decreased VOR function contributes to impaired gait performance that includes the ability to modify gait in response to changing task demands in post-stroke patients (Mitsutake *et al* 2017:745).

The second activity limitation on activity and participation level as result of central vestibular dysfunction to consider is functional ability, discussed in detail in Section 2.3.2.2.

2.3.2.2. Functional ability

A significant proportion of patients, following a stroke, may present with unrecognised central vestibular dysfunction identified through the presence of (1) oculomotor impairment (Section 2.3.1.1); (2) impaired reflexive control of gaze (Section 2.3.1.2); (3) saccule, inferior vestibular nerve function impairment (Section 2.3.1.3); (4) utricle and superior vestibular nerve function impairment (Section 2.3.1.4); (5) impaired higher vestibular function (Section 2.3.1.5); and (6) anxiety and/or depression (Section 2.3.1.6) as a result of central vestibular dysfunction post-stroke. Stroke patients may receive minimal management of their central vestibular dysfunction during rehabilitation which may result in impaired functional ability post-stroke. Although the relationship between functional ability and stroke is described in the literature (Vossel *et al* 2013:1782), limited evidence on the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population, has been described in the literature. The researcher therefore identified the need to investigate the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population. In order to study the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke

population, the literature search strategy indicated in Figure 2.16., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “prevalence”; “functional ability”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

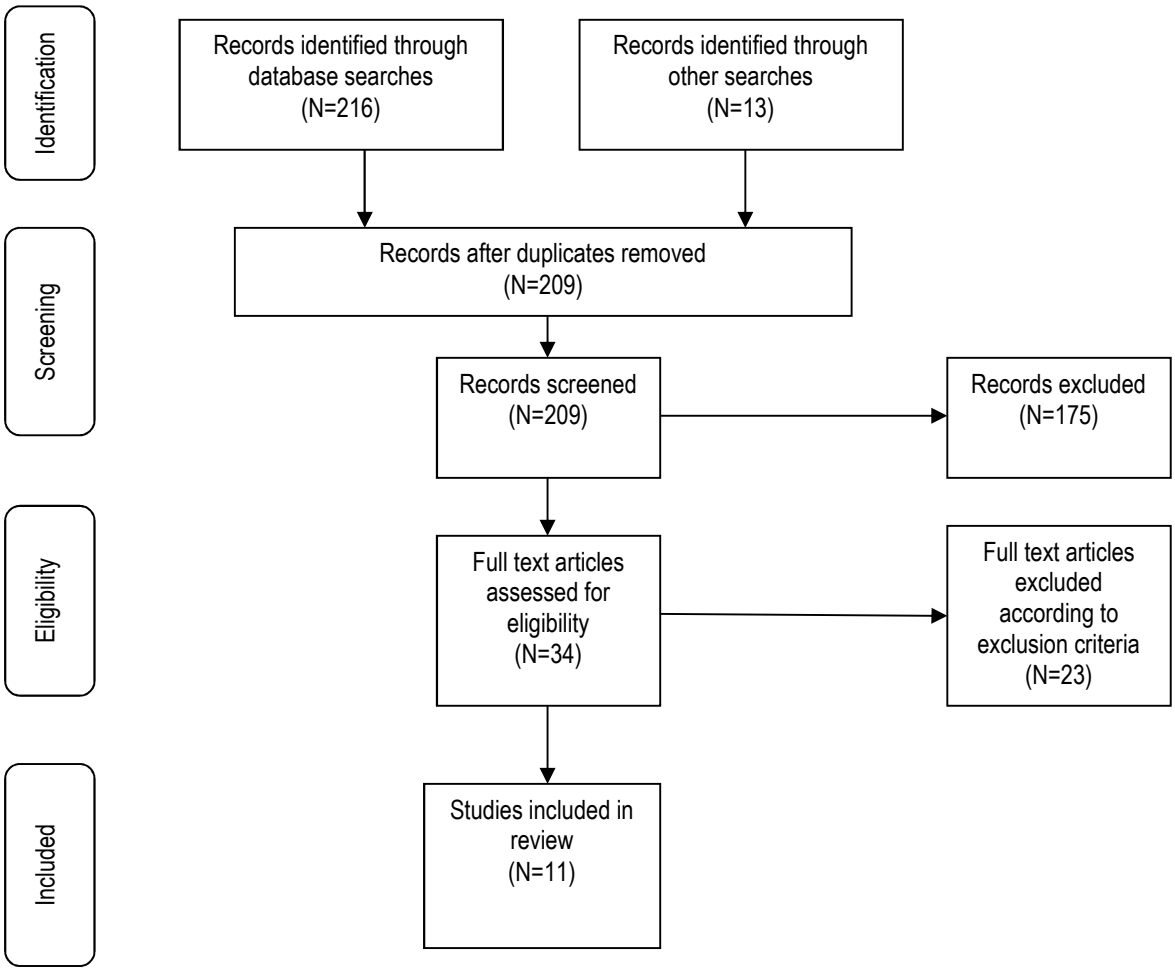


Figure 2.16.: Results of the literature search strategy on the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Eleven (11) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, four (4) prospective observational studies, four (4) case control studies and a retrospective study. Articles appraised are presented in Table 2.16.

Table 2.16.: Appraised articles on the prevalence of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=11)				
Level of Evidence				
I (N=6)	**II**	**III** (N=5)	**IV**	**V**
Lotery *et al* (2000:221)		Ng *et al* (2005:2138)		
Nijboer *et al* (2013:2021)		Oliveira *et al* (2011:2043)		
Vossel *et al* (2013:1782)		Bonan *et al* (2013:713)		
Kerkhoff *et al* (2014:557)		Mitsutake, Chuda, Oka, Hirata, Matsuo and Horikawa (2014:1799)		
Siong *et al* (2014:438)		Bonan *et al* (2015:521)		
Van Wyk *et al* (2014:856)				

Although eleven (11) articles were critically reviewed and an assessment of the quality of evidence was completed, none of the articles reviewed reported on the prevalence of impaired functional ability of post-stroke patients due to central vestibular dysfunction. Outcome measures used by the articles reviewed, included the Barthel Index (BI) (Lotery *et al* 2000:221; Oliveira *et al* 2011:2043; Bonan *et al* 2013:713; Nijboer *et al* 2013:2021; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856; Bonan *et al* 2015:521); (b) Functional Independent Measures (FIM) (Ng *et al* 2005:2138; Mitsutake *et al* 2014:1799; Siong *et al* 2014:438); and (c) ADLs (address copying, telephone number dialling, clock reading, face creaming, hair combing, filling out a form, tray assembling, counting money) (Vossel *et al* 2013:1782). The BI assesses the performance of ten (10) basic ADLs regarding feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing, as well as the patient's dependence (on assistance) to perform these

activities (Mahoney and Barthel 1965:61). Although numerous authors utilised the BI to quantify patients' functional ability, the results were limited to mean±SD and interquartile range (IQR) (25%-75%) of the respective study samples. The reported mean±SD score on the BI in post-stroke patients ranged between 3.41±2.15 (Nijboer *et al* 2013:2021) and 82.6±17.3 (Bonan et al 2015:521) respectively. The mean±SD score on the BI by Nijboer *et al* (2013:2021) was indicative of patients' total to severe dependence in ADL, compared to the score by Bonan *et al* (2015:521) that was indicative of patients' moderate dependence in ADL post-stroke.

It may be summarised that a large difference in the reported prevalence of the clinical features and activity limitations associated with central vestibular disorders on body structure and function, as well as activity and participation level in post-stroke patients, exists. The large difference in the reported prevalence of the clinical features and activity limitations associated with central vestibular dysfunction may be attributed to the respective assessment methods used in the studies reviewed. The existing research evidence that investigated the various objective measures used to identify and quantify the clinical features and activity limitations associated with central vestibular dysfunction based on impairment on the level of body structure and function, as well as activity limitations on activity and participation level in post-stroke patients, are discussed in Section 2.4.

2.4. OBJECTIVE MEASURES USED TO IDENTIFY AND QUANTIFY CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS

In the literature reviewed, various objective measures were used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients. These various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction, are summarised in Table 2.17.

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	(1) MR-eye tracker during fMRI (Baumann *et al* 2007:237) (2) No specific method noted (Ciuffreda *et al* 2007:155) (3) Electronystagmography (ENG) (Kikuchi and Yamasoba 2007:59) (4) Observation only (Rowe *et al* 2013:2) (5) Occupational therapy vision screening tool (Herron 2016:69)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(1) Berg Balance Scale (BBS) (Stapleton *et al* 2001:437; Wee and Hopman 2005:604; Van Nes *et al* 2009:819; Oliveira *et al* 2011:2043; Påhlman *et al* 2011:1952; Balci *et al* 2013:259; Bonan *et al* 2013:713; Bonan *et al* 2015:521) (2) Sensory Organization Test (SOT) used with computerized dynamic posturography (EquiTest) (Bonan *et al* 2004:268; Bonan *et al* 2004:274; Smania *et al* 2008:313; Oliveira *et al* 2011:2043)

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
OCULOMOTOR CONTROL	**Saccadic eye movements**	(1) Electro-oculography (Catz *et al* 1997:175) (2) MR-eye tracker during fMRI (Baumann *et al* 2007:237) (3) No specific method noted (Ciuffreda *et al* 2007:155; Dong *et al* 2013:337) (4) Electronystagmography (ENG) (Kikuchi and Yamasoba 2007:59) (5) Observation only (Rowe *et al* 2009:188; Rowe *et al* 2011:406; Rowe *et al* 2013:2) (6) Observation only: Pen torch as fixation target (Siong *et al* 2014:438) (7) Occupational therapy vision screening tool (Herron 2016:69) (8) Video-based eye tracker (Rizzo *et al* 2017:12)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(3) Vestibular evoked postural responses obtained using galvanic vestibular stimulation (GVS) (Marsden *et al* 2005:677) (4) Timed “Up and Go” (TUG) test (Brown *et al* 2006:76; Balci *et al* 2013:259; Bonan *et al* 2013:713; Bonan *et al* 2015:521) (5) Activities-Specific Balance Confidence Scale (Brown *et al* 2006:76) (6) Five Times Sit-to-Stand (FTSTS) Test (Brown *et al* 2006:76)

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
OCULOMOTOR CONTROL	**Static visual acuity**	(1) Snellen chart (Lotery *et al* 2000:221; Rowe *et al* 2009:188; Rowe *et al* 2011:406) (2) LogMar chart (Lotery *et al* 2000:221; Rowe *et al* 2009:188; Rowe *et al* 2011:406; Naeem 2012:55) (3) Single letter, symbol charts for patients who were unable to read more complex Snellen or LogMar chart(s) (Lotery *et al* 2000:221) (4) MIS Pocket Vision Guide (Edwards *et al* 2006:45) (5) Sheridan-Gardner chart (Shrestha *et al* 2012:46) (6) Lea number chart (Siong *et al* 2014:438) (7) Pinhole assessment was used for visual acuity worse than 0.3 LogMAR (Siong *et al* 2014:438) (8) Occupational therapy vision screening tool (Herron 2016:69)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(7) Force plate (De Haart *et al* 2004:886; Manor *et al* 2010:458; Bonan *et al* 2013:713; Mitsutake *et al* 2014:1799; Bonan *et al* 2015:521) (8) Modified Clinical Test of Sensory Interaction on Balance (mCTSIB) (Balci *et al* 2013:259) (9) Postural Assessment Scale (PASS) (Dai *et al* 2013:477) (10) Balance Evaluation Systems Test (BESTest) (Schow *et al* 2016:333)

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	(1) Head impulse test (HIT) using the search coil system (Park *et al* 2013:1576; Chen *et al* 2014:83; Kim *et al* 2014:121) (2) Bedside HIT (Baek *et al* 2015:279) (3) Gaze-stabilization test (GST) (Mitsutake *et al* 2017:745)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(1) Self-assessment of ease of gait (Bonan *et al* 2004:274) (2) Functional Ambulation Categories (FAC) (De Haart *et al* 2004:886; Van Nes *et al* 2009:819; Oliveira *et al* 2011:2043) (3) DGI (Brown *et al* 2006:76; Balci *et al* 2013:259; Mitsutake *et al* 2017:745) (4) Motion capture system and eye tracker (Lamontagne and Fung 2009:256) (5) Ten-Meter Walk Test (10MWT) (Schow *et al* 2016:333)
	Dynamic visual acuity	(1) Landolt C-ring test (Niwa *et al* 2015:203) (2) Gaze-stabilization test (GST) (Mitsutake *et al* 2017:745)			

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	(1) cVEMP (Chen and Young 2003:990; Pollak *et al* 2006:227; Heide *et al* 2010:1102; Kim *et al* 2010:825; Tseng and Young 2010:267; Ahn *et al* 2011:114; Kim *et al* 2011:1; Su and Young 2011:923; Choi *et al* 2014:362; Kim *et al* 2016:2424)	**FUNCTIONAL ABILITY**	**Functional ability**	(1) Barthel Index (BI) (Lotery *et al* 2000:221; Oliveira *et al* 2011:2043; Bonan *et al* 2013:713; Nijboer *et al* 2013:2021; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856; Bonan *et al* 2015:521) (2) Functional Independent Measures (FIM) (Ng *et al* 2005:2138; Mitsutake *et al* 2014:1799; Siong *et al* 2014:438)
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	(1) oVEMP (Su and Young 2011:923; Oh *et al* 2013:770; Park *et al* 2013:1576; Choi *et al* 2014:362; Kim *et al* 2014:1042; Kim *et al* 2014:121; Kim *et al* 2016:2424)			

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	(1) Assessment of reading acuity (Cate and Richards 2000:326) (2) Single-line and multiple-line simulated reading objectively recorded with a computer-based Visagraph device (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9) (3) Subjective reading-related questionnaire (Kapoor *et al* 2004:1667) (4) Oral reading (Gottesman *et al* 2008:1439) (5) Subjective description of the inability to read (despite being able to see the text) (Rowe *et al* 2011:406) (6) King-Devick Test (Van Wyk *et al* 2014:856)	**FUNCTIONAL ABILITY**	**Functional ability**	(3) ADLs (address copying, telephone number dialling, clock reading, face creaming, hair combing, filling out a form, tray assembling, counting money) (Vossel *et al* 2013:1782)

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**		
HIGHER VESTIBULAR FUNCTION	**Visual-perceptual function**	(1) Letter Detection Task (Behrmann *et al* 1997:1445) (2) Letter Cancellation Test (Karnath *et al* 1998:2357; Cate and Richards 2000:326; Olk *et al* 2002:306; Fruhmann-Berger and Karnath 2005:1194; Van Nes *et al* 2009:819; Van Kessel *et al* 2010:603; Kettunen *et al* 2012:359; Nijboer *et al* 2013:2021) (3) Line Bisection Test (Karnath *et al* 1998:2357; Bailey *et al* 2000:139; Cate and Richards 2000:326; Gottesman *et al* 2008:1439; Kettunen *et al* 2012:359; Nijboer *et al* 2013:2021; Vossel *et al* 2013:1782) (4) Copying (Karnath *et al* 1998:2357; Bailey *et al* 2000:139; Fruhmann-Berger and Karnath 2005:1194; Gottesman *et al* 2008:1439; Kettunen *et al* 2012:359; Vossel *et al* 2013:1782)		

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**		
HIGHER VESTIBULAR FUNCTION	**Visual-perceptual function**	(5) Star Cancellation Test (Bailey *et al* 2000:139; Kizony and Katz 2002:82; Olk *et al* 2002:306; Van Nes *et al* 2009:819; Van Kessel *et al* 2010:603; Kettunen *et al* 2012:359; Vossel *et al* 2013:1782; Van Wyk *et al* 2014:856) (6) 'Baking Tray Task' (Bailey *et al* 2000:139) (7) Clock-drawing (Bailey *et al* 2000:139; Vossel *et al* 2013:1782) (8) Motor-Free Visual Perception Test (MVPT) (Bailey *et al* 2000:139) (9) Bells test (Fruhmann-Berger and Karnath 2005:1194) (10) Line Cancellation Test (Gottesman *et al* 2008:1439; Vossel *et al* 2013:1782)		

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**		
HIGHER VESTIBULAR FUNCTION	**Visual-perceptual function**	(11) Visual extinction (Gottesman *et al* 2008:1439) (12) Tactile extinction (Gottesman *et al* 2008:1439) (13) Line Crossing (Kettunen *et al* 2012:359) (14) Representational drawing (Kettunen *et al* 2012:359) (15) Clinical observation only (Ng *et al* 2005:2138) (16) Occupational therapy vision screening tool (Herron 2016:69)		
	Cognition	(1) Thinking Operations from the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) battery (Kizony and Katz 2002:82) (2) Contextual Memory Test (Kizony and Katz 2002:82) (3) 'Exploratory Motor Task' (Bailey *et al* 2000:139)		

Table 2.17.: Summary of the various objective measures used to identify and quantify clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)			
Level of body structure and function			
Clinical feature		**Objective measure(s)**	
HIGHER VESTIBULAR FUNCTION	**Cognition**	(4) Rey Complex Figure-copy (Kizony and Katz 2002:82) (5) COGNISTAT (Kizony and Katz 2002:82) (6) FIM cognition score (Ng *et al* 2005:2138) (7) Cognitive Impairment Questionnaire (CIMP-QUEST) (Påhlman *et al* 2011:1952) (8) MMSE (Påhlman *et al* 2011:1952; Dong *et al* 2013:337; Nijboer *et al* 2013:2021)	
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	(1) Geriatric Depression Scale–Short Form (Edwards *et al* 2006:45) (2) State-Trait Anxiety Inventory (STAI) (Meli *et al* 2007:185) (3) Centre for Epidemiological Studies Depression Scale (CES-D) (Meli *et al* 2007:185) (4) EQ-5D (Ali *et al* 2013:133)	

Each of the clinical features and activity limitations associated with central vestibular dysfunction are discussed from Section 2.4.1. to Section 2.4.2. The first clinical feature on the level of body structure and function to be discussed is oculomotor control in Section 2.4.1.

2.4.1. Level of body structure and function

2.4.1.1. Oculomotor control

In the current study, oculomotor control and the impairment thereof are limited to smooth pursuit eye movements, saccadic eye movements and static visual acuity. The first feature of oculomotor control to be discussed is smooth pursuit eye movement.

(i). Smooth pursuit eye movement

Smooth pursuit eye movements are quantified using VNG to determine the gain of the smooth pursuit eye movements which is defined as the relation of smooth pursuit eye movement velocity to target velocity (Sharpe 2008:241). During VNG, a patient's smooth pursuit eye movement-gain of the left and right eyes into the left and right visual fields, are measured. In order to determine the various measures used to quantify smooth pursuit eye movements in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.17., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "measure"; "quantify"; "smooth pursuit eye movement"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify smooth pursuit eye movements due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

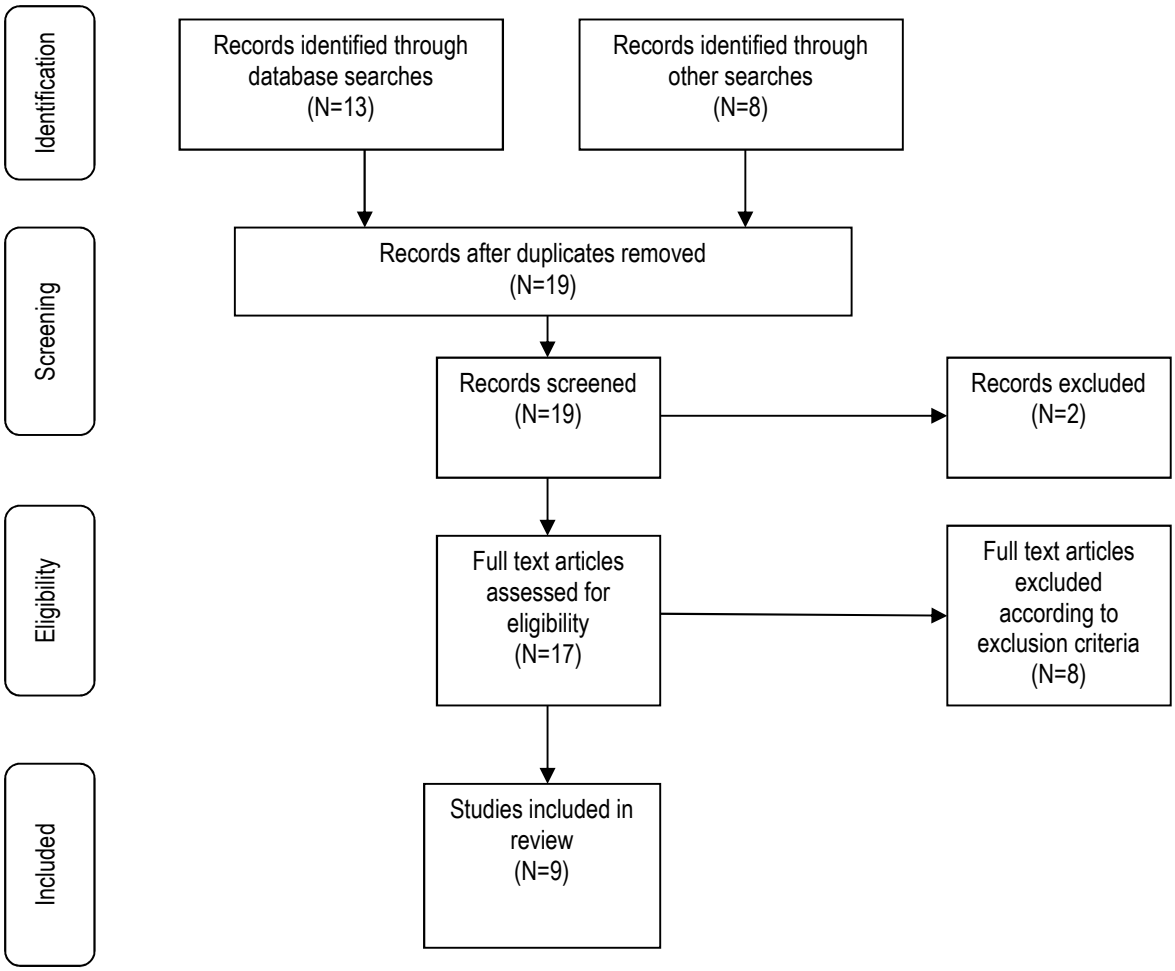


Figure 2.17.: Results of the literature search strategy on the various measures used to quantify smooth pursuit eye movements due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Nine (9) articles were critically reviewed and an assessment of the quality of evidence, was completed. The articles appraised included four (4) RCTs, a prospective observational study, case control study and three (3) retrospective studies. Articles appraised are presented in Table 2.18.

Table 2.18.: Appraised articles on the various measures used to quantify smooth pursuit eye movements due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=9)				
Level of Evidence				
I (N=5)	**II**	**III** (N=4)	**IV**	**V**
Kerkhoff *et al* (2012:1164)		Baumann *et al* (2007:237)		
Kerkhoff *et al* (2013:789)		Ciuffreda *et al* (2007:155)		
Rowe *et al* (2013:2)		Kikuchi and Yamasoba (2007:59)		
Kerkhoff *et al* (2014:557)		Herron (2016:69)		
Carrick *et al* (2016:3)				

Findings of the literature appraised indicated that smooth pursuit eye movements in post-stroke patients, were quantified using various measures such as an MR-Eye tracker during fMRI (Baumann *et al* 2007:237), ENG (Kikuchi and Yamasoba 2007:59), observation only (Rowe *et al* 2013:2) and an occupational therapy vision screening tool (Herron 2016:69). Baumann *et al* (2007:237) quantified smooth pursuit eye movements of twelve (12) patients with isolated cerebellar infarctions by recording their eye movements using a MR-Eye tracker during an fMRI session. Findings of the study by Baumann *et al* (2007:237) did not include measurement of the gain of the smooth pursuit eye movements; measurements were limited to the mean onset latency of the patient's smooth pursuit eye movements during completion of a task that required the execution of smooth pursuit eye movements during an fMRI session.

Findings of the study by Ciuffreda *et al* (2007:155) were based on information obtained from a computer-based query for stroke patients over a three (3)-year period. The study sample consisted of ambulatory out-patients with vision-based symptoms that underwent visual examinations performed by optometrists. Ciuffreda *et al* (2007:155) did not specify the methods used by the optometrists to quantify smooth pursuit eye movement impairment in the study sample. Kikuchi and Yamasoba (2007:59) used ENG to quantify smooth pursuit eye movements. Electronystagmography (ENG) is a commonly used method for recording eye movements by applying the corneal-retinal

potential variation principle during eye movements to record and quantify smooth pursuit eye movements (Ganança *et al* 2010:400).

The method of assessment of smooth pursuit eye movements used by Rowe *et al* (2013:2) was based upon observation only. The absence of objective quantification of smooth pursuit eye movements of post-stroke patients may result in limited accuracy in the identification and quantification of smooth pursuit eye movements, compared to the detailed assessment of smooth pursuit eye movements using objective measures such as VNG. Herron (2016:69) identified smooth pursuit eye movement impairment using an occupational therapy vision screening tool developed by an interdisciplinary team that included occupational therapists and an optometrist. Although Herron (2016:73) stated that the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study, the psychometric properties of the vision screening tool were not determined prior to the study.

The studies by Kerkhoff *et al* (2012:1164), Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) were included in the literature review as the authors implemented optokinetic stimulation that elicited smooth pursuit eye movements (Kerkhoff *et al* 2012:1164) and smooth pursuit eye movement training (Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557) in the treatment of impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.3.1.5). Kerkhoff *et al* (2012:1164), Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) did not quantify smooth pursuit eye movements in their study samples; assessment measurements were limited to the assessment of higher vestibular function that included various visual-perceptual function tests such as; (i) horizontal line, visual-perceptual- and motor line bisection; (ii) number or digit cancellation tests; (iii) paragraph reading; (iv) auditory subjective median plane (ASMP); (v) Functional Neglect Index (FNI); and (vi) Unawareness and Behavioural Neglect Index (UBNI).

Lastly, Carrick *et al* (2016:3) implemented smooth pursuit eye movement training in the treatment of patients (N=34) who suffered a MCA ischemic stroke. Carrick *et al* (2016:3) did not quantify the patients' smooth pursuit eye movements; assessment measurements were limited to the assessment of electrical brain activity using quantitative Electroencephalography (qEEG) and the functional outcome of patients using the NIH Stroke Scale (NIHSS). Although results of the study by Yeo *et al*

(2017:1) support findings from previous studies that central vestibular dysfunction is relatively common after MCA territory infarction, Carrick *et al* (2016:3) did not mention the role of the central vestibular system involved in oculomotor control, specifically smooth pursuit eye movements post-stroke. The second feature of oculomotor control to be discussed, is saccadic eye movement.

(ii). Saccadic eye movement

Saccadic eye movements are quantified using VNG to determine the latency, velocity and accuracy of saccadic eye movements of the left and right eyes into the left and right visual fields (Strupp *et al* 2014:542) respectively. The latency of saccadic eye movements is quantified by measuring the time between the presentation of a stimulus and the initiation of eye movement (Carrick *et al* 2016:3). The velocity of saccadic eye movements is measured by the number of degrees per second (°/s) the eyes move upon presentation of a stimulus (Carrick *et al* 2016:3). The accuracy of saccadic eye movements is measured by the ability of a patient to perform accurate saccadic eye movements upon presentation of a stimulus (Strupp *et al* 2014:542). In order to determine the various assessment measures used to quantify saccadic eye movements in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.18., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “saccadic eye movement”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify saccadic eye movements due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

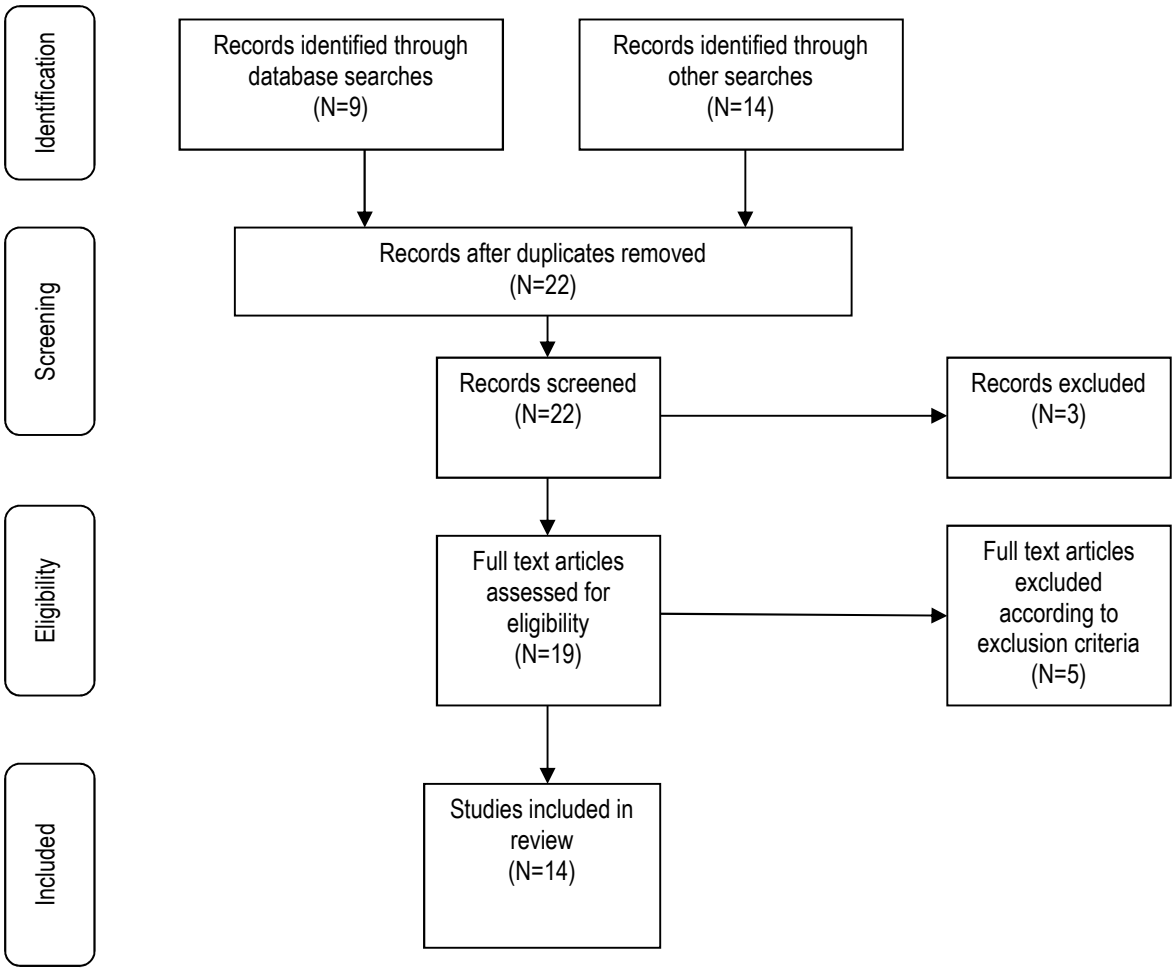


Figure 2.18.: Results of the literature search strategy on the various measures used to quantify saccadic eye movements due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Fourteen (14) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included three (3) RCTs, four (4) prospective observational studies, four (4) case control studies and three (3) retrospective studies. Articles appraised are presented in Table 2.19.

Table 2.19.: Appraised articles on the various measures used to quantify saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=14)				
Level of Evidence				
I (N=7)	**II**	**III** (N=7)	**IV**	**V**
Rowe *et al* (2009:188)		Catz *et al* (1997:175)		
Rowe *et al* (2011:406)		Baumann *et al* (2007:237)		
Kerkhoff *et al* (2013:789)		Ciuffreda *et al* (2007:155)		
Rowe *et al* (2013:2)		Kikuchi and Yamasoba (2007:59)		
Kerkhoff *et al* (2014:557)		Dong *et al* (2013:337)		
Siong *et al* (2014:438)		Herron (2016:69)		
Carrick *et al* (2016:3)		Rizzo *et al* (2017:12)		

Findings of the literature critically reviewed indicated that saccadic eye movements in post-stroke patients were quantified using various measures that included electro-oculography (Catz *et al* 1997:175), MR-eye tracker during fMRI (Baumann *et al* 2007:237), ENG (Kikuchi and Yamasoba 2007:59), observation only (Rowe *et al* 2009:188; Rowe *et al* 2011:406; Rowe *et al* 2013:2), observation with a pen torch as fixation target (Siong *et al* 2014:438), occupational therapy vision screening tool (Herron 2016:69) and a video-based eye tracker (Rizzo *et al* 2017:12).

Catz *et al* (1997:175) quantified saccadic eye movements of thirteen (13) patients with unilateral hemispheric infarction and six (6) control subjects with electro-oculography. Measurements were limited to saccadic eye movement velocity and duration. Only one eye of each patient was measured, specifically the eye on the hemiplegic side of each stroke patient and the right eye of each control subject. The assessment of only one eye of the patient poses a limitation for the study. As demonstrated in Figure 2.3, the left and right visual fields of a patient are represented in the contralateral hemisphere to the visual field (Si, Zhang, Zhang and Jiang 2017:2018). It is therefore essential to present the results of the quantification of smooth pursuit eye movements and saccadic eye movements of both eyes into both visual fields separately to assess

the possible differences in oculomotor function and visual activation between the two hemispheres of post-stroke patients (Hougaard, Jensen, Amin, Rostrup, Hoffmann and Ashina 2015:2). Baumann *et al* (2007:237) quantified saccadic eye movements of twelve (12) patients with isolated cerebellar infarctions by recording their eye movements using a MR-eye tracker during an fMRI. Measurements were limited to the mean onset latency of saccadic eye movements during completion of a task that required the execution of saccadic eye movements during an fMRI session. Patients' saccadic eye movement velocity and accuracy were not measured by Baumann *et al* (2007:237). Rizzo *et al* (2017:12) also utilised an eye tracker to quantify saccadic eye movements of ten (10) stroke patients and sixteen (16) control subjects. Unlike Baumann *et al* (2007:237) that used the eye tracker during fMRI, Rizzo *et al* (2017:12) measured patients' saccadic eye movements with a video-based eye tracker while viewing a display monitor in a dark room while their heads were stabilised in a chin and forehead rest. Recordings of the patients' saccadic eye movements were performed monocularly (only one eye) (Rizzo *et al* 2017:12).

Findings of the study by Ciuffreda *et al* (2007:155) were based on information obtained from a computer-based search for stroke patients over a three (3)-year period. The study sample consisted of ambulatory out-patients with vision-based symptoms that underwent visual examinations performed by optometrists. Ciuffreda *et al* (2007:155) did not specify the methods used by the optometrists to quantify saccadic eye movement impairment in the study sample. In contrast, Kikuchi and Yamasoba (2007:59) used ENG to quantify saccadic eye movements. Electronystagmography (ENG) is a commonly used method for recording eye movements by applying the corneal-retinal potential variation principle during eye movements to record and quantify saccadic eye movements (Ganança *et al* 2010:400).

The method of assessment of saccadic eye movements used by Rowe *et al* (2009:188), Rowe *et al* (2011:406), Rowe *et al* (2013:2) and Siong *et al* (2014:438) was based upon observation only. Siong *et al* (2014:438) indicated that a pen torch was used as a fixation target during examination. 'Jerky' saccadic eye movements made during the examination were categorised as saccadic eye movement impairment. The absence of objective quantification of saccadic eye movements of post-stroke patients may result in limited accuracy in the quantification of saccadic eye

movements compared to the detailed assessment of saccadic eye movements using objective measures such as VNG.

Dong *et al* (2013:337) assessed saccadic eye movements to evaluate the sensitivity of measuring cognitive processing in the ocular motor system as a marker for recovery in patients post-stroke. Although findings of the study by Dong *et al* (2013:337) demonstrated measurements of saccadic eye movements that included both latency, amplitude and position error, Dong *et al* (2013:337) did not specify the methods used to quantify saccadic eye movements in the study sample. Alternatively, Herron (2016:69) identified saccadic eye movement impairment using an occupational therapy vision screening tool developed by an interdisciplinary team which included occupational therapists and an optometrist. Although Herron (2016:73) stated that the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study, the psychometric properties of the vision screening tool were not determined prior to the study.

The studies by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) were included in the literature review as the authors implemented saccadic eye movement training in the treatment of impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.3.1.5). Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) did not quantify saccadic eye movements in their respective study samples. Assessment were limited to the evaluation of higher vestibular function that included various visual-perceptual function tests, such as cancellation tests, paragraph reading, line bisection tests, auditory tests, FNI and UBNI. Carrick *et al* (2016:3) also implemented saccadic eye movement training in the treatment of patients (N=34) who have suffered a MCA ischemic stroke. Carrick *et al* (2016:3) also did not quantify the patients' saccadic eye movements; assessment measurements were limited to the assessment of electrical brain activity and functional outcome using quantitative qEEG and NIHSS respectively. Although results of the study by Yeo *et al* (2017:1) support findings from previous studies that central vestibular dysfunction is relatively common after MCA territory infarction, Carrick *et al* (2016:3) did not mention the role of the central vestibular system involvement in oculomotor function, specifically saccadic eye movements post-stroke. The third feature of oculomotor control to be discussed is static visual acuity.

(iii). Static visual acuity

The presence of impaired static visual acuity is based on a visual acuity score of higher than 0.5 LogMAR as prescribed by the World Health Organisation (WHO) (Rowe *et al* 2009:188; Rowe *et al* 2011:406; Shrestha *et al* 2012:46; Siong *et al* 2014:438). The LogMar chart is considered the gold standard for the assessment of static visual acuity (Noushad *et al* 2012:87). In order to determine the various measures used to quantify static visual acuity in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.19., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “static visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

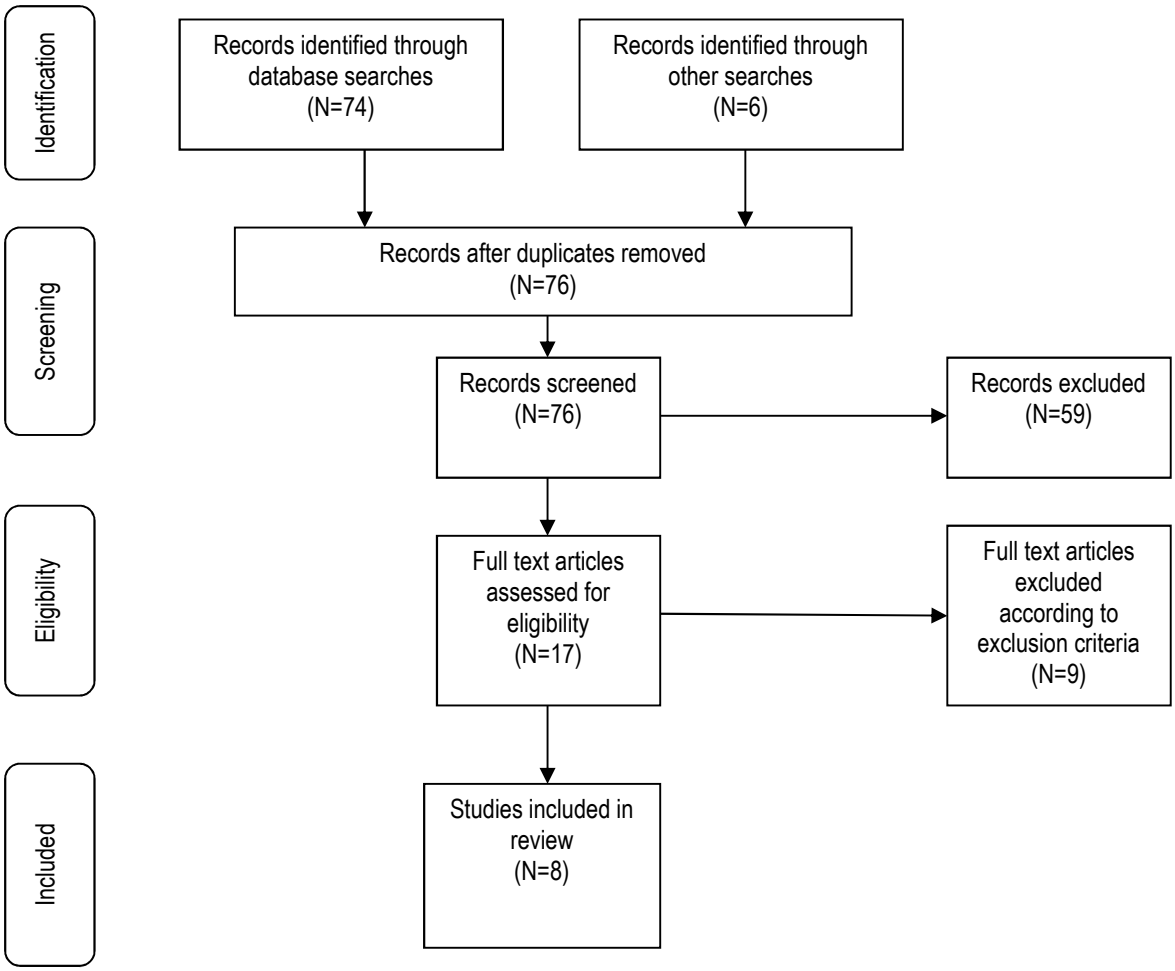


Figure 2.19.: Results of the literature search strategy on the various measures used to quantify reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Eight (8) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included seven (7) prospective observational studies and a retrospective study. Articles appraised are presented in Table 2.20.

Table 2.20.: Appraised articles on the various measures used to quantify reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=8)				
Level of Evidence				
I (N=7)	**II**	**III** (N=1)	**IV**	**V**
Lotery *et al* (2000:221)		Herron (2016:69)		
Edwards *et al* (2006:45)				
Rowe *et al* (2009:188)				
Rowe *et al* (2011:406)				
Naeem (2012:55)				
Shrestha *et al* (2012:46)				
Siong *et al* (2014:438)				

Findings of the literature critically reviewed indicated that static visual acuity in post-stroke patients were quantified using various measures that included: (1) Snellen chart (Lotery *et al* 2000:221; Rowe *et al* 2009:188; Rowe *et al* 2011:406); (2) LogMar chart (Lotery *et al* 2000:221; Rowe *et al* 2009:188; Rowe *et al* 2011:406; Naeem 2012:55); (3) Single letter, symbol charts for patients who were unable to read more complex Snellen or LogMar charts (Lotery *et al* 2000:221); (4) MIS Pocket Vision Guide (Edwards *et al* 2006:45); (5) Sheridan-Gardner chart (Shrestha *et al* 2012:46); (6) Lea number chart (Siong *et al* 2014:438); (7) Pinhole assessment was used for visual acuity worse than 0.3 LogMAR (Siong *et al* 2014:438); and (8) occupational therapy vision screening tool (Herron 2016:69).

The LogMar chart is regarded as the gold standard for the assessment of visual acuity (Noushad *et al* 2012:87; Van Wyk *et al* 2016:140; Lotery *et al* 2000:221), Rowe *et al* (2009:188), Rowe *et al* (2011:406) and Naeem (2012:55) quantified static visual acuity using the LogMar chart. Alternatively, the Snellen chart is also an accepted tool for testing visual acuity (Hussain, Saleh, Sivaprasad and Hammond 2006:6). Lotery *et al* (2000:221), Rowe *et al* (2009:188) and Rowe *et al* (2011:406) also used the Snellen chart to quantify static visual acuity. When patients were unable to read more complex

Snellen or LogMar charts, Lotery *et al* (2000:221) used single letter and symbol charts to assess static visual acuity.

Edwards *et al* (2006:45) quantified static visual acuity using the MIS Pocket Vision Guide (N=53). Edwards *et al* (2006:45) stated that results of their study may have reflected an error in the sensitivity of the MIS Pocket Vision Guide that resulted in a possible inflated number of patients diagnosed with impaired static visual acuity due to increased false positives (type I error).

Shrestha *et al* (2012:46) utilised the Sheridan-Gardner chart compared to Siong *et al* (2014:438) that used the Lea number chart to quantify static visual acuity. When patients presented with visual acuity worse than 0.3 LogMAR, Siong *et al* (2014:438) used the pinhole assessment to measure static visual acuity. Herron (2016:69) implemented an occupational therapy vision screening tool to measure static visual acuity. Although the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study, as stated by Herron (2016:73), the psychometric properties of the vision screening tool were not determined prior to the study. The second clinical feature on the level of body structure and function to be discussed, is reflexive control of gaze in Section 2.4.1.2.

2.4.1.2. Reflexive control of gaze

Impairment of reflexive control of gaze may include deficits of the VOR-gain and dynamic visual acuity. The first feature of reflexive control of gaze to be discussed, is VOR-gain.

(i). Vestibular-ocular reflex gain

Prior to 2009, the caloric test was considered the best method to quantify the VOR (Tusa 2007:125; Halmagyi, Chen, MacDougall, Weber, McGarvie and Curthoys 2017:1). Recently, Burston, Mossman, Mossman and Weatherall (2018:294) investigated the vHIT compared to the caloric test in patients with sub-acute and chronic vestibular disorders (N=173). Findings of the study by Burston *et al* (2018:294) indicated that with caloric testing considered as the gold standard, the vHIT demonstrated a sensitivity of 34.6% (22.0-49.1) (95% CI) and specificity of 93.4%

(87.4-97.1) (95% CI). However, the vHIT was more sensitive in patients with bilateral hypofunction (N=9) whom presented with 100% abnormal vHIT results compared to only 44% that presented with abnormal caloric results. Results of the study support the continued use of both vHIT and caloric tests in patients with sub-acute and chronic vestibular symptoms, especially if the vHIT is normal (Burston *et al* 2018:294).

In the current study, the quantification of the VOR are limited to vHIT and caloric testing will thus not be further addressed in this study. The vHIT is a small, light-weight head-mounted video camera system that allows accurate measurement of eye movements during passive head rotation at a peak angular velocity of ± 200°/s and a peak angular acceleration of 2500 - 3000°/s. The vHIT specifically quantifies the VOR-gain which is the ratio of the corrective eye movement response to the passive head movement stimulus. The perfect VOR-gain is thus 1.0 – the corrective eye movement is exactly equal and opposite of the head movement. A VOR-gain of 1.0 suggests that the corrective eye movement exactly corrects for the head movement and thus the retinal image remains stable during the head movement (MacDougall and Curthoys 2012:1). It is important to note that according to Halmagyi *et al* (2017:1), apart from the use of high-speed video-oculography (VOG) such as the vHIT, the HIT gain may also be quantified using the search coil system. The search coil system is considered expensive, complicated and a semi-invasive technique that never translated from the research to practice (Halmagyi *et al* 2017:1).

In order to determine the various measures used to VOR-gain dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.20., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “vestibulo-ocular reflex”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

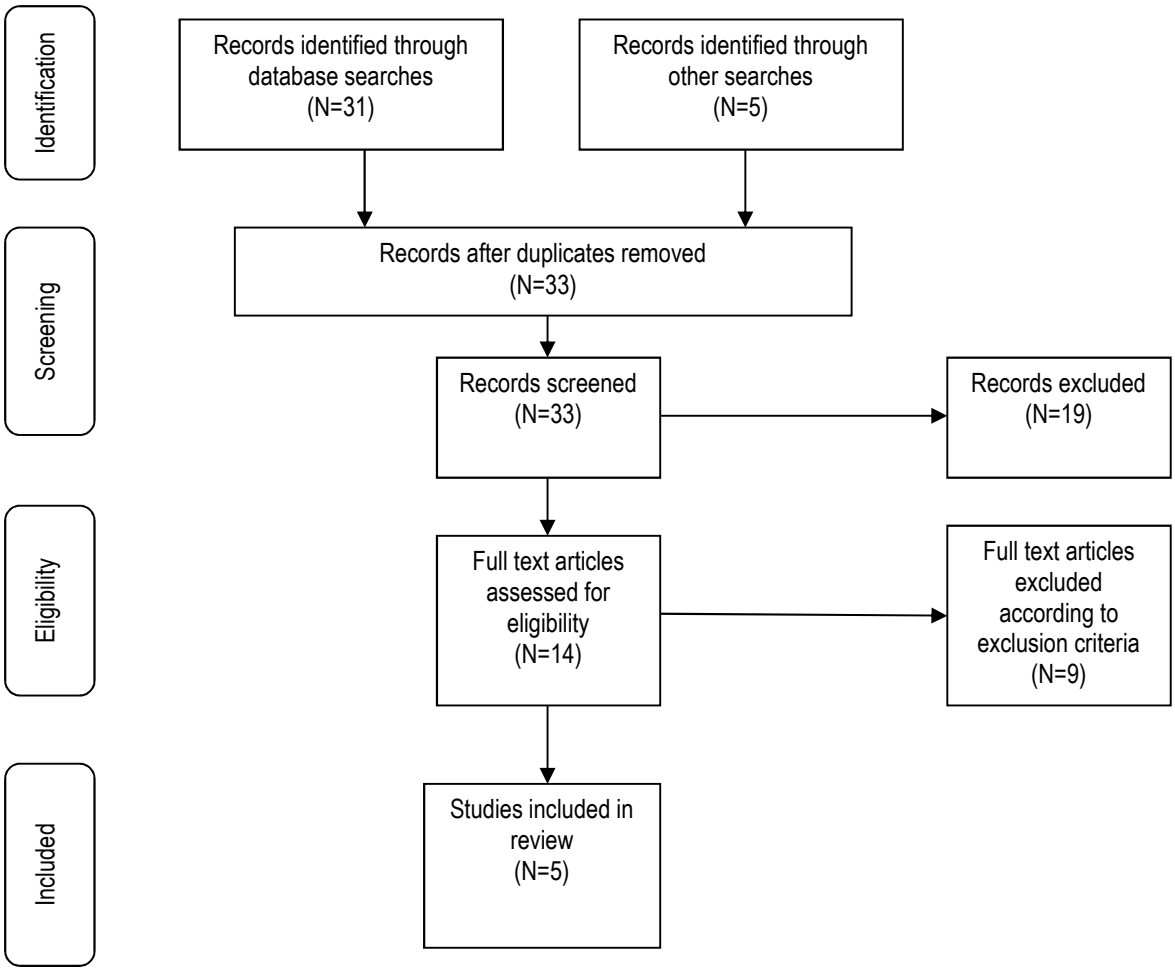


Figure 2.20.: Results of the literature search strategy on the various measures used to quantify VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA Flow diagram, Moher *et al* 2015:1).

Five (5) articles were critically reviewed and an assessment of the quality of evidence was completed. Of the five (5) articles appraised, two (2) were prospective observational studies and three (3) were case studies. Articles appraised are presented in Table 2.21.

Table 2.21.: Appraised articles on the various measures used to quantify VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=5)				
Level of Evidence				
I (N=2)	**II**	**III**	**IV** (N=3)	**V**
Chen *et al* (2014:83)			Park *et al* (2013:1576)	
Mitsutake *et al* (2017:745)			Kim *et al* (2014:121)	
			Baek *et al* (2015:279)	

Findings of the literature reviewed indicated that the VOR in post-stroke patients were quantified using three (3) methods of assessment that included the head impulse test (HIT) using the search coil system (Park *et al* 2013:1576; Chen *et al* 2014:83; Kim *et al* 2014:121), bedside HIT (Baek *et al* 2015:279) and GST (Mitsutake *et al* 2017:745). Park *et al* (2013:1576), Chen *et al* (2014:83), Kim *et al* (2014:121) assessed the VOR with the head impulse test (HIT) using the search coil system to quantify the VOR-gain in the respective study samples. Baek *et al* (2015:279) assessed the VOR of one (1) patient with unilateral circumscribed cerebellar lesion near the flocculus using a bedside HIT. The absence of objective quantification of the VOR of post-stroke patients may result in limited accuracy in the quantification of the VOR-gain compared to the detailed assessment of the VOR using objective measures such as the vHIT. Choi *et al* (2018:90) postulated that recent studies that evaluated HITs using magnetic search coils or video-based techniques such as vHIT, have demonstrated that specific patterns of HIT abnormalities are associated with central vestibular dysfunction. Although patients with central vestibular dysfunction may present with 'normal' clinical HITs, discrepancies have been observed between clinical and quantitative HITs in patients with central vestibular dysfunction (Choi *et al* 2018:90). A recent study by Choi *et al* (2018:90) demonstrated that patients with lesions involving the central vestibular system that includes the vestibular nucleus, nucleus prepositus hypoglossi or flocculus, may present with vestibular hypofunction as result of significantly reduced

unilateral or bilateral horizontal VOR-gain. Patients with diffuse cerebellar lesions may present with vestibular hyperfunction as result of an increased (hyperactive) horizontal VOR-gain (Choi *et al* 2018:90). Choi *et al* (2018:90) remarked that the identification and definition of differences in patterns observed during the assessment of the VOR may aid therapists to localise the lesions in the central vestibular system to facilitate the management of patients with impaired reflexive control of gaze post-stroke. The second feature of reflexive control of gaze to be considered, is dynamic visual acuity.

(ii). Dynamic visual acuity

Dynamic visual acuity (DVA) is the measurement of visual acuity during head movement in relation to baseline static visual acuity (SVA) (Swanenburg, Wild, Straumann and De Bruin 2018:1). Similar to the measurement of SVA, DVA is measured as the logarithm of the minimal angle of resolution (LogMAR) (Tusa 2007:131). Dynamic visual acuity may be quantified by the LogMar chart (non-computerised), computerised standard optotype Landolt C-ring test (Swanenburg *et al* 2018:1), computerised letter E test (Tusa 2007:131; Li *et al* 2014:1; Mitsutake *et al* 2017:745).

In order to determine the various measures used to quantify impaired dynamic visual acuity in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.21., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “dynamic visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify reduced dynamic visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

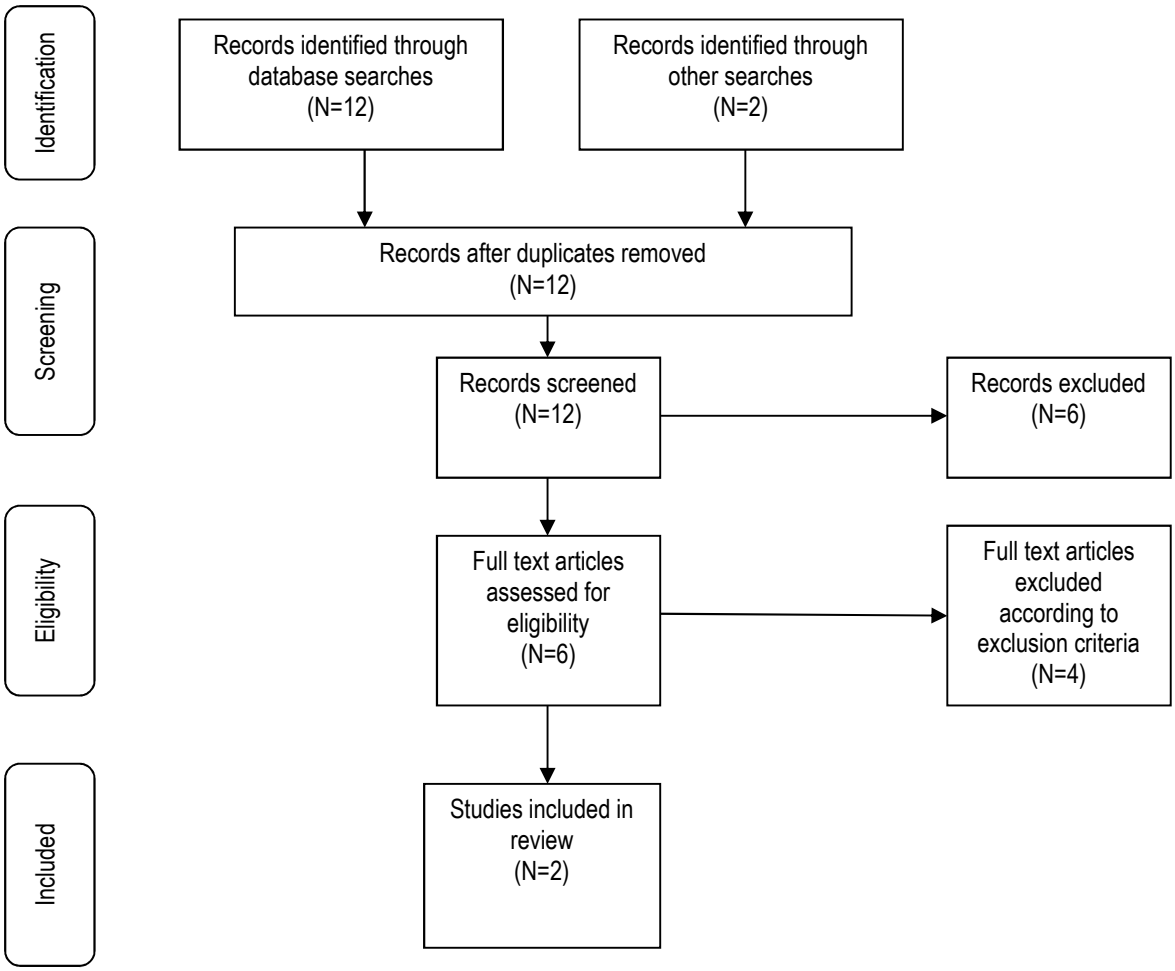


Figure 2.21.: Results of the literature search strategy on the various measures used to quantify reduced dynamic visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Two (2) articles were critically reviewed and an assessment of the quality of evidence was completed. Of the two (2) articles appraised, one (1) was a prospective observational study (Mitsutake *et al* 2017:745) and the other article a non-randomised case control study (Niwa *et al* 2015:203). Articles appraised are presented in in Table 2.22.

Table 2.22.: Appraised article on the various measures used to quantify reduced dynamic visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population.

Article appraised for the quality of evidence (N=2)				
Level of Evidence				
I (N=1)	**II**	**III** (N=1)	**IV**	**V**
Mitsutake *et al* (2017:745)		Niwa *et al* (2015:203)		

Mitsutake *et al* (2017:745) assessed dynamic visual acuity using a computerised letter E test. Patients were positioned (seated) 1.5m from a computer screen in a well-lit room and were asked to perform a gaze-stability test. During completion of the GST, head velocity and movement were respectively measured and monitored using a head-mounted accelerometer and a webcam. Niwa *et al* (2015:203) quantified dynamic visual acuity using a HI-10 testing device while patients were seated facing a semi-circular screen with their chins placed on a chin-support to keep their heads stationary. The patients followed a visual target (a Landolt C-ring) that moved from left to right on the screen. The subjects were required to judge the direction of the gap of the Landolt C-ring (up, down, right or left) by pushing one of four buttons that corresponded to each direction, followed by the recording of the rotating velocity of the visual target at that moment. Patients who were able to identify the gap in the C-ring correctly at a high velocity, were considered to have no DVA impairment. If patients were unable to identify the gap of the visual target (Landolt C-ring), the presence of DVA impairment was documented. No articles were found that assessed DVA using the non-computerised LogMar chart in post-stroke patients.

The third clinical feature of central vestibular dysfunction on the level of body structure and function is saccule and inferior vestibular nerve function, discussed in Section 2.4.1.3.

2.4.1.3. Saccule and inferior vestibular nerve function

The cervical vestibular-evoked myogenic potential (cVEMP) is the only test for the assessment of the saccule and inferior vestibular nerve function (Section 2.3.1.3) (Tusa 2007:132). In order to determine the various measures used to quantify saccule and inferior vestibular nerve function in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.22., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “saccule”; inferior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

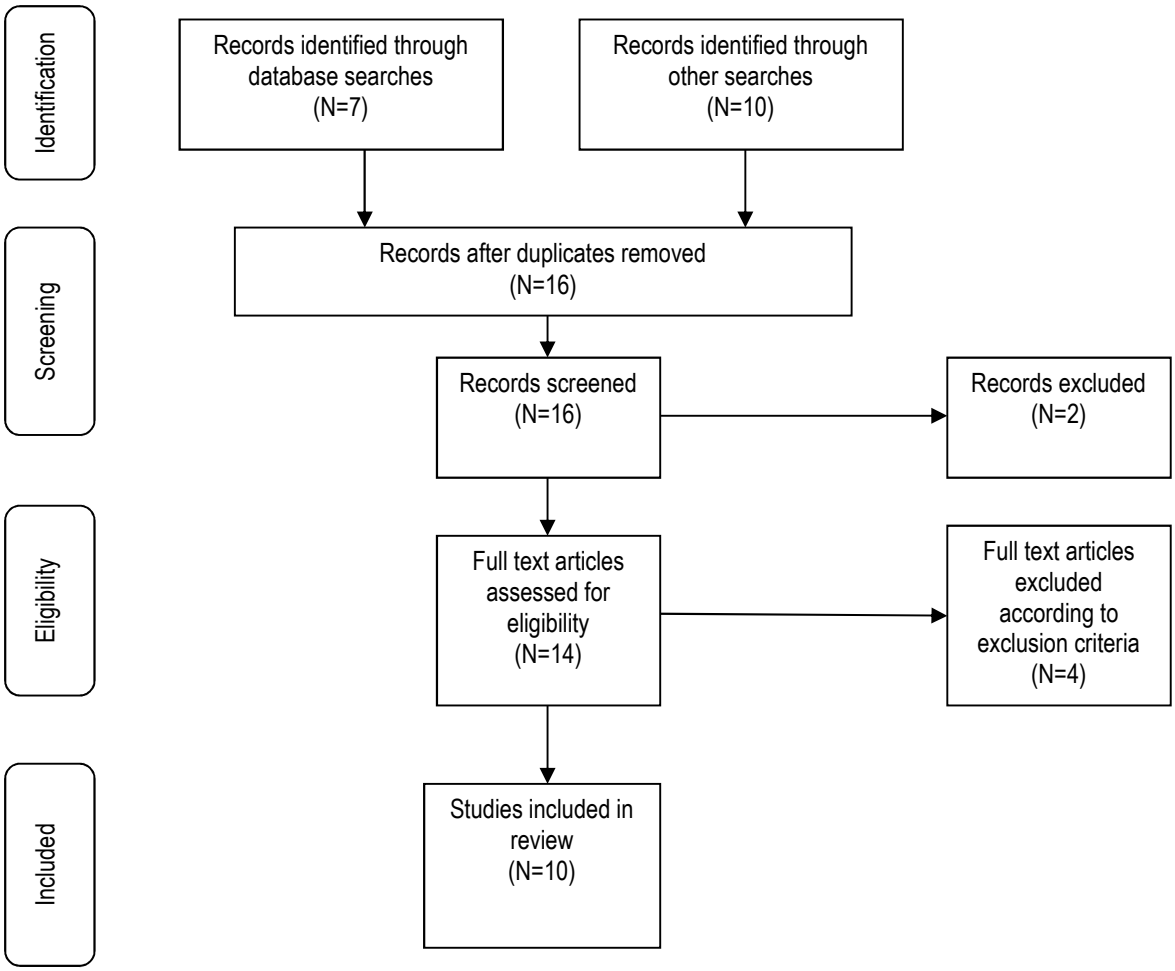


Figure 2.22.: Results of the literature search strategy on the various measures used to quantify impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Ten (10) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included nine (9) prospective observational studies and a case study. Articles appraised are presented in Table 2.23.

Table 2.23.: Appraised articles on the various measures used to quantify impaired saccule and inferior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=10)				
Level of Evidence				
I (N=9)	**II**	**III**	**IV** (N=1)	**V**
Chen and Young (2003:990)			Tseng and Young (2010:267)	
Pollak *et al* (2006:227)				
Heide *et al* (2010:1102)				
Kim *et al* (2010:825)				
Ahn *et al* (2011:114)				
Kim *et al* (2011:1)				
Su and Young (2011:923)				
Choi *et al* (2014:362)				
Kim *et al* (2016:2424)				

All ten (10) articles appraised utilised cVEMP to quantify saccule and inferior vestibular nerve function in post-stroke patients (Chen and Young 2003:990; Pollak *et al* 2006:227; Heide *et al* 2010:1102; Kim *et al* 2010:825; Tseng and Young 2010:267; Ahn *et al* 2011:114; Kim *et al* 2011:1; Su and Young 2011:923; Choi *et al* 2014:362; Kim *et al* 2016:2424). The fourth clinical feature of central vestibular dysfunction on the level of body structure and function is utricle and superior vestibular nerve function, discussed in Section 2.4.1.4.

2.4.1.4. Utricle and superior vestibular nerve function

Utricle and superior vestibular nerve function may be quantified with ocular vestibular-evoked myogenic potential (oVEMP) (Section 2.3.1.4) and subjective visual vertical (SVV) test (Tusa 2007:133). In the study, the quantification of utricle and superior vestibular nerve function are limited to oVEMP testing; SVV will thus not be further addressed within this study as the assessment of SVV is considered beyond the scope of this study. In order to determine the various measures used to quantify utricle and superior vestibular nerve function in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.23., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “utricle”; “superior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

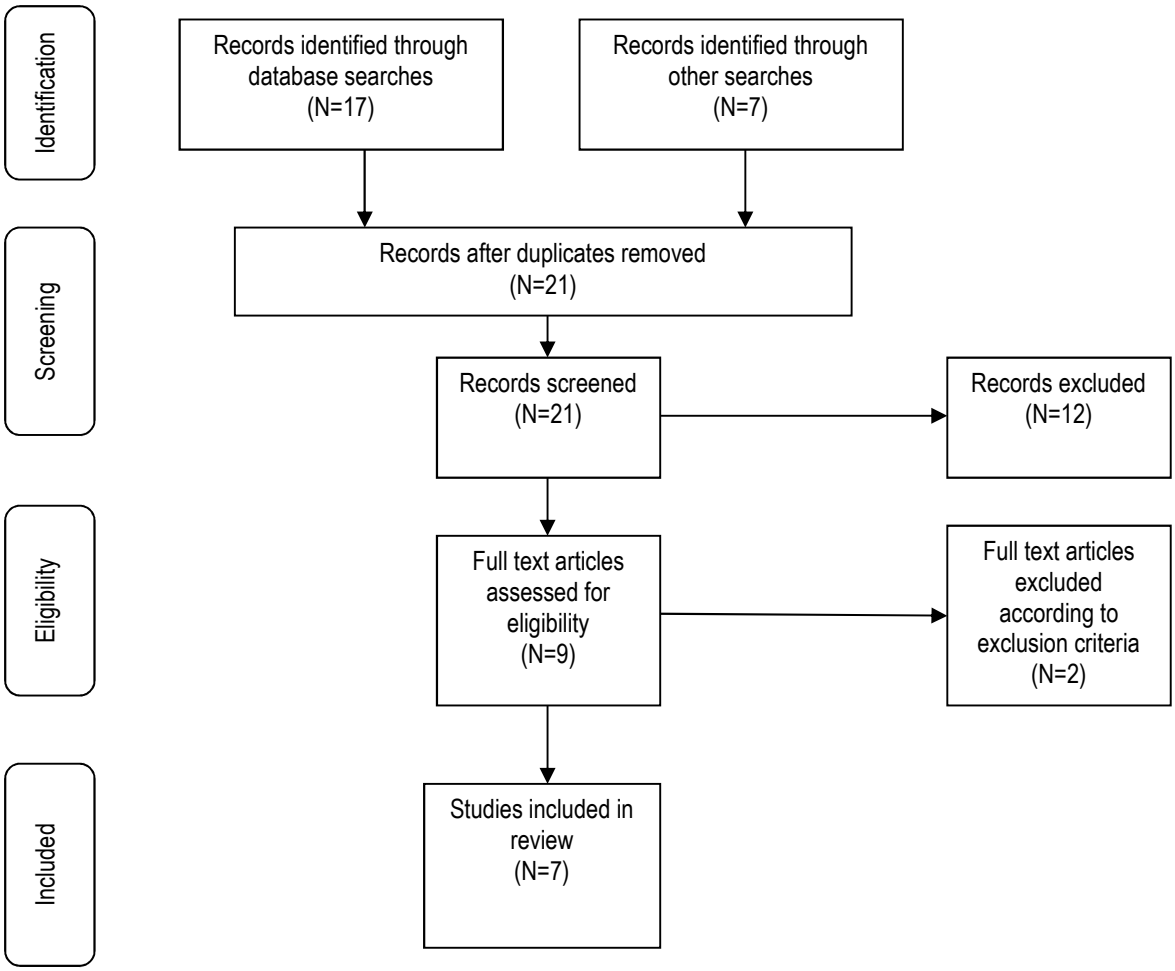


Figure 2.23.: Results of the literature search strategy on the various measures used to quantify impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Seven (7) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included five (5) prospective observational studies and two (2) case studies. Articles appraised are presented in Table 2.24.

Table 2.24.: Appraised articles on the various measures used to quantify impaired utricle and superior vestibular nerve function due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=7)				
Level of Evidence				
I (N=5)	**II**	**III**	**IV** (N=2)	**V**
Su and Young (2011:923)			Park *et al* (2013:1576)	
Oh *et al* (2013:770)			Kim *et al* (2014:121)	
Choi *et al* (2014:362)				
Kim *et al* (2014:1042)				
Kim *et al* (2016:2424)				

All seven (7) articles appraised utilised oVEMP to quantify utricle and superior vestibular nerve function in post-stroke patients (Su and Young 2011:923; Oh *et al* 2013:770; Park *et al* 2013:1576; Choi *et al* 2014:362; Kim *et al* 2014:1042; Kim *et al* 2014:121; Kim *et al* 2016:2424). The fifth clinical feature of central vestibular dysfunction on the level of body structure and function to consider is higher vestibular function, discussed in Section 2.4.1.5.

2.4.1.5. Higher vestibular function

In the current study, the management of impaired higher vestibular function is limited to the impairment of residual oculomotor visual performance, visual-perceptual function and cognitive function. The first feature of higher vestibular function to be discussed is residual oculomotor visual performance function.

(i). Residual oculomotor visual performance function

Stroke patients' residual oculomotor visual performance is quantified to differentiate between residual oculomotor visual performance and visual-perceptual dysfunction in the assessment of higher vestibular function due to central vestibular dysfunction post-

stroke (Chaikin 2013:867). In order to determine the various measures used to quantify residual oculomotor visual performance in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.24., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “residual oculomotor visual performance”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

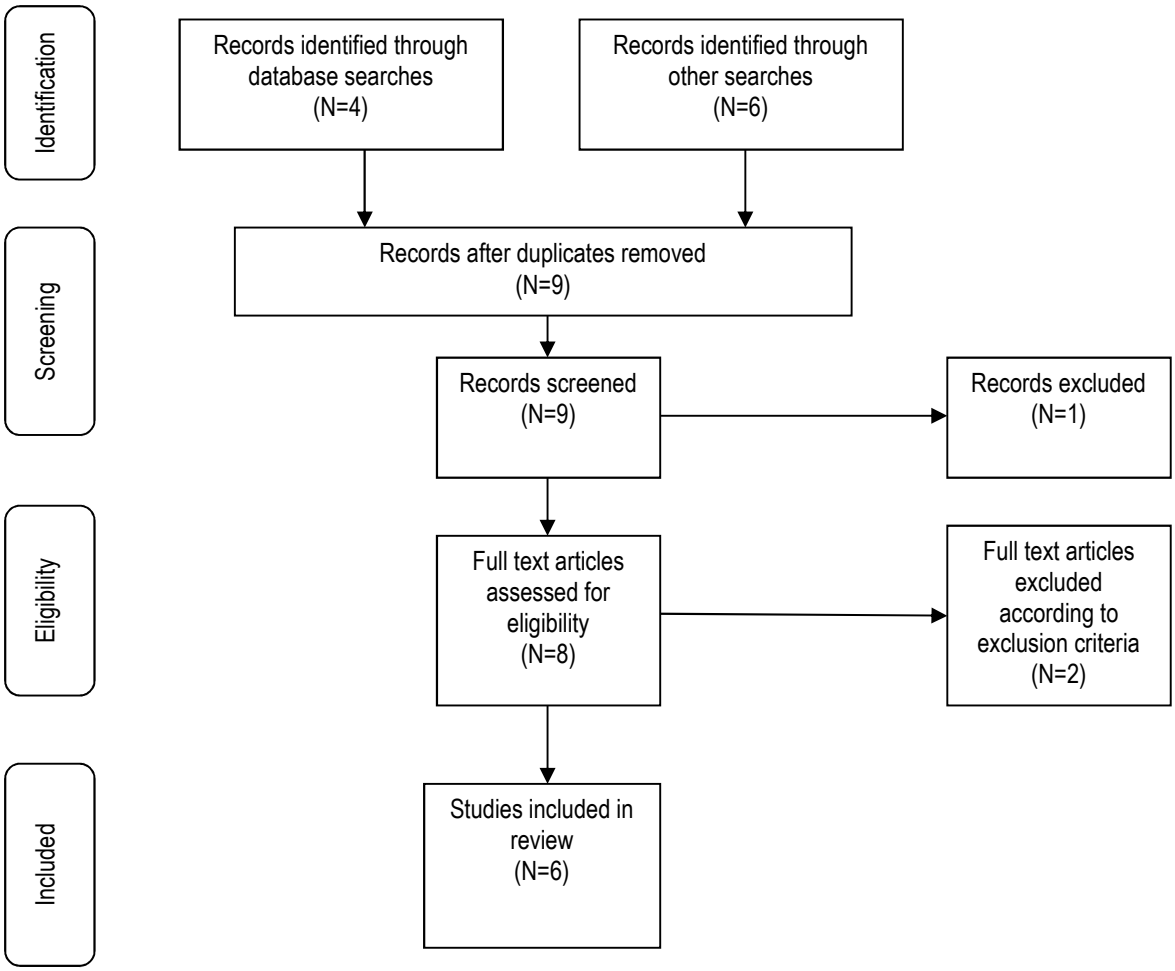


Figure 2.24.: Results of the literature search strategy on the various measures used to quantify impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Six (6) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a RCT, two (2) prospective observational studies, a case control study, a case study and case series. Articles appraised are presented in Table 2.25.

Table 2.25.: Appraised articles on the various measures used to quantify impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=6)				
Level of Evidence				
I (N=3)	**II**	**III** (N=1)	**IV** (N=2)	**V**
Gottesman *et al* (2008:1439)		Cate and Richards (2000:326)	Kapoor *et al* (2004:1667)	
Rowe *et al* (2011:406)			Ciuffreda *et al* (2006:9)	
Van Wyk *et al* (2014:856)				

The outcome of the literature appraised, indicated that residual oculomotor visual performance in post-stroke patients were quantified using various measures, such as the assessment of reading acuity (Cate and Richards 2000:326), single-line and multiple-line simulated reading objectively recorded with a computer-based Visagraph device (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9), subjective reading-related questionnaire (Kapoor *et al* 2004:1667), oral reading (Gottesman *et al* 2008:1439), subjective description of the inability to read (despite being able to see the text) (Rowe *et al* 2011:406) and the King-Devick Test (Markowitz 2006:289; Galetta *et al* 2011:1456; Chaikin 2013:867; Van Wyk *et al* 2014:856).

Cate and Richards (2000:326) showed that reading acuity was assessed as part of a basic visual skill screening battery. Although Cate and Richards (2000:326) mentioned that the visual skill screening battery was selected based on the battery's 'established' reliability and short administration time, no information was provided on the specific measure used to assess reading acuity. The authors only stated that information on the basic visual skill screening battery may be acquired from the first author.

Both Kapoor *et al* (2004:1667) and Ciuffreda *et al* (2006:9) quantified residual oculomotor visual performance by recording a single-line and multiple-line simulated reading with a computer-based Visagraph device. Kapoor *et al* (2004:1667) also utilised a reading-related questionnaire which consisted of a subjective assessment of patients' own reading ability. Alternatively, Gottesman *et al* (2008:1439) assessed oral

reading that required a patient to read 30 words that were displayed over two (2) columns and five (5) sentences on a single sheet of paper.

Rowe *et al* (2011:406) diagnosed the presence of 'alexia' which is an acquired reading disorder (Pflugshaupt *et al* 2009:1907) when patients subjectively described an inability to read (despite being able to see the letters), the inability to decipher the words or to understand the meaning of the text. Lastly, Van Wyk *et al* (2014:856) quantified residual oculomotor visual performance using the King-Devick Test©. The King-Devick Test© consists of three (3) sub-tests. The measurement of residual oculomotor functions of post-stroke patients is based on the measurement of the speed with which the patient can read the three (3) sub-tests aloud (Markowitz 2006:289; Galetta *et al* 2011:1456; Chaikin 2013:867). The level of difficulty increases as the patient progresses through the three (3) sub-tests in the sense that the King-Devick Sub-test 2 requires larger saccadic eye movements and visual search strategies compared to King-Devick Sub-test 1. The King-Devick Sub-test 3 requires even larger saccadic eye movements and visual search strategies compared to King-Devick Sub-test 2.

The second feature of higher vestibular function to be discussed is visual-perceptual function.

(ii). Visual-perceptual function

The bilaterally organised central vestibular network demonstrates structural neural connectivity with limbic, hippocampal, cerebellar and non-vestibular cortical structures via numerous polysynaptic pathways and multisensory convergence to mediate higher vestibular function that includes visual-perceptual function (Brandt *et al* 2014:47). Visual-perceptual dysfunction in post-stroke patients may be quantified by conventional paper-and-pencil tests such as the Star Cancellation Test (Wilson, Cockburn and Halligan 1987:98; Van Wyk *et al* 2014:856). The Star Cancellation Test was developed to identify the presence of visual-perceptual dysfunction, specifically unilateral spatial neglect and visual-spatial disorders, in participants who have suffered a stroke. The Star Cancellation Test's scoring entail (i) the average number of errors made during the completion of the test and (ii) the time taken to complete the test (speed). In order to determine the various measures used to quantify visual-perceptual dysfunction in the sub-acute post-stroke population, the literature search strategy

indicated in Figure 2.25., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “visual-perceptual dysfunction”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

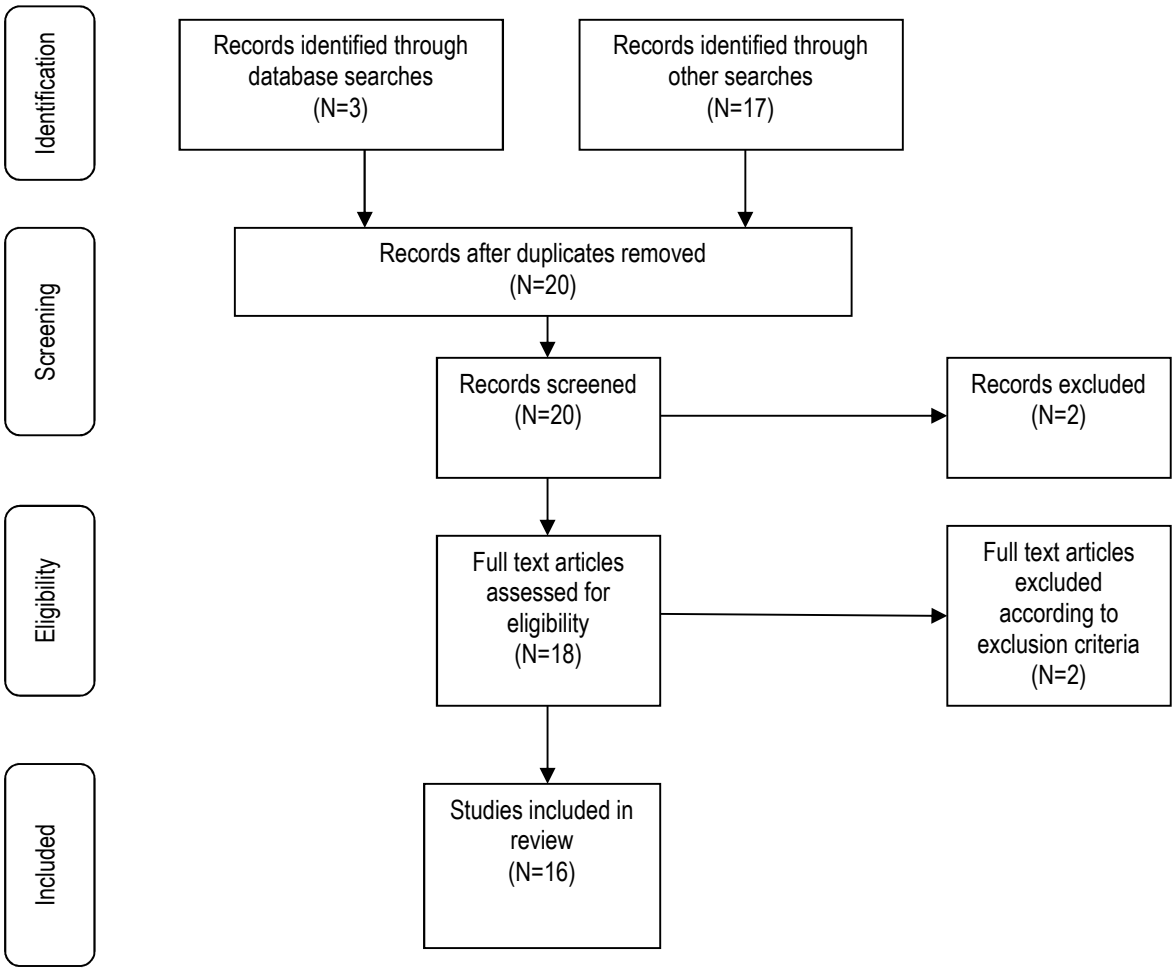


Figure 2.25.: Results of the literature search strategy on the various measures used to quantify visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Sixteen (16) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a single-centre double blind matched-pair RCT, five (5) prospective observational studies, seven (7) case control studies, two (2) retrospective studies and a case study. Articles appraised are presented in Table 2.26.

Table 2.26.: Appraised articles on the various measures used to quantify visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=16)				
Level of Evidence				
I (N=6)	**II**	**III** (N=9)	**IV** (N=1)	**V**
Kizony and Katz (2002:82)		Behrmann *et al* (1997:1445)	Olk *et al* (2002:306)	
Gottesman *et al* (2008:1439)		Karnath *et al* (1998:2357)		
Van Nes *et al* (2009:819)		Bailey *et al* (2000:139)		
Nijboer *et al* (2013:2021)		Cate and Richards (2000:326)		
Vossel *et al* (2013:1782)		Fruhmann-Berger and Karnath (2005:1194)		
Van Wyk *et al* (2014:856)		Ng *et al* (2005:2138)		
		Van Kessel *et al* (2010:603)		
		Kettunen *et al* (2012:359)		
		Herron (2016:69)		

Findings of the literature reviewed indicated that visual-perceptual function in post-stroke patients were quantified using various measures which include the (a) Letter Detection Task (Behrmann *et al* 1997:1445); (b) Letter Cancellation Test (Karnath *et al* 1998:2357; Cate and Richards 2000:326; Olk *et al* 2002:306; Fruhmann-Berger and Karnath 2005:1194; Van Nes *et al* 2009:819; Van Kessel *et al* 2010:603; Kettunen *et al* 2012:359; Nijboer *et al* 2013:2021); (c) Line Bisection Test (Karnath *et al* 1998:2357; Bailey *et al* 2000:139; Cate and Richards 2000:326; Gottesman *et al* 2008:1439; Kettunen *et al* 2012:359; Nijboer *et al* 2013:2021; Vossel *et al* 2013:1782); (d) Copying

(Karnath *et al* 1998:2357; Bailey *et al* 2000:139; Fruhmann-Berger and Karnath 2005:1194; Gottesman *et al* 2008:1439; Kettunen *et al* 2012:359; Vossel *et al* 2013:1782); (e) Star Cancellation Test (Bailey *et al* 2000:139; Kizony and Katz 2002:82; Olk *et al* 2002:306; Van Nes *et al* 2009:819; Van Kessel *et al* 2010:603; Kettunen *et al* 2012:359; Vossel *et al* 2013:1782; Van Wyk *et al* 2014:856); (f) 'Baking Tray Task' (Bailey *et al* 2000:139); (g) Clock-drawing (Bailey *et al* 2000:139; Vossel *et al* 2013:1782); (h) Motor-Free Visual Perception Test (MVPT) (Bailey *et al* 2000:139); (i) Bells test (Fruhmann-Berger and Karnath 2005:1194); (j) Line Cancellation Test (Gottesman *et al* 2008:1439; Vossel *et al* 2013:1782); (k) Visual extinction (Gottesman *et al* 2008:1439); (l) Tactile extinction (Gottesman *et al* 2008:1439); (m) Line Crossing (Kettunen *et al* 2012:359); (n) Representational drawing (Kettunen *et al* 2012:359); (o) clinical observation only (Ng *et al* 2005:2138); and (p) occupational therapy vision screening tool (Herron 2016:69).

The presence of visual-perceptual function in the study-sample reported by Ng *et al* (2005:2138) was based on information obtained from a stroke registry over an eight (8)-year period. The information was based upon clinical observation only (Ng *et al* 2005:2138). The absence of objective quantification of visual-perceptual dysfunction may have resulted in limited accuracy in the identification and quantification of visual-perceptual dysfunction compared to detailed visual-perceptual function assessment using objective measures such as the Star Cancellation Test to determine the prevalence of visual-perceptual dysfunction in patients post-stroke.

Herron (2016:69) quantified visual-perceptual function using the occupational therapy vision screening tool to measure visual-perceptual function of patients post-stroke. Although the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study as stated by Herron (2016:73); the psychometric properties of the vision screening tool were not determined prior to the current study. In the current study, the visual-perceptual function of post-stroke patients were assessed using the Star Cancellation Test (Section 2.4.3). The validity and reliability of the Star Cancellation Test, are discussed in Section 3.1.7.1.

The third feature of higher vestibular function to be discussed is cognitive function.

(iii). Cognitive function

Cognitive functions which result from the integration of the central vestibular network at the cortical level, hippocampus and limbic system, include the internal representation of an individual's body schema, the internal model of the surrounding space of an individual, multisensory motion perception, attention, spatial memory and navigation (Brandt *et al* 2014:47). Pineault, Pearson, Wei, Kamil, Klatt and Agrawal (2019:1) assessed the association between saccule and semi-circular canal impairments and cognitive performance among vestibular patients (N=54) compared to age-matched healthy controls (N=125). Patients' saccule and semi-circular canal function were measured using cVEMP and caloric irrigation respectively. Patients' cognitive performance was measured using the Trail-Making test and Benton Visual Retention test part-C. Findings of the study by Pineault *et al* (2019:1) indicated that the presence of bilateral saccule and semi-circular canal impairments may significantly affect various domains of cognitive performance. The cognitive performance of patients in the study was significantly poorer relative to the age-matched healthy adults. The results of the study by Pineault *et al* (2019:1) suggest that the evaluation of cognitive function should be included in the management of vestibular patients with saccule and semi-circular canal impairments.

Cognitive function in post-stroke patients may be quantified by conventional paper-and-pencil tests such as the MMSE. The MMSE was developed to provide a quantitative assessment of cognitive impairment and to record cognitive changes over time (Folstein, Folstein and McHugh 1975:189). In order to determine the various measures used to quantify cognitive impairment in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.26., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "measure"; "quantify"; "cognitive impairment"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

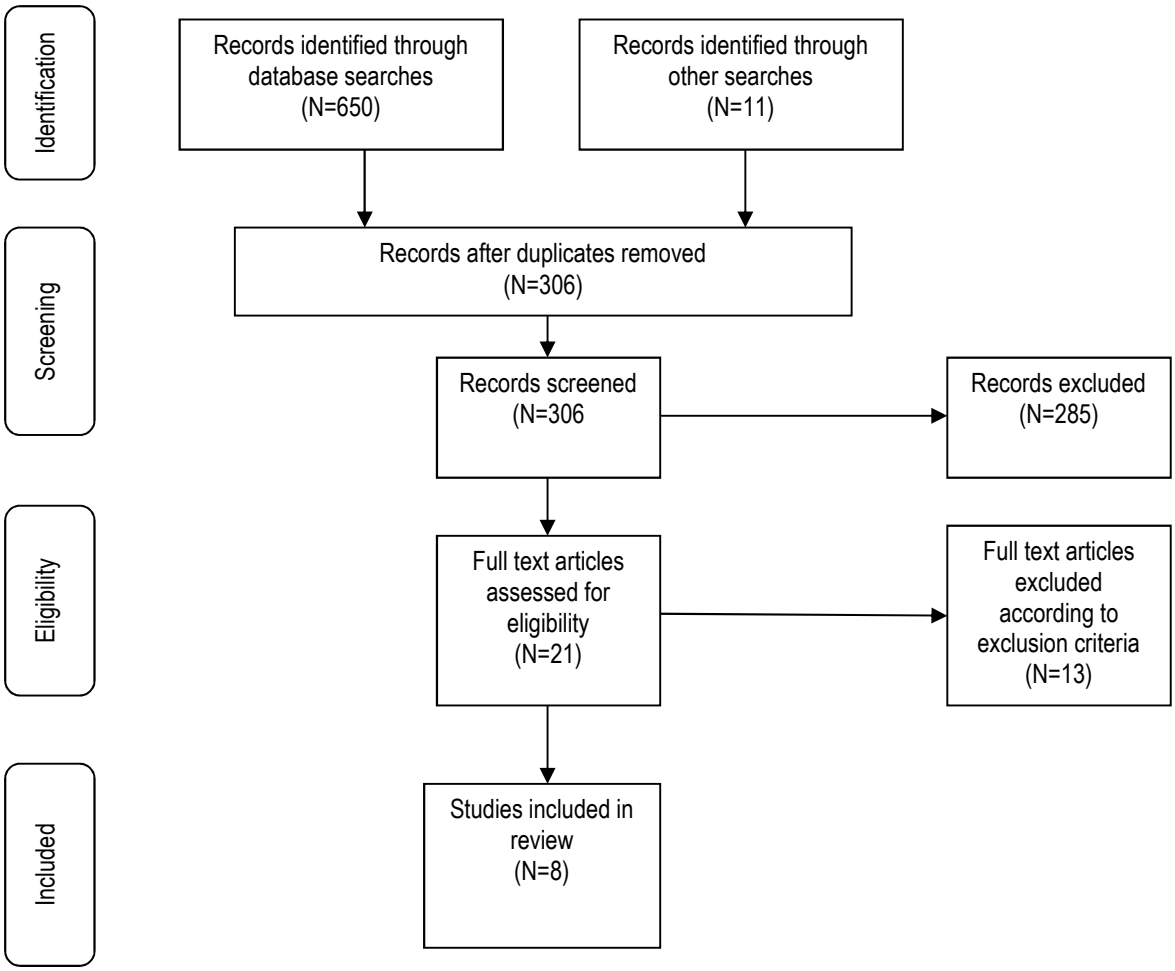


Figure 2.26.: Results of the literature search strategy on the various measures used to quantify cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Eight (8) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included three (3) prospective observational studies, two (2) case control studies, a retrospective study, review (expert opinion) and editorial commentary (expert opinion). Articles appraised are presented in Table 2.27.

Table 2.27.: Appraised articles on the various measures used to quantify cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=8)				
Level of Evidence				
I (N=3)	**II**	**III** (N=3)	**IV**	**V** (N=2)
Kizony and Katz (2002:82)		Bailey *et al* (2000:139)		Anderson (2013:242)
Påhlman *et al* (2011:1952)		Ng *et al* (2005:2138)		Willard and Lueck (2014:75)
Nijboer *et al* (2013:2021)		Dong *et al* (2013:337)		

Findings of the literature reviewed indicated that cognitive function in post-stroke patients were quantified using various measures that include the (a) Thinking Operations from the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) battery (Kizony and Katz 2002:82); (b) Contextual Memory Test (Kizony and Katz 2002:82); (c) 'Exploratory Motor Task' (Bailey *et al* 2000:139); (d) Rey Complex Figure-copy (Kizony and Katz 2002:82); (e) COGNISTAT (Kizony and Katz 2002:82); (f) FIM cognition score (Ng *et al* 2005:2138); (g) Cognitive Impairment Questionnaire (CIMP-QUEST) (Påhlman *et al* 2011:1952); and (h) MMSE (Påhlman *et al* 2011:1952; Dong *et al* 2013:337; Nijboer *et al* 2013:2021).

In the current study, the cognitive function of post-stroke patients was assessed using the MMSE (Section 2.4.3). The validity and reliability of the MMSE are discussed in Section 3.1.7.1.

The sixth and final clinical feature of central vestibular dysfunction on the level of body structure and function to consider, is the presence of anxiety and/or depression in the sub-acute phase post-stroke. The level of anxiety and/or depression post-stroke, is discussed in Section 2.4.1.6.

2.4.1.6. Level of anxiety and/ or depression post-stroke

As vestibular dysfunction, anxiety and/or depression may present concurrently in post-stroke patients (Section 2.3.1.6), it is important to recognise and acknowledge the complex interaction between the vestibular system anxiety and depression in post-stroke patients. Stroke patients' participation in rehabilitation, functional ability, quality of life and social integration may be affected by their level of anxiety and depression post-stroke (Ali *et al* 2013:133; Hepworth *et al* 2016:1). The level of anxiety and depression present in stroke patients may be assessed with an outcome measure such as the Hospital Anxiety and Depression Scale (HADS). In order to determine the various outcome measures used to quantify the level of anxiety and/or depression in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.27, was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "measure"; "quantify"; "anxiety"; "depression'; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

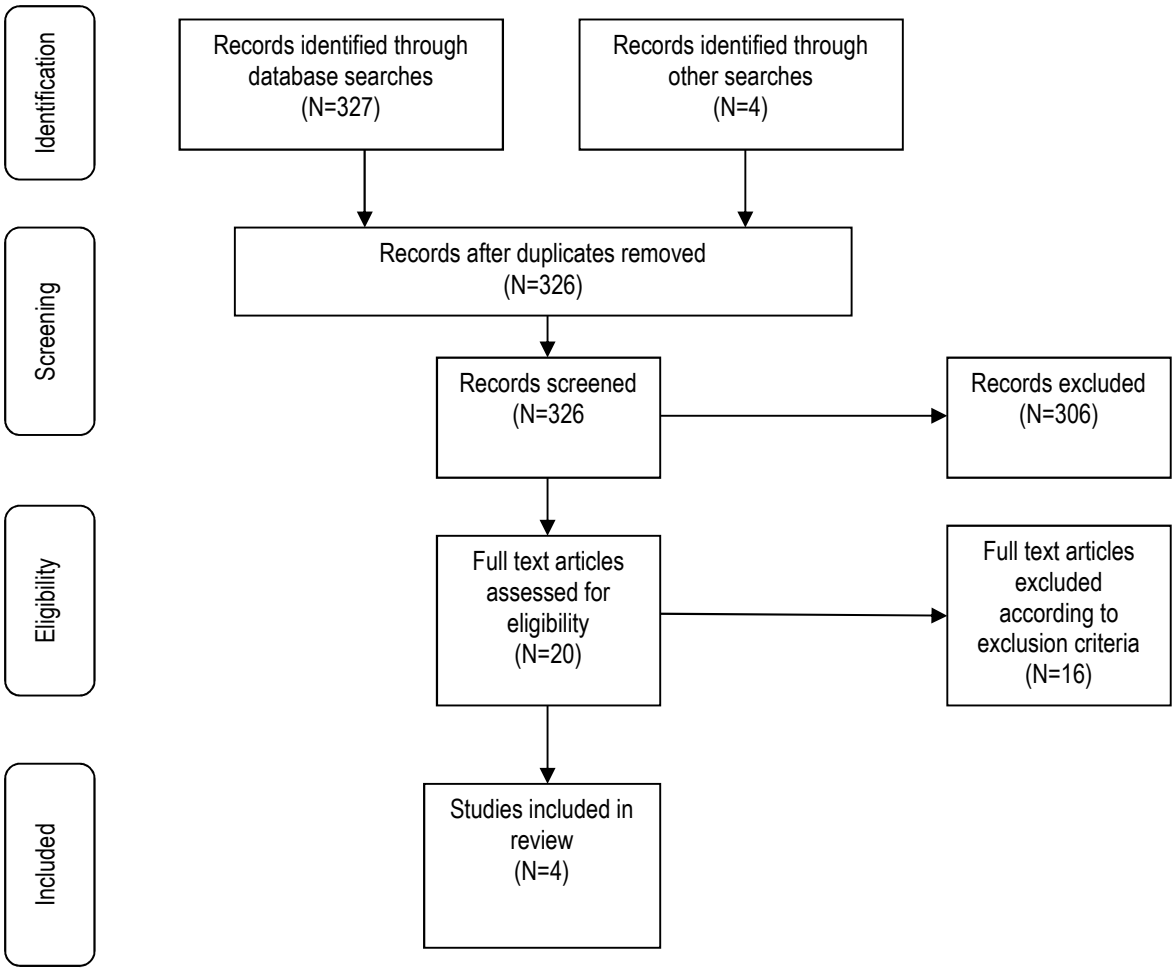


Figure 2.27.: Results of the literature search strategy on the various measures used to quantify anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Four (4) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a RCT, a prospective observational study, a retrospective study and a case-study. Articles appraised are presented in Table 2.28.

Table 2.28.: Appraised articles on the various measures used to quantify anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=4)				
Level of Evidence				
I (N=1)	**II** (N=1)	**III** (N=1)	**IV** (N=1)	**V**
Edwards *et al* (2006:45)	Meli *et al* (2007:185)	Ali *et al* (2013:133)	Nagaratnam *et al* (2005:253)	

The presence of anxiety and/or depression in post-stroke patients were quantified by the; (a) Geriatric Depression Scale–Short Form (Edwards *et al* 2006:45); (b) State-Trait Anxiety Inventory (STAI) (Meli *et al* 2007:185); (c) Centre for Epidemiological Studies Depression Scale (CES-D) (Meli *et al* 2007:185); and (d) EQ-5D (Ali *et al* 2013:133).

The method of assessment of level of anxiety and depression used by Ali *et al* (2013:133) was the EQ-5D. The EQ-5D is a visual analogue scale that enable patients to assess their own level of mobility, self-care, 'usual' activities, anxiety/depression and pain/discomfort. The EQ-5D is thus a combined score that quantifies patients' perceived quality of life and is a subjective reflection of their perceived level of anxiety and depression post-stroke. In the current study, the level of anxiety and depression of post-stroke patients were assessed using the HADS (Section 2.4.3). The validity and reliability of the HADS are discussed in Section 3.1.7.1.

Central vestibular dysfunction is also categorised by impairment on activity and participation level that includes: (1) impaired sensorimotor control of balance, mobility and gait; and (2) functional ability. The first activity limitation on activity and participation level to be discussed is sensorimotor control of balance, mobility and gait in Section 2.4.2.

2.4.2. Activity and participation level

2.4.2.1. Impaired sensorimotor balance, mobility and gait

In the current study, the management of sensorimotor balance, mobility and gait were limited to the impairment of functional balance and the ability to modify gait in response to changing task demands. The first feature of sensorimotor balance, mobility and gait to be discussed, is functional balance.

(i). Functional balance

The assessment of functional balance is considered part of standard clinical practice in stroke patients (Winstein *et al* 2016:29). Standardised tests of functional balance assess different aspects of postural control, such as anticipatory postural reactions, during both static and dynamic functional positions (Winstein *et al* 2016:29). The quantification of patients' functional balance also determines their risk of falling and guide the selection and progression of balance exercises aimed to improve patients' sensorimotor balance, mobility and gait post-stroke (Winstein *et al* 2016:29). In order to determine the various measures used to quantify functional balance in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.28., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "measure"; "quantify"; "functional balance"; "sitting balance"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

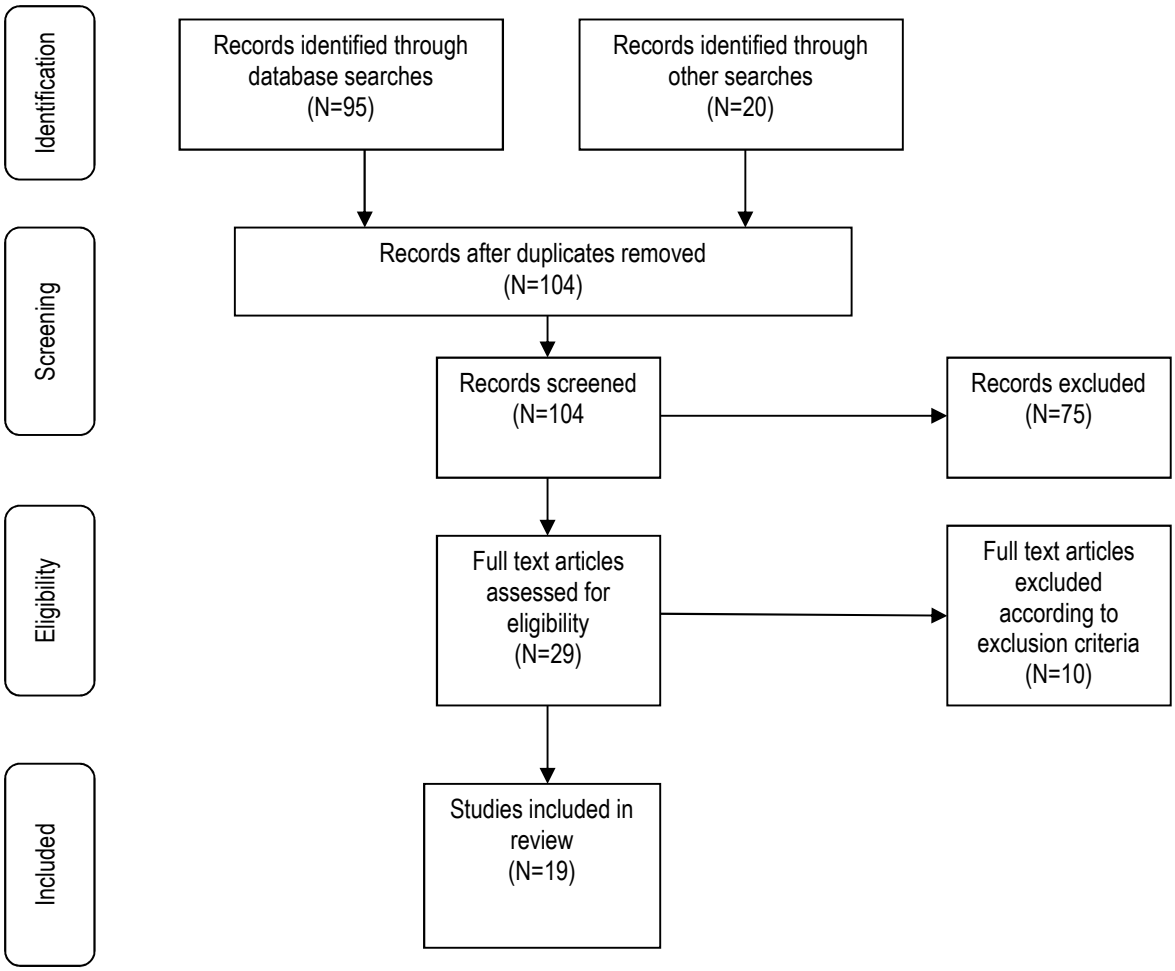


Figure 2.28.: Results of the literature search strategy on the various measures used to quantify impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Nineteen (19) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included three (3) RCTs, five (5) prospective observational studies, seven (7) case control studies and four (4) case series studies. Articles appraised are presented in Table 2.29.

Table 2.29. Appraised articles on the various measures used to quantify impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=18)				
Level of Evidence				
I (N=8)	**II**	**III** (N=6)	**IV** (N=4)	**V**
Stapleton *et al* (2001:437)		Marsden *et al* (2005:677)	De Haart *et al* (2004:886)	
Bonan *et al* (2004:268)		Manor *et al* (2010:458)	Brown *et al* (2006:76)	
Bonan *et al* (2004:274)		Oliveira *et al* (2011:2043)	Smania *et al* (2008:313)	
Wee and Hopman (2005:604)		Bonan *et al* (2013:713)	Schow *et al* (2016:333)	
Van Nes *et al* (2009:819)		Mitsutake *et al* (2014:1799)		
Påhlman *et al* (2011:1952)		Bonan *et al* (2015:521)		
Balci *et al* (2013:259)				
Dai *et al* (2013:477)				

Findings of the literature appraised indicated that functional balance in post-stroke patients were quantified using various measures that include the; (a) Berg Balance Scale (BBS) (Stapleton *et al* 2001:437; Wee and Hopman 2005:604; Van Nes *et al* 2009:819; Oliveira *et al* 2011:2043; Påhlman *et al* 2011:1952; Balci *et al* 2013:259; Bonan *et al* 2013:713; Bonan *et al* 2015:521); (b) Sensory Organization Test (SOT) used with computerized dynamic posturography (EquiTest) (Bonan *et al* 2004:268; Bonan *et al* 2004:274; Smania *et al* 2008:313; Oliveira *et al* 2011:2043); (c) vestibular evoked postural responses obtained using galvanic vestibular stimulation (GVS) (Marsden *et al* 2005:677); (d) Timed “Up and Go” (TUG) test (Brown *et al* 2006:76; Balci *et al* 2013:259; Bonan *et al* 2013:713; Bonan *et al* 2015:521); (e) Activities-Specific Balance Confidence Scale (Brown *et al* 2006:76); (f) Five Times Sit-to-Stand (FTSTS) Test (Brown *et al* 2006:76); (g) foot center of pressure (COP) using a force plate (De Haart *et al* 2004:886; Manor *et al* 2010:458; Bonan *et al* 2013:713; Mitsutake *et al* 2014:1799; Bonan *et al* 2015:521); (h) Modified Clinical Test of Sensory Interaction on Balance (mCTSIB) (Balci *et al* 2013:259); (i) Postural Assessment Scale

(PASS) (Dai *et al* 2013:477); and (j) Balance Evaluation Systems Test (BESTest) (Schow *et al* 2016:333).

The majority of authors used the BBS to quantify patients' functional balance post-stroke (Stapleton *et al* 2001:437; Wee and Hopman 2005:604; Van Nes *et al* 2009:819; Oliveira *et al* 2011:2043; Påhlman *et al* 2011:1952; Balci *et al* 2013:259; Bonan *et al* 2013:713; Bonan *et al* 2015:521). The BBS was developed as a performance-oriented measure of functional balance in elderly individuals (Berg, Wood-Dauphinėe, Williams and Gayton 1989:304; Steffen, Hacker and Mollinger 2002:128; Shumway-Cook and Woollacott 2007:234). The BBS consists of 14 items that are scored on a scale of zero (0) to four (4). A score of zero (0) is given if the participant is unable to perform the task, and a score of four (4) is given if the participant is able to complete the task based on the criteria that has been assigned to it. The maximum total score on the test is 56. The items include simple mobility tasks that include transfers, standing unsupported, sit-to-stand, tandem standing, turning 360° and single-leg stance. In the current study, the quantification of patients' functional balance is limited to the BBS. The BBS presents with an excellent test–retest reliability (ICC=0.88) (Flansbjer, Blom and Brogardh 2012:165) and moderate to excellent relationship with other functional measurements which include the BI (Pearson coefficient r=0.67, N=31), Fugl-Meyer Test motor and balance subscales (Pearson coefficient r=0.62–0.94, N=60), TUG test (Pearson coefficient r=0.76, N=31) and the DGI (Spearman coefficient r=0.67, N=44) (Steffen *et al* 2002:128).

Another method of assessment of functional balance utilised by various researchers, is the Sensory Organization Test (SOT) measured with computerized dynamic posturography (EquiTest) (Bonan *et al* 2004:268; Bonan *et al* 2004:274; Smania *et al* 2008:313; Oliveira *et al* 2011:2043). It is important to highlight that dynamic posturography does not assess peripheral or central vestibular function directly, but is used in research to identify disorders of the vestibulospinal system (Keshner 2007:65). The study samples of Bonan *et al* (2004:268), Bonan *et al* (2004:274), Smania *et al* (2008:313) and Oliveira *et al* (2011:2043) only included patients who present with good functional balance who were able to maintain their balance independently while on the moving platform that is used during the computerised dynamic posturography. Therefore, this method of assessment is only used in stroke patients who present with good functional balance and the ability to walk without supervision.

Marsden *et al* (2005:677) quantified patients' functional balance by means of vestibular evoked postural responses obtained with the use of galvanic vestibular stimulation (GVS) while patients stood with equal weight-bearing on both legs while their heads were facing forward and their eyes were closed. Similar to the use of dynamic posturography, the study sample only included patients who were able to walk ten (10) metres independently (no human assistance), with or without the use of a walking aid. Therefore, this method of assessment is limited to stroke patients who present with good functional balance and the ability to walk ten (10) metres independently, with or without the use of an assistive device.

Brown *et al* (2006:76) utilised the Activities-Specific Balance Confidence (ABC) scale to quantify the functional balance of ten (10) stroke patients. The ABC is a self-report scale where patients rate their level of confidence in their ability to maintain balance while performing sixteen (16) activities (Powell and Myers 1995:28; Brown *et al* 2006:76; Shumway-Cook and Woollacott 2007:259). The overall score for the ABC is calculated by adding the item scores of listed ADLs and then dividing by the total number of listed ADLs. Although the ABC presents with excellent four (4)-week total score test-retest reliability (ICC=0.85; 95% CI 0.68–0.93) and little to fair relationship between the ABC and the TUG (r=-0.40, P<0.01) (Marchetti, Whitney, Redfern and Furman 2011:1884), this method of assessment is mainly used in stroke patients who present with good functional balance and functional ability post-stroke. Patients perceived confidence in their ability to maintain balance while performing specific ADLs assessed by the ABC scale, which include walking up or down stairs, standing on tip-toes and reaching above head-level, sweep the floor, walk outside the house to a car parked in the driveway, walking across a parking lot to a shopping mall and to step onto or off of an escalator while holding onto parcels.

Apart from using the BBS, TUG and DGI, Balci *et al* (2013:259) also implemented the modified Clinical Test of Sensory Interaction on Balance (mCTSIB) to quantify patients' functional balance post-stroke. The mCTSIB measured the velocity of patients' postural sway during four (4) different sensory conditions that included; (1) standing with eyes open (EO) on a firm surface, (2) standing with eyes closed (EC) on a firm surface, (3) standing with EO on a foam surface, and (4) standing with EC on a foam surface. Alternatively, Dai *et al* (2013:477) quantified stroke patients' functional balance using the PASS. Although Dai *et al* (2013:477) mentioned that the PASS

presents with excellent reliability and validity, no additional information on the measure was provided.

Schow *et al* (2016:333) quantified stroke patients' functional balance using the Balance Evaluation Systems Test (BESTest) (Horak, Wrisley and Frank 2009:484). The BESTest consists of thirty-six (36) tasks that assesses six (6) underlying systems that may constrain patients' functional balance. The six (6) systems include the biomechanical system, stability limits / verticality, anticipatory postural adjustments, sensory orientation, postural responses and stability in gait (dynamic balance during gait). Each system is assessed by five (5) to seven (7) tasks and scored on a rating scale from zero (0) to three (3). The BESTest presents with excellent interrater reliability (ICC r=0.91) and the six (6) sections' ICCs ranged between 0.79 and 0.96. The BESTest also presents with a moderate to good relationship with the ABC Scale (r=0.636, P<0.01) (Horak *et al* 2009:484). The second feature of sensorimotor balance, mobility and gait to be discussed is the ability to modify gait in response to changing task demands.

(ii). Ability to modify gait in response to changing task demands

Findings from the study by Gimmon *et al* (2017:3347) demonstrated that central vestibular processing is a control parameter regulating gait. Central vestibular dysfunction may thus result in impaired bilateral coordination of gait Gimmon *et al* (2017:3347) and decreased ability to modify gait in response to changing task demands. In order to determine the various measures used to quantify the ability to modify gait in response to changing task demands in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.29., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "measure"; "quantify"; "ability to modify gait in response to changing task demands"; "gait modification"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

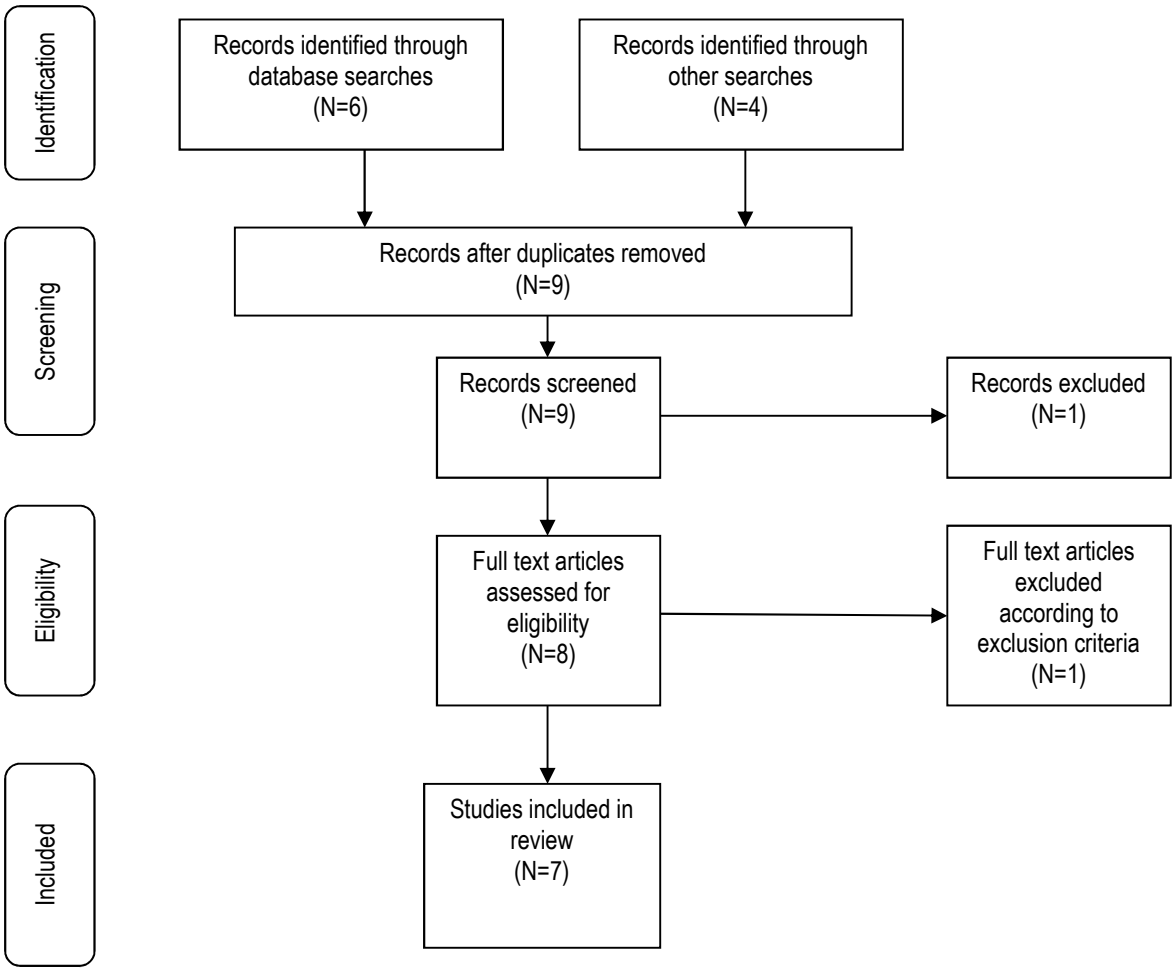


Figure 2.29.: Results of the literature search strategy on the various measures used to quantify impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Seven (7) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, a prospective observational study, two (2) case control studies and two (2) case series studies. Articles appraised are presented in Table 2.30.

Table 2.30.: Appraised articles on the various measures used to quantify impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=8)				
Level of Evidence				
I (N=3)	**II**	**III** (N=2)	**IV** (N=3)	**V**
Bonan *et al* (2004:274)		Lamontagne and Fung (2009:256)	De Haart *et al* (2004:886)	
Van Nes *et al* (2009:819)		Oliveira *et al* (2011:2043)	Brown *et al* (2006:76)	
Balci *et al* (2013:259)			Schow *et al* (2016:333)	

Findings of the literature reviewed indicated patients' ability to modify gait in response to changing task demands post-stroke, were quantified using various measures that include; (a) self-assessment of ease of gait (Bonan *et al* 2004:274); (b) Functional Ambulation Categories (FAC) (De Haart *et al* 2004:886; Van Nes *et al* 2009:819; Oliveira *et al* 2011:2043); (c) DGI (Brown *et al* 2006:76; Balci *et al* 2013:259); (d) motion capture system and eye tracker (Lamontagne and Fung 2009:256); and (e) Ten-Meter Walk Test (10MWT) (Schow *et al* 2016:333).

Bonan *et al* (2004:274) quantified patients' gait post-stroke by implementing a subjective self-assessment of ease of gait using a visual analogue scale (VAS). De Haart *et al* (2004:886), Van Nes *et al* (2009:819) and Oliveira *et al* (2011:2043) utilised the FAC to quantify patients' functional ambulation post-stroke. The FAC distinguishes between six (6) levels of walking ability based upon the amount of physical support the patient required during ambulation (Mehrholz, Wagner, Rutte, Meißner and Pohl 2007:1314). The levels of functional ambulation include; (1) non-functional ambulation (individual is not able to ambulate, ambulates in parallel bars only, or requires supervision or physical assistance from more than one person to ambulate safely outside of parallel bars); (2) ambulatory-dependent for physical assistance Level II (patient requires manual contacts of maximum one person during ambulation on level surfaces to prevent falling, manual contacts are continuous and necessary to support body weight as well as maintain balance and/or assist coordination); (3) ambulatory-

dependent for physical assistance Level I (patient requires manual contact of maximum one (1) person during ambulation on level surfaces to prevent falling, manual contact consists of continuous or intermittent light touch to assist balance or coordination); (4) ambulatory-dependent for supervision (patient is able to physically ambulate on level surfaces without manual contact of another person but for safety requires standby guarding on no more than one person); (5) ambulatory-independent level surfaces only (patient is able to ambulate independently on level surfaces but requires supervision or physical assistance to negotiate stairs, inclines or non-level surfaces) and (6) ambulatory-independent (patient is able to ambulate independently on non-level and level surfaces, stairs, and inclines).

Brown *et al* (2006:76) and Balci *et al* (2013:259) quantified patients' ability to modify gait in response to changing task demands post-stroke using the DGI. The DGI presents with excellent test–retest reliability (ICC=0.96) (N=25) (Jonsdottir and Cattaneo 2007:1410) and (ICC>0.94; 0.91–0.97) (N=48) (Lin, Hsu, Hsu, Wu and Hsieh 2010:2021). The DGI also presents with excellent interrater reliability (ICC=0.96), good to excellent relationship with the BBS (r=0.83) and a moderate to good relationship with the ABC (r=0.68) (Jonsdottir and Cattaneo 2007:1410).

In contrast, Lamontagne and Fung (2009:256) used a motion capture system and eye tracker to measure patients' ability to modify gait in response to changing task demands. Mehrholz *et al* (2007:1314) suggest that expensive laboratory techniques, such as the use of a motion capture system and eye tracker to conduct detailed analyses of kinematic and kinetic variables, may be associated with high costs, limited accessibility and difficulties in interpretation and communication of study results.

Finally, Schow *et al* (2016:333) utilised the 10MWT to quantify the ability to modify gait in response to changing task demands of thirty (30) post-stroke patients. The 10MWT measures walking speed (m/s) and step length over ten (10) metres. Although the 10MWT is a low cost measure that is immediately available and easy to administer, as well as interpret, the test does not assess an individual's ability to change gait speed, perform head turns (vertical and horizontal) during gait, stepping over and around obstacles or ascend and descend stairs (Shumway-Cook and Woollacott 2007:396).

The second activity limitation on activity and participation level as a result of central vestibular dysfunction to consider is functional ability, discussed in detail in Section 2.4.2.2.

2.4.2.2. Functional ability

The assessment of functional ability is considered part of standard clinical practice in post-stroke patients (Winstein *et al* 2016:17). Standardised tests of functional ability assess basic ADLs that include personal self-care and fundamental mobility that patients perform as part of their everyday life. In order to determine the various measures used to quantify functional ability in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.30., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “measure”; “quantify”; “functional ability”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various measures used to quantify impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

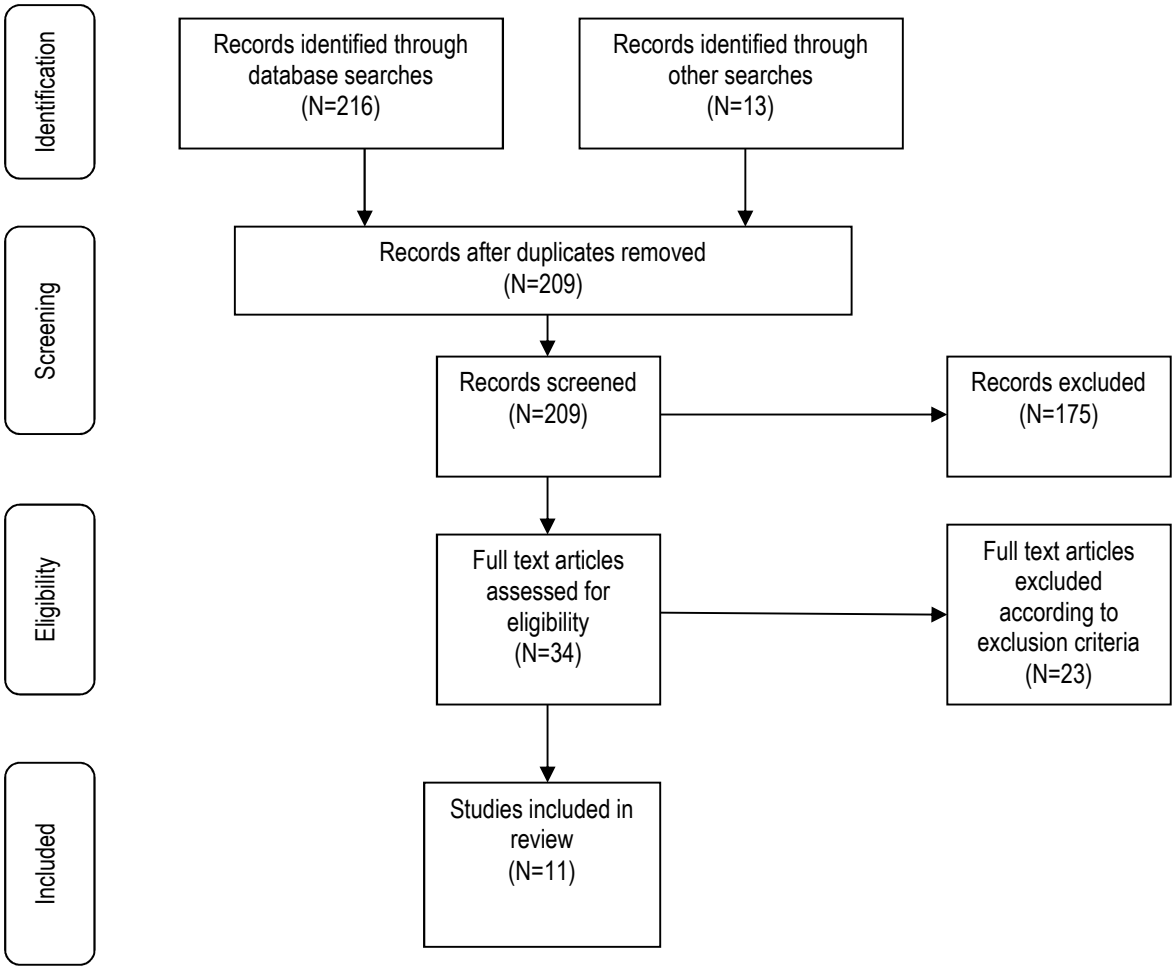


Figure 2.30.: Results of the literature search strategy on the various measures used to quantify impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Eleven (11) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, four (4) prospective observational studies, four (4) case control studies and a retrospective study. Articles appraised are presented in Table 2.31.

Table 2.31.: Appraised articles on the various measures used to quantify impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=11)				
Level of Evidence				
I (N=6)	**II**	**III** (N=5)	**IV**	**V**
Lotery *et al* (2000:221)		Ng *et al* (2005:2138)		
Nijboer *et al* (2013:2021)		Oliveira *et al* (2011:2043)		
Vossel *et al* (2013:1782)		Bonan *et al* (2013:713)		
Kerkhoff *et al* (2014:557)		Mitsutake *et al* (2014:1799)		
Siong *et al* (2014:438)		Bonan *et al* (2015:521)		
Van Wyk *et al* (2014:856)				

Findings of the literature reviewed indicated patients' functional ability were quantified using various measures that include the BI (Lotery *et al* 2000:221; Oliveira *et al* 2011:2043; Bonan *et al* 2013:713; Nijboer *et al* 2013:2021; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856; Bonan *et al* 2015:521), FIM (Ng *et al* 2005:2138; Mitsutake *et al* 2014:1799; Siong *et al* 2014:438) and standardised ADLs (such as address copying, telephone number dialling, clock reading, face creaming, hair combing, filling out a form, tray assembling, counting money) (Vossel *et al* 2013:1782).

The majority of authors used the BI to quantify patients' functional ability post-stroke (Lotery *et al* 2000:221; Oliveira *et al* 2011:2043; Bonan *et al* 2013:713; Nijboer *et al* 2013:2021; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856; Bonan *et al* 2015:521). The BI assesses the performance of ten (10) basic ADLs regarding feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing, as well as the patient's dependence (on assistance) to perform these activities (Mahoney and Barthel 1965:61). The BI presents with excellent interrater reliability (ICC=0.94) and a good to excellent relationship with the BBS ($r \geq 0.78$) and the Fugl-Meyer motor assessment in patients with stroke ($r \geq 0.78$) (Hsueh, Lee and Hsieh (2001:526).

Ng *et al* (2005:2138), Mitsutake *et al* (2014:1799) and Siong *et al* (2014:438) used the FIM to quantify patients' functional ability post-stroke. The FIM instrument is a widely used general disability scale that consists of thirteen (13) motor and five (5) cognitive items. Scoring of the FIM is based upon a seven (7) point scale that ranges between total assistance (Grade 1) to complete independence with no aid (Grade 7). The full score of the FIM-motor is 91 and the FIM-cognitive is 35, with a total score of 126. Although the FIM presents with established content validity, construct validity, sensitivity and interrater reliability (Ng *et al* 2005:2138), the utilisation of the FIM requires a licence and is therefore associated with increased costs which may limit the accessibility of the outcome measure in low-resource settings.

Alternatively, Vossel *et al* (2013:1782) assessed eight (8) standardised ADLs that included address copying, telephone number dialling, clock reading, face creaming, hair combing, filling out a form, tray assembling and counting money. Scoring of the patient's task performance during completion of the eight ADLs were based on a five (5) point scale that ranged between (1) the patient is not able to complete the task; (2) the patient experience severe difficulty during completion of the task (unable to complete the task); (3) although the patient experiences moderate difficulty during completion of the task, the patient is able to solve the task sufficiently; (4) the patient experiences mild difficulties but is able to solve the task well; and (5) the patient completes the task without any difficulty. Vossel *et al* (2013:1782) determined the interrater reliability of the evaluation of the ADL task performance with three (3) independent raters. Two (2) of the three (3) independent raters evaluated the patients' ADL task performance off-line on the basis of video recordings (N=36). The ADL task assessment presented with excellent interrater reliability (ICC>0.95, P<0.001) (Vossel *et al* 2013:1782).

Based on the extensive literature review, it may be summarised that various assessment methods and outcome measures were used to quantify the various clinical features and activity limitations associated with central vestibular disorders in the post-stroke population. Assessment methods used to quantify central vestibular disorders in the post-stroke population ranged from conventional paper-and-pencil tests to expensive, complicated and semi-invasive techniques. The assessment battery used within the study is discussed in Section 2.4.3.

2.4.3. Assessment battery for the quantification of the clinical features and activity limitations associated with central vestibular dysfunction

The assessment battery used within the study were selected to address the limitations identified in the literature study during which the various assessment methods and objective measures used to quantify the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients, were critically reviewed and appraised (Section 2.4.1. to 2.4.2). Summary of the assessment battery used within the study, is presented in Table 2.32.

Table 2.32.: Summary of the assessment battery used in the current study.

Assessment battery used in the current study					
International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical feature		**Objective measure(s)**	**Activity and participation level impairment**		**Objective measure(s)**
OCULOMOTOR FUNCTION	**Smooth pursuit eye movements**	Video nystagmography (VNG)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	Berg Balance Scale
	Saccadic eye movements	Video nystagmography (VNG)		**Ability to modify gait in response to changing task demands**	Dynamic Gait Index
	Static visual acuity	LogMAR chart			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	video Head Impulse Test (vHIT)	**FUNCTIONAL ABILITY**	**Functional ability**	Barthel Index
	Dynamic visual acuity	LogMAR chart			
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**Cervical vestibular-evoked myogenic potential (cVEMP)**	cVEMP	**PARTICIPATION IN SOCIETAL PHYSICAL ACTIVITIES POST-STROKE**	**Participation in societal physical activities post-stroke**	Telephonic-administered international physical activity questionnaire (IPAQ)

Table 2.32.: Summary of the assessment battery used in the current study (continued).

Assessment battery used in the current study			
International Classification of Functioning, Disability and Health (ICF)			
Level of body structure and function			
Clinical feature		**Objective measure(s)**	
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	oVEMP	
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	King-Devick Test©	
	Visual-perceptual function	Star Cancellation Test	
	Cognition	Mini-Mental State Examination	
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	Hospital Anxiety and Depression Scale (HADS)	

In the current study, the assessment of oculomotor control consisted of the quantification of smooth pursuit and saccadic eye movements using VNG and static visual acuity, using the LogMAR chart (Section 1.1.3.1). These tests were selected to determine whether a visual-vestibular activation-deactivation pattern in the central vestibular system, were present in post-stroke patients (Figure 1.2) (Dieterich and Brandt 2008:2538; Brandt *et al* 2014:47). A visual-vestibular activation-deactivation pattern may be observed between the contralateral and ipsilateral lesioned sides of the central vestibular system due to the bilateral ascending vestibular pathways and interhemispheric transcallosal connections. Following a stroke, the regional cerebral glucose metabolism (rCGM) increases in the multisensory vestibular cortical and subcortical areas, but simultaneously also significantly decreases in the visual and somatosensory cortex areas (Dieterich and Brandt 2008:2538; Brandt *et al* 2014:47), which may result in an oculomotor impairment, such as impaired smooth pursuit-, saccadic eye movements and reduced static visual acuity. It was, therefore, imperative that the smooth pursuit and saccadic eye movements and visual acuity of both eyes into both visual fields, were assessed to determine the possible differences in oculomotor function and visual activation between the two hemispheres (Hougaard *et al* 2015:2) of post-stroke patients. The normative values, validity and reliability of the VNG and LogMAR chart, are discussed in Section 3.1.7.1.

The assessment of reflexive control of gaze consisted of the quantification of the VOR-gain using the vHIT and DVA, using the LogMAR chart (Section 1.1.3.1). These tests were selected to determine whether a lesion in the central vestibular system that includes the vestibular nuclei, the ascending tracts (medial longitudinal fasciculus (MLF), central ventral tegmental tract (CVTT), brachium conjunctivum (BC) and the ocular motor nuclei (III, IV, VI) in the ponto-mesencephalic brainstem tegmentum and their corresponding pair of extraocular eye muscles (Dieterich and Brandt 2008:2539), were present post-stroke. The assessment of the impaired reflexive control of gaze would have also indicated if lesions in the nucleus prepositus hypoglossi, flocculus (cerebellum) or diffuse cerebellar lesions, were present in post-stroke patients (Choi *et al* 2018:90). The normative values, validity and reliability of the vHIT and DVA, are discussed in Section 3.1.7.1.

The air conduction cVEMP test (Tusa 2007:132) (Section 1.1.3.1) was selected to determine whether saccule and inferior vestibular nerve function impairment due to central vestibular dysfunction, were present in post-stroke patients (Section 1.1.3.1). The air conduction oVEMP test (Curthoys *et al* 2012:41) was selected to assess whether utricle and superior vestibular nerve function due to central vestibular dysfunction, were present in post-stroke patients (Section 1.1.3.1). Interpretation of the cVEMP and oVEMP assisted the researcher to localise possible lesions in the central vestibular system patients might presented with, following the stroke. An absent cVEMP suggested a lesion at or below the vestibular nucleus in the MVST (Section 2.3.2.1) or spinal accessory nucleus. An absent oVEMP suggested a lesion at or above the vestibular nucleus in the MLF (Section 1.1.1.2) or oculomotor nucleus. A simultaneous absent cVEMP and oVEMP suggested a lesion in the vestibular nucleus or root entry zone (Rosengren and Colebatch 2018:481). The normative values, validity and reliability of the cVEMP and oVEMP, are discussed in Section 3.1.7.1.

In the current study, the evaluation of higher vestibular function consisted of the assessment of residual oculomotor visual performance using the King-Devick Test©, visual-perceptual function using the Star Cancellation Test and cognitive function using the Mini-Mental State Examination. These tests were selected to determine whether a stroke might have resulted in impaired higher vestibular function which include impaired residual oculomotor visual performance, visual-perceptual dysfunction and cognitive impairment. Similar to oculomotor impairment post-stroke, stroke patients may present with impaired higher vestibular function due a visual-vestibular activation-deactivation pattern in the central vestibular system, due to ipsilateral visual cortex deactivation and increased inhibition from the contralateral visual cortex following a stroke (Brandt *et al* 2014:47). Another possible underlying mechanism of impaired higher vestibular function that was considered, was the presence of a vestibular tone imbalance post-stroke (Brandt *et al* 2014:47; Karnath and Dieterich 2006:293). Although visual fields might have been preserved post-stroke, stroke patients might have spontaneously directed their eye movements, head movements and spatial attention to the ipsilesional visual field. Increased spatial attention to the ipsilesional visual field would have resulted in a visual-spatial neglect

of stimuli in the contralateral visual field which further contributed to impaired higher vestibular function (Brandt *et al* 2014:47). It was, therefore, imperative that impaired higher vestibular function was assessed in addition to oculomotor function in post-stroke patients. The normative values, validity and reliability of the King-Devick Test©, Star Cancellation Test and Mini-Mental State Examination, are discussed in Section 3.1.7.1.

As the networks responsible for vestibular processing and anxiety are functionally intertwined and demonstrate reciprocal influences upon each other (Bednarczuk, Ortega, Fluri and Arshad 2018:1517), the HADS were selected to assess the level of anxiety and/or depression (Section 1.1.3.1) in post-stroke patients. The possible underlying mechanisms of the concurrent symptoms of vestibular dysfunction and increased anxiety may be explained by overlapping and interacting brainstem pathways of both the vestibular system and the parabrachial nucleus network in the brainstem (Nagaratnam *et al* 2005:253). The assessment of the clinical feature of increased anxiety observed in post-stroke patients might be explained by the involvement of the parabrachial nucleus network that is under the control of the higher cortical centres that receive inputs from the vestibular nuclei via the thalamo-cortical projections and is connected to the vestibular nuclei. It is also important to highlight that the parabrachial nucleus is also connected to the central amygdaloid nucleus, infralimbic cortex, hypothalamus, brainstem respiratory centre and other regions that control the parasympathetic and sympathetic connections and are involved in avoidance conditioning, anxiety and conditioned fear. The normative values, validity and reliability of the HADS, are discussed in Section 3.1.7.1.

Activity and participation limitations included the assessment of sensorimotor balance, mobility and gait in post-stroke patients. Stroke patients' functional balance were determined using the BBS, as well as their ability to modify gait in response to changing task demands, using the DGI. The BBS and DGI were selected to determine whether a stroke patients' ability to complete mobility tasks such as transfers, standing unsupported, sit-to-stand, turning 360°, walking while changing gait speed, walking over and around obstacles, were influenced by the possible presence of clinical features of central vestibular dysfunction, such as impaired MVST and LVST (Section 2.3.2.1) that resulted in activity and participation limitations in post-stroke patients. The

normative values, validity and reliability of the BBS and DGI, are discussed in Section 3.1.7.2.

It was important to the researcher to determine whether the possible presence of the clinical features associated with central vestibular dysfunction had an effect on stroke patients' functional ability and participation in societal physical activities post-stroke. Stroke patients' functional ability and participation in societal physical activities post-stroke, were determined by the BI and IPAQ respectively. The normative values, validity and reliability of the BI and IPAQ, are discussed in Section 3.1.7.2.

The various interventions used in the treatment of the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients, are discussed in Section 2.5.

2.5. INTERVENTIONS USED IN THE TREATMENT OF CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION

In the literature reviewed, various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients, were described. The various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction, are summarised in Table 2.33.

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	(1) Advice on adaptive strategies to optimise visual function, specifically smooth pursuit eye movements (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5; Herron 2016:72) (5) Orthoptic exercises (Rowe *et al* 2013:5) (6) Smooth pursuit eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda, Han, Kapoor and Ficarra 2006:9; Carrick *et al* 2016:3; Herron 2016:72) (7) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(1) Exercises performed in supine or prone position (Bonan *et al* 2004:274) (2) Exercises performed in a sitting position (Bonan *et al* 2004:274) (3) Exercises performed in four (4) point kneeling (Bonan *et al* 2004:274) (4) Exercises performed in an upright position (Bonan *et al* 2004:274; Smania, Picelli, Gandolfi, Fiaschi and Tinazzi 2008:313) (5) Balance training on a treadmill (Bonan *et al* 2004:274)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Saccadic eye movements**	(1) Advice on adaptive strategies to optimise visual function, specifically saccadic eye movements (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5; Herron 2016:72) (5) Saccadic eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9; Carrick *et al* 2016:3; Herron 2016:72) (6) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9) (7) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(6) Balance training on a stationary bicycle (Bonan *et al* 2004:274) (7) Walking on a foam rubber track with obstacles (Bonan *et al* 2004:274) (8) Individual physiotherapy embedded in an extensive, individualized neurodevelopmental treatment (NDT) rehabilitation program. The NDT program had a general emphasis on optimal use of the paretic body side (De Haart *et al* 2004:886).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
OCULOMOTOR CONTROL	**Static visual acuity**	(1) Refractive correction (Lotery *et al* 2000:221; Shrestha *et al* 2012:46; Herron 2016:72) (2) Occlusion of a spectacle lens (Lotery *et al* 2000:221)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(9) Individualised physiotherapy sessions (Van Nes, van Kessel, Schils, Fasotti, Geurts and Kwakkel 2009:819) (10) Group sessions of physiotherapy (Van Nes *et al* 2009:819) (11) Vestibular rehabilitation therapy: balance and gait training, general strengthening and flexibility exercises, utilization of somatosensation and vision to aid in maintaining balance, vestibular adaptation exercises, substitution exercises (continued)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	(1) Advice on adaptive strategies to optimise visual function related to gaze stabilisation (Rowe *et al* 2013:5) (2) Occlusion of a spectacle lens (Rowe *et al* 2013:5) (3) Fresnel prisms (Rowe *et al* 2013:5; Herron 2016:72) (4) Refractive correction (Rowe *et al* 2013:5) (5) Vestibular adaptation exercises (gaze stabilisation exercises) (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477; Herron 2016:72)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(11) (continued) Vestibular rehabilitation therapy: education in the use of assistive devices and safety awareness techniques to avoid falls (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). (12) Visual feedback posturography training (VFPT) using (2) force plates that provided continuous visual feedback of the position of the center of gravity in relation to the theoretical limits of stability during exercise. Patients were required to maintain postural stability on a stable/unstable surface (continued)
	Dynamic visual acuity	None reported			

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	None reported	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(12) (continued) VFPT: The exercise program included dynamic weight shifting, leaning plus stepping tasks with different bases of support and temporal demands (larger distances, different movement directions and faster speeds (Balci *et al* 2013:259). (13) Basic balance and mobility home exercise programme that included strengthening of pelvic stabilisation muscles and improvement of balance and gait ability. The exercise program consisted of weight shifting in sitting, sit to stand activity, weight shifting in standing with hip abduction and extension (continued)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	None reported	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	(13) (continued) Gait training such as marching on the spot, forward and backward walking with a progressively narrowing base of support (Balci *et al* 2013:259; Dai *et al* 2013:477). (14) Combination of balance training and visual therapy. Balance training included individualized sensory integration, vestibular and proprioceptive exercises. Visual therapy included training of binocularity, fixation, tracking, vergence, visual attention, accommodation, eye-hand coordination and binocularity (Schow *et al* 2016:333).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	(1) Single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9) (2) Advice on adaptive strategies to optimise residual oculomotor visual performance function (Rowe *et al* 2011:408) (3) Refractive correction (Rowe *et al* 2011:408) (4) Typoscope reading guide (Rowe *et al* 2011:408)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(1) Exercises performed in supine or prone position (Bonan *et al* 2004:274) (2) Exercises performed in a sitting position (Bonan *et al* 2004:274) (3) Exercises performed in four (4) point kneeling (Bonan *et al* 2004:274) (4) Exercises performed in an upright position (Bonan *et al* 2004:274) (5) Balance training on a treadmill (Bonan *et al* 2004:274)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	(5) Use of prisms (Rowe *et al* 2011:408) (6) Tracking exercises (Rowe *et al* 2011:408) (7) Low vision aids (Rowe *et al* 2011:408) (8) Occlusion of a spectacle lens (Rowe *et al* 2011:408) (9) Use of Peli prisms (Rowe *et al* 2011:408) (10) Convergence exercises (Rowe *et al* 2011:408) (11) Cortical visual impairment registration (Rowe *et al* 2011:408) (12) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(6) Balance training on a stationary bicycle (Bonan *et al* 2004:274) (7) Walking on a foam rubber track with obstacles (Bonan *et al* 2004:274) (8) Individual physiotherapy embedded in an extensive, individualized neurodevelopmental treatment (NDT) rehabilitation program. The NDT program had a general emphasis on optimal use of the paretic body side (De Haart *et al* 2004:886) (9) Individualised physiotherapy sessions (Van Nes *et al* 2009:819) (10) Group sessions of physiotherapy (Van Nes *et al* 2009:819)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Visual-perceptual function**	(1) Optokinetic stimulation to elicit smooth pursuit eye movements (Kerkhoff *et al* 2012:1164) (2) Vestibular rehabilitation therapy (Dai *et al* 2013:477) (3) Smooth pursuit eye movement training (Kerkhoff, Reinhart, Ziegler, Artinger, Marquardt and Keller, 2013:789; Kerkhoff *et al* 2014:557) (4) Saccadic eye movement training (Kerkhoff *et al* 2013:789); Kerkhoff *et al* 2014:557) (5) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(11) Vestibular rehabilitation therapy: balance and gait training, general strengthening and flexibility exercises, utilization of somatosensation and vision to aid in maintaining balance, vestibular adaptation exercises, substitution exercises, education in the use of assistive devices and safety awareness techniques to avoid falls (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
HIGHER VESTIBULAR FUNCTION	**Cognition**	(1) Comprehensive rehabilitation programme that included physiotherapy, occupational therapy and speech and language therapy (Ng *et al* 2005:2138)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(12) Visual feedback posturography training (VFPT) using (2) force plates that provided continuous visual feedback of the position of the center of gravity in relation to the theoretical limits of stability during exercise. Patients were required to maintain postural stability on a stable/unstable surface. The exercise program included dynamic weight shifting, leaning plus stepping tasks with different bases of support and temporal demands (larger distances, different movement directions and faster speeds (Balci *et al* 2013:259).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Intervention(s)**	**Activity limitations associated with central vestibular dysfunction**		**Intervention(s)**
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	(1) Combination of pharmacological and rehabilitation therapy (Nagaratnam, Ip and Bou-Haidar 2005:253) (2) Vestibular rehabilitation therapy (VRT) (Meli, Zimatore, Badaracco, De Angelis and Tufarelli 2007:185)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Ability to modify gait in response to changing task demands**	(13) Basic balance and mobility home exercise programme that included strengthening of pelvic stabilisation muscles and improvement of balance and gait ability. The exercise program consisted of weight shifting in sitting, sit to stand activity, weight shifting in standing with hip abduction and extension. Gait training such as marching on the spot, forward and backward walking with a progressively narrowing base of support (Balci *et al* 2013:259; Dai *et al* 2013:477).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
		Activity and participation level		
		Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
		SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT	**Ability to modify gait in response to changing task demands**	(14) Combination of balance training and visual therapy. Balance training included individualized sensory integration, vestibular and proprioceptive exercises. Visual therapy included training of binocularity, fixation, tracking, vergence, visual attention, accommodation, eye-hand coordination and binocularity (Schow *et al* 2016:333).

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
		Activity and participation level		
		Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
		FUNCTIONAL ABILITY	**Functional ability**	(1) Comprehensive rehabilitation programme (Ng *et al* 2005:2138) (2) Vestibular rehabilitation therapy (Dai *et al* 2013:477) (3) Active and passive exercises, resistance exercises and ambulation training (Dai *et al* 2013:477) (4) Computerised bedside saccadic eye movement training (Kerkhoff *et al* 2014:557) (5) Computerised bedside smooth pursuit eye movement training (Kerkhoff *et al* 2014:557)

Table 2.33.: Summary of the various interventions used in the treatment of clinical features and activity limitations associated with central vestibular dysfunction (continued).

International Classification of Functioning, Disability and Health (ICF)				
		Activity and participation level		
		Activity limitations associated with central vestibular dysfunction		**Intervention(s)**
		FUNCTIONAL ABILITY	**Functional ability**	(6) Saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856)

Each of the clinical features and activity limitations associated with central vestibular dysfunction, are discussed from Section 2.5.1. to Section 2.5.2. The first impairment on the level of body structure and function to be discussed in Section 2.5.1., is oculomotor control.

2.5.1. Level of body structure and function

2.5.1.1. Oculomotor control

Interventions used in the treatment of the clinical feature of oculomotor control included interventions for smooth pursuit eye movements, saccadic eye movements and static visual acuity. Interventions for smooth pursuit eye movement impairment, are to be discussed first.

(i). Intervention for smooth pursuit eye movement impairment

To determine the various interventions implemented in the treatment of smooth pursuit eye movements in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.31., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “oculomotor impairment”; “smooth pursuit eye movement”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

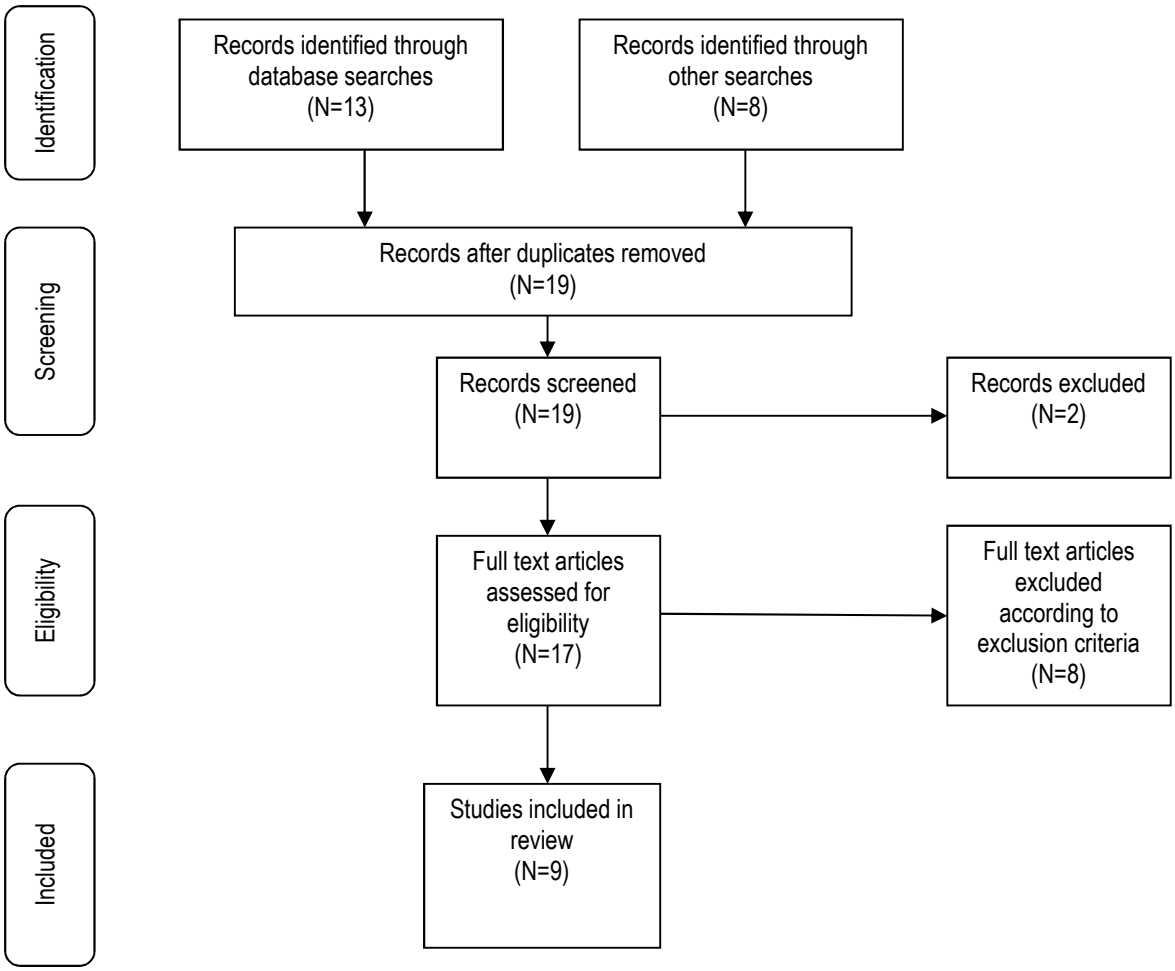


Figure 2.31.: Results of the literature search strategy on the various interventions implemented in the treatment of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Nine (9) articles were critically reviewed and an assessment for the quality of evidence was completed. The articles appraised included four (4) single-centre double blind RCTs, a prospective multi-centre observational case cohort trial study, a retrospective study, a case study, a case series and a systematic literature review. Articles appraised are presented in Table 2.34.

Table 2.34.: Appraised articles on the various interventions for the treatment of smooth pursuit eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=1328)				
Level of Evidence				
I (N=1191)	**II**	**III** (N=131)	**IV** (N=6)	**V**
Kerkhoff *et al* (2012:1164)		Herron (2016:72)	Kapoor *et al* (2004:1667)	
Kerkhoff *et al* (2013:789)			Ciuffreda *et al* (2006:9)	
Rowe *et al* (2013:5)				
Kerkhoff *et al* (2014:557)				
Hill *et al* (2015:410)				
Carrick *et al* (2016:3)				

Findings of the literature appraised indicated that the clinical feature of impaired smooth pursuit eye movements in post-stroke patients were treated by using interventions that included; (a) advice on adaptive strategies to optimise visual function specifically smooth pursuit eye movements (Rowe *et al* 2013:5); (b) occlusion of a spectacle lens (Rowe *et al* 2013:5); (c) fresnel prisms aimed to improve diplopia (Rowe *et al* 2013:5; Herron 2016:72); (d) refractive correction (Rowe *et al* 2013:5; Herron 2016:72); (e) orthoptic exercises (Rowe *et al* 2013:5); (f) smooth pursuit eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9; Carrick *et al* 2016:3; Herron 2016:72); and (g) single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9).

Findings of the study by Rowe *et al* (2013:5) indicated that 5.0% (N=46) of the study sample presented with smooth pursuit eye movement impairment (Section 2.3.1.1). Of the 5.0% of patients who presented with smooth pursuit eye movement impairment, 32.6% (N=15) received advice on adaptive strategies to optimise visual function, specifically smooth pursuit eye movements. Advice on adaptive strategies included compensatory head posture, visual field awareness, visual scanning, reading options and the use of appropriate task lighting (Rowe *et al* 2013:5). Seven (7) patients (15.2%) received occlusion of a spectacle lens compared to five (5) patients (10.9%)

who received fresnel prisms, aimed to improve diplopia (double vision) (Rowe *et al* 2013:5). Ten (10) patients (21.7%) received refraction and only one (1) patient (2.2%) received orthoptic exercises (Rowe *et al* 2013:5).

Carrick *et al* (2016:3) implemented smooth pursuit eye movement training in combination with saccadic eye movement training in the treatment of patients (N=34) who have suffered a MCA ischemic stroke. Carrick *et al* (2016:3) did not quantify the patients' smooth pursuit eye movements; assessment measurements were limited to the assessment of electrical brain activity using qEEG and the functional outcome of patients using the NIHSS. Findings of the study indicated statistically significant changes in qEEG and NIHSS in patients who received smooth pursuit eye movement training post-stroke. Carrick *et al* (2016:3) concluded that smooth pursuit eye movement training is a low cost, safe and effective complement to patients' treatment programme following a MCA ischemic stroke (Carrick *et al* 2016:3).

Findings of the retrospective study by Herron (2016:69) indicated that after the visual function of stroke patients (N=131) were assessed by an optometrist, the results of the visual assessment were returned to an occupational therapist. Thereafter, the occupational therapist implemented a treatment plan based on the recommendations compiled by the optometrist. Recommendations made by the optometrist included saccadic eye movement exercises (82.4%), smooth pursuit eye movement exercises (67.9%), convergence exercises (55.0%), gaze stabilisation exercises (35.9%), glasses issued (25.2%) and prisms applied (2.3%) (Herron 2016:69). Although smooth pursuit eye movement exercises were provided to more than two thirds of the study sample, the author did not mention if these exercises were specifically aimed to improve smooth pursuit eye movements of post-stroke patients. Interestingly, the number of patients (67.9%) that received smooth pursuit eye movement exercises, exceeded the number of patients who presented with smooth pursuit eye movement impairment (61.8%), who were identified during the assessment of smooth pursuit eye movements using an occupational therapy vision screening tool developed by an interdisciplinary team prior to the implementation in the study (Herron 2016:69). The unequal number of patients who were diagnosed with smooth pursuit impairment and those who received smooth pursuit eye movement exercises, highlight several limitations of the study. Limitations of the study include whether the number of patients who presented with impaired smooth pursuit eye movements, were underreported or

whether a number of patients who were not diagnosed with smooth pursuit eye movement impairment, also received these exercises, regardless of the absence of the diagnosis of smooth pursuit eye movement impairment.

Kapoor *et al* (2004:1667) and Ciuffreda *et al* (2006:9) implemented the same intervention that consisted of single-line and multiple-line simulated reading, visual fixation exercises, saccadic eye movement exercises and smooth pursuit eye movement exercises provided twice per week over an eight (8) week period. Both studies concluded that patients presented with improved basic ocular motility and reading ability following oculomotor rehabilitation that specifically included smooth pursuit eye movement training. Although these studies demonstrated significant improvement of basic oculomotor and reading-related oculomotor parameters, the studies' sample sizes were limited to only one (1) stroke patient in the case study by Kapoor *et al* (2004:1667) and five (5) stroke patients in the case series by Ciuffreda *et al* (2006:9).

The studies by Kerkhoff *et al* (2012:1164), Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) were included in the literature review as the authors implemented optokinetic stimulation that elicited saccadic eye movements (Kerkhoff *et al* 2012:1164) and smooth pursuit eye movement training (Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557) in the treatment of impaired higher vestibular function specifically visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.3.1.5). Kerkhoff *et al* (2012:1164), Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) did not quantify smooth pursuit eye movements in the patients in their study samples; measurements were limited to the assessment of higher vestibular function that included various conventional paper-and-pencil visual-perceptual function tests, which included line bisection tests, number or digit cancellation tests, paragraph reading, ASMP, FNI and UBNI. Findings of the study by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) demonstrated that repetitive contralesional smooth pursuit eye movement training was associated with superior, multimodal therapeutic effects compared to saccadic eye movement training in patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect). Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) concluded that smooth pursuit eye movement training is effective and feasible in the treatment of patients who present with higher vestibular function impairment, specifically visual-

perceptual dysfunction post-stroke. Findings of the studies by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) are supported by Hill *et al* (2015:410) that concluded that strong evidence supports the use of smooth pursuit eye movement training in the rehabilitation of patients post-stroke. Smooth pursuit eye movement training implemented in the treatment of higher vestibular function impairment, specifically visual-perceptual dysfunction, may be superior to traditional interventions based on saccadic eye movement training (Hill *et al* 2015:410). Saccadic eye movement training described by Hill *et al* (2015:410) included visual scanning training that consisted of visual scanning of an array of stationary horizontal and vertical target symbols on the display of a computer screen by starting at the top left corner and ending at the bottom right without using head movements to see and read the symbols / letters (Hill *et al* 2015:410).

Kerkhoff *et al* (2013:789), Kerkhoff *et al* (2014:557) and Hill *et al* (2015:410) postulate that smooth pursuit eye movement training may facilitate brain plasticity that allows for compensatory strategies to be learned through the recruitment of other brain areas that may rely on the reactivation of a cortico-subcortical network, which include the occipitotemporal, parietal, insular, occipital cortex, basal ganglia, cerebellum and brainstem, as well as activation of the vestibulo-ocular system via optokinetic nystagmus. It is important to note that although Kerkhoff *et al* (2013:789), Kerkhoff *et al* (2014:557) and Hill *et al* (2015:410) identified the potential activation of these brain areas with smooth pursuit eye movement training, the authors did not mention the role of the central vestibular system involved in oculomotor impairment that specifically include smooth pursuit eye movement dysfunction post-stroke. The generation of smooth pursuit eye movements is controlled by the visual cortex, MT, MST, FEF, dorsolateral pontine nuclei, cerebellum (flocculus and oculomotor vermis), vestibular nuclei and oculomotor nuclei (Strupp *et al* 2014:542). The brain regions responsible for the generation of smooth pursuit eye movements described by Strupp *et al* (2014:542), is supported by findings by Jang *et al* (2018:727) who investigated the structural neural connectivity of the vestibular nuclei using DTT. Findings of the study demonstrated 100% connectivity between the vestibular nuclei and the cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus and reticular formation. These connected brain regions thus relate (100%) to the functions of the vestibular nuclei (Strupp *et al* 2014:542; Brandt and Dieterich 2017:352; Jang *et al*

2018:727) which include amongst others the control of eye movements, such as smooth pursuit eye movements. Another limitation identified by the researcher is that although smooth pursuit eye movement impairment is a clinical feature of central vestibular dysfunction (Section 1.1.3.1), none of the studies reviewed the implementation of VRT as an intervention in the treatment of patients who present with oculomotor impairment, specifically smooth pursuit eye movement impairment, as result of central vestibular dysfunction in the early reorganisation (sub-acute) phase post-stroke. The second feature of oculomotor control to be discussed, is saccadic eye movement.

(ii). Intervention for saccadic eye movement impairment

To determine the various interventions implemented in the treatment of saccadic eye movements in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.32., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “oculomotor impairment”; “saccadic eye movement”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

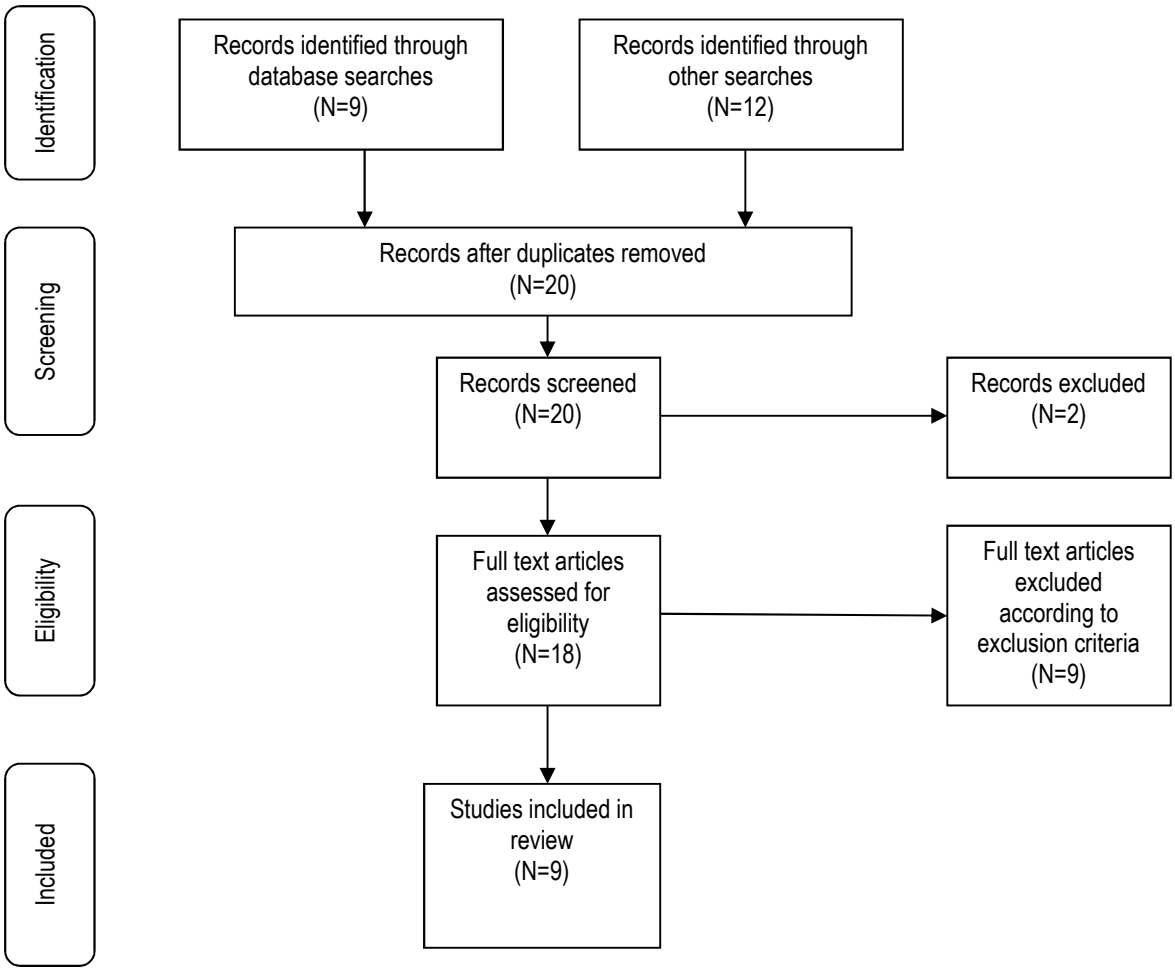


Figure 2.32.: Results of the literature search strategy on the various interventions implemented in the treatment of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Nine (9) articles were critically reviewed and an appraisal of the quality of evidence was completed. The articles appraised included three (3) RCTs, two (2) prospective multi-centre observational case cohort trial studies, a retrospective study, a case control study, a case study and a case series. Articles appraised are presented in Table 2.35.

Table 2.35.: Appraised articles on the various interventions for the treatment of saccadic eye movement impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=8)				
Level of Evidence				
I (N=5)	**II**	**III** (N=1)	**IV** (N=2)	**V**
Kerkhoff *et al* (2013:789)		Herron (2016:72)	Kapoor *et al* (2004:1667)	
Rowe *et al* (2013:5)			Ciuffreda *et al* (2006:9)	
Kerkhoff *et al* (2014:557)				
Carrick *et al* (2016:3)				
Van Wyk *et al* (2014:856)				

Findings of the literature reviewed indicated that the clinical feature of impaired saccadic eye movements in post-stroke patients, were treated using interventions that included; (a) advice on adaptive strategies to optimise visual function specifically saccadic eye movements (Rowe *et al* 2013:5); (b) occlusion of a spectacle lens (Rowe *et al* 2013:5); (c) use of fresnel prisms aimed to improve diplopia (Rowe *et al* 2013:5; Herron 2016:72); (d) refractive correction (Rowe *et al* 2013:5; Herron 2016:72); (e) saccadic eye movement exercises (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9; Carrick *et al* 2016:3; Herron 2016:72); (f) single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9); and (g) saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856).

Findings of the study by Rowe *et al* (2013:2) indicated that 3.1% (N=28) of the study sample presented with saccadic eye movement impairment (Section 2.3.1.1). Of the 3.1% of patients who presented with saccadic eye movement impairment, 42.9% (N=12) received advice on adaptive strategies to optimise visual function, specifically saccadic eye movements. Advice on adaptive strategies included compensatory head posture, visual field awareness, visual scanning, reading options and the use of appropriate task lighting (Rowe *et al* 2013:5). Two (2) patients (7.1%) received occlusion of a spectacle lens compared to three (3) patients (10.7%) who received

fresnel prisms aimed to improve diplopia (double vision) (Rowe *et al* 2013:5). Only one (1) patient (3.6%) received refractive correction (Rowe *et al* 2013:5).

As discussed in (Section 2.5.1.1), Carrick *et al* (2016:3) implemented saccadic eye movement training in addition to smooth pursuit eye movement training in the treatment of patients (N=34) who have suffered a MCA ischemic stroke. Carrick *et al* (2016:3) did not quantify the latency, velocity or accuracy of patients' saccadic eye movements; measurements were limited to the assessment of electrical brain activity using qEEG and the functional outcome of patients using the NIHSS. Findings of the study indicated statistically significant changes in qEEG and NIHSS in post-stroke patients who received saccadic movement training. Carrick *et al* (2016:3) concluded that saccadic eye movement training is a low cost, safe and effective complement to patients' treatment programme following a MCA ischemic stroke (Carrick *et al* 2016:3).

As discussed in Section 2.5.1.1., findings of the retrospective study by Herron (2016:69) indicated that after the visual function of stroke patients (N=131) were assessed by an optometrist, the results of the visual assessment were returned to an occupational therapist. Thereafter, the occupational therapist implemented a treatment plan based on the recommendations made by the optometrist. Recommendations made by the optometrist included saccadic eye movement exercises (82.4%), smooth pursuit eye movement exercises (67.9%), convergence exercises (55.0%), gaze stabilisation exercises (35.9%), glasses issued for refractive correction (25.2%) and prisms applied aimed to improve diplopia (double vision) (2.3%) (Herron 2016:72). Although saccadic eye movement exercises were provided to the majority of the study sample, the author did not mention if these exercises were specifically aimed to improve saccadic eye movements of post-stroke patients. Interestingly, the number of patients (82.4%) that received saccadic eye movement exercises exceeded the number of patients who presented with saccadic eye movement impairment (77.1%) prior to the implementation in the study (Herron 2016:69). The unequal number of patients who were diagnosed with saccadic eye movement impairment and those that received saccadic eye movement exercises, highlight several limitations of the study. Limitations of the study include whether the number of patients who presented with impaired saccadic eye movements were underreported or whether a number of patients who were not diagnosed with saccadic

eye movement impairment, also received these exercises regardless of the absence of the diagnosis of saccadic impairment.

Kapoor *et al* (2004:1667) and Ciuffreda *et al* (2006:9) implemented the same intervention that consisted of single-line and multiple-line simulated reading, visual fixation exercises, saccadic eye movement exercises and smooth pursuit eye movement exercises provided twice per week over an eight (8)-week period. Both studies concluded that patients presented with improved basic ocular motility and reading ability following oculomotor rehabilitation that specifically included saccadic eye movement training. Although these studies demonstrated significant improvement of basic oculomotor and reading-related oculomotor parameters, the studies' sample sizes were limited to only one (1) stroke patient in the case study by Kapoor *et al* (2004:1667) and five (5) stroke patients in the case series by Ciuffreda *et al* (2006:9) (Section 2.5.1.1).

The studies by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) were included in the literature review as the authors implemented saccadic eye movement training, to compare the effect of saccadic eye movement training to smooth pursuit eye movement in the treatment of impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.3.1.5). Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) did not quantify saccadic eye movements in their study samples, their assessment measurements were limited to the assessment of higher vestibular function that included various visual-perceptual function tests such as cancellation tests, paragraph reading, line bisection tests, auditory tests, FNI and UBNI. Findings of the study by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) demonstrated that repetitive contra-lesional smooth pursuit eye movement training was associated with superior, multimodal therapeutic effects compared to saccadic eye movement training in patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) (Section 2.3.1.5).

Alternatively, Van Wyk *et al* (2014:856) conducted a matched-pair randomised control trial to determine the effect of saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities on patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect)

post-stroke. All patients received task-specific activities for a four (4)-week intervention period. The experimental group received saccadic eye movement training with VSE, integrated with task specific activities as an “add-on” intervention. Findings of the study by Van Wyk *et al* (2014:856) demonstrated that intensive saccadic eye movement training with VSE, integrated with task-specific activities, has a significant effect on patients’ higher vestibular function post-stroke. It is important to highlight that saccadic eye movement may also be implemented as a component of the VRT-approach (Section 1.1.4). The process of ‘substitution’ facilitates the use of individual or combinations of sensory input such as visual or somatosensory (including proprioceptive) information, to facilitate vestibular compensation through the process of sensory re-weighting due to dysfunctional vestibular input (McDonnell and Hillier 2015:3). Saccadic eye movement substitution may be achieved by the implementation of visual scanning exercises (VSE), integrated with task-specific activities (Van Wyk *et al* 2014:856). Progression of these exercises is guided by the patient’s ability to allocate information-processing resources between two (2) tasks and to maintain sufficient attention on the visual scanning task during the dual-task performance of horizontal and vertical saccadic eye movements, as well as head movement while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856). The rehabilitation programme also included substitution exercises that alter somatosensory cues, for example, let the patient stand on different surfaces, i.e., foam with eyes open and closed; challenges the vestibular system by letting the patient perform activities with and without visual input; modified center of gravity exercises; and weight shifting (Whitney *et al* 2016:13). By removing or altering visual/somatosensory cues, the patient is forced to use remaining sensory–motor cues which will result in the fostering of responses by reacting on mainly vestibular cues (Herdman and Whitney 2007:315). Although saccadic eye movement training with VSE, integrated with task-specific activities, is a component of the VRT-approach, Van Wyk *et al* (2014:856) did not mention the role of the central vestibular system involved in oculomotor impairment that specifically include saccadic eye movement dysfunction post-stroke. None of the other studies reviewed implemented VRT as an intervention in the treatment of patients who present with oculomotor impairment, specifically saccadic eye movement impairment as a result of central vestibular dysfunction in the early reorganisation (sub-acute) phase post-stroke.

The third feature of oculomotor control to be discussed, is static visual acuity.

(iii). Intervention for reduced static visual acuity

To determine the various interventions implemented in the treatment of reduced static visual acuity in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.33., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “oculomotor impairment”; “static visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

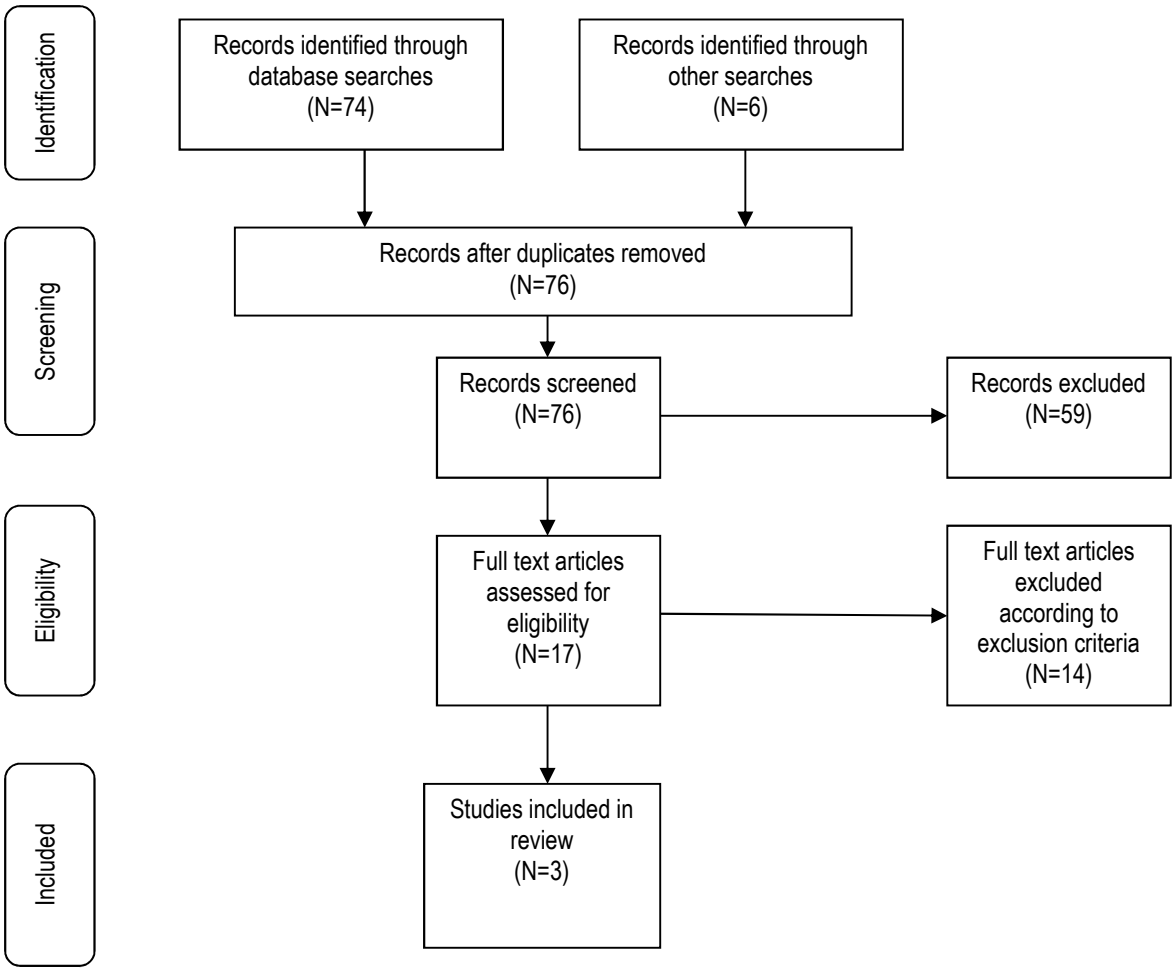


Figure 2.33.: Results of the literature search strategy on the various interventions implemented in the treatment of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Three (3) articles were critically reviewed and an assessment of the quality of evidence was completed. Of the three (3) articles appraised, two (2) articles were prospective observational studies and one (1) article was a retrospective study. Articles appraised are presented in Table 2.36.

Table 2.36.: Appraised articles on the various interventions for the treatment of reduced static visual acuity due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=3)				
Level of Evidence				
I (N=2)	**II**	**III** (N=1)	**IV**	**V**
Lotery *et al* (2000:221)		Herron (2016:72)		
Shrestha *et al* (2012:46)				

Findings of the appraised literature indicated that the clinical feature of reduced static visual acuity in post-stroke patients were treated using interventions that included refractive correction (Lotery *et al* 2000:221; Shrestha *et al* 2012:46; Herron 2016:72) and occlusion of a spectacle lens (Lotery *et al* 2000:221). Findings from the study by Lotery *et al* (2000:221) and Shrestha *et al* (2012:46) indicated that 14.0% and 12.5% of patients who presented with reduced static visual acuity post-stroke, benefited from refractive correction respectively. Findings of the study by Herron (2016:72) indicated that 27.5% (N=131) of the study sample presented with reduced static visual acuity post-stroke. Nearly ninety-two percent (91.67%) of these patients who presented with reduced static visual acuity, received refractive correction (Herron 2016:72). Lotery *et al* (2000:221) implemented temporary occlusion of a spectacle lens in two (2) patients who presented with reduced visual acuity as a result of diplopia associated with third ocular motor cranial nerve palsy post-stroke. Only one (1) patient (N=77) demonstrated marked improvement of static visual acuity post-stroke after occlusion of a spectacle lens (Lotery *et al* 2000:221). The second impairment on the level of body structure and function to be discussed in Section 2.5.1.2, is reflexive control of gaze impairment.

2.5.1.2. Reflexive control of gaze

Impairment of reflexive control of gaze may include deficits of the VOR-gain and dynamic visual acuity. The first feature of reflexive control of gaze to be discussed, is VOR-gain.

(i). Intervention for vestibular-ocular reflex gain dysfunction

Vestibular compensation as a network for investigating dynamic neural reorganization of sensorimotor processes, is supported by a considerable body of evidence that plasticity of the VOR is facilitated by protein kinase C (PKC)-dependent mechanisms in modular vestibulocerebellar cortico-nuclear microcircuits (Ito 2001:1143; Balaban *et al* 2012:101). These modular vestibulocerebellar cortico-nuclear microcircuits are small networks involving the inferior olive, vestibular nuclei, nucleus prepositus hypoglossi and the flocculonodular lobe (Ito 2001:1143; Balaban *et al* 2012:101). The cerebellum plays a crucial role in motor learning, especially during the learning of new motor skills and to maintain and improve learned motor performance throughout life. It is postulated that the cerebellar flocculus is responsible for the adaptive control of the VOR. Sensory-motor signals are projected from the vestibular nucleus, dorsolateral pontine nucleus, and neurons in the paramedian tract, respectively, via mossy fibers, evoking simple spikes (SSs) in a Purkinje cell synapses and transferred to the cerebellar flocculus (Inagaki and Hirata 2017:827). Inhibition of flocculonodular lobe Purkinje cell protein kinase C (PKC) prevents: (i) adaptive modification of vestibulo-ocular and optokinetic responses (Balaban *et al* 2012:101); and (ii) a compensatory increase in the intrinsic excitability of medial vestibular nucleus neurons during early vestibular compensation (Balaban *et al* 2012:101). Purkinje cells may induce cerebellar long-term depression (LTD) by processes that require simultaneous parallel and climbing fiber activity and PKC activation (Balaban *et al* 2012:101). Findings from a study completed by (Inagaki and Hirata 2017:827) demonstrated that acute VOR motor learning is accomplished by simultaneous enhancement of eye movement signals via LTP and suppression of vestibular signals via LTD to increase VOR-gain (gain-up learning). To decrease VOR-gain (gain-down learning), the eye movement and vestibular signals are modified in the opposite directions, via LTD and suppression of eye movement signals and LTP enhancement of vestibular signals (Inagaki and Hirata 2017:827). The findings by Balaban *et al* (2012:101) as well as

Inagaki and Hirata (2017:827), is supported by the findings of the study by Jang *et al* (2018:727) (Section 1.1.2) that a hundred percent (100%) structural neural connectivity was observed between the vestibular nuclei and the cerebellum, oculomotor nucleus, trochlear nucleus, abducens nucleus, thalamus, and reticular formation using DTT.

Vestibular rehabilitation therapy (VRT) for treatment of central vestibular dysfunction consists of a programme of exercises designed to facilitate adaptation of the vestibular system, habituate the person to movement, teach sensory substitution and improve a person's balance and postural control (Alghadir *et al* 2013:1). The process of 'vestibular adaptation' includes repetitive and provocative movements of a patient's head and/or eyes to stimulate a retinal slip to optimise vision during head movement (Herdman and Whitney 2007:315). The best stimulus to induce 'adaptation' is to produce an error signal that the CNS attempts to reduce by modifying the gain of the VOR (Herdman and Whitney 2007:315; Cullen *et al* 2009:171; Balaban *et al* 2012:101; McDonnell and Hillier 2015:3). The first exercise consists of having the patient focus on a target while moving their head as fast as they can while still maintaining fixation on the target. The exercise is performed in various functional positions, during gait, walking at a different speed, against various backgrounds, at different distances from the target and in different planes of movement (Whitney *et al* 2015:61; Whitney *et al* 2016:13). The second exercise consists of having the patient focus on a target while the target and the head move in opposite directions while the patient keeps the target in focus by maintaining visual fixation on the target (Herdman and Whitney 2007:315). The exercise is performed in various functional positions, during gait, walking with a different speed, against various backgrounds, during different distances and in different planes (Whitney *et al* 2015:61; Whitney *et al* 2016:13).

The process of 'habituation' is aimed to 'habituate' or reduce a patient's responsiveness to repetitive stimuli aimed to re-balance tonic activity within the vestibular nuclei (Gans 2002:149; McDonnell and Hillier 2015:3). 'Habituation' is based on the inherent plasticity of the CNS and is more likely to be a compensatory or neuroplastic process (Hain 2011:127; McDonnell and Hillier 2015:3), rather than a physiological synaptic habituation response. Positions and movements used during the process of 'habituation' may include moving from sitting to lying in supine, rolling from supine to left side lying, rolling from supine to right side lying, moving from supine

to sitting, left and right Dix-Hallpike position; return to sitting from the Dix-Hallpike position; horizontal and vertical movement of the head and turning 180° to the left and right (Herdman and Whitney 2007:317). Thirdly, the process of substitution facilitates the use of individual or combinations of sensory input, such as visual or somatosensory (including proprioceptive) information, to facilitate vestibular compensation through the process of sensory re-weighting due to dysfunctional vestibular input (McDonnell and Hillier 2015:3). Substitution through saccadic eye movement may also be implemented as a process of 'adaptation'. Saccadic eye movement substitution may be achieved by the implementation of visual scanning exercises (VSE) integrated with task-specific activities (Van Wyk *et al* 2014:856). Progression of these exercises is guided by the patient's ability to allocate information-processing resources between two (2) tasks and to maintain sufficient attention on the visual scanning task during the dual-task performance of horizontal and vertical saccadic eye movements, as well as head movement while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856). The rehabilitation programme may also include substitution exercises that alter somatosensory cues, for example, let the patient stand on different surfaces, i.e., on foam with eyes open and closed, challenges the vestibular system by letting the patient perform activities with and without visual input; modified center of gravity exercises; and weight shifting (Whitney *et al* 2016:13). By removing or altering visual/somatosensory cues, the patient is forced to use remaining sensory–motor cues which will result in the fostering of responses by reacting on mainly vestibular cues (Herdman and Whitney 2007:315). Lastly, a comprehensive VRT exercise programme includes higher-balance activities aimed at improving an individual's balance and postural control. Standing and walking exercises are progressed by changing the patients' base of support and speed at which activities are performed (Alghadir *et al* 2013:1). Progression to dual-task activities is incorporated within safety limits as the patients' postural control improves.

To determine the various interventions implemented in the treatment of VOR-gain dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.34., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: "intervention", "vestibulo-ocular reflex"; "central vestibular dysfunction"; "stroke"

OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

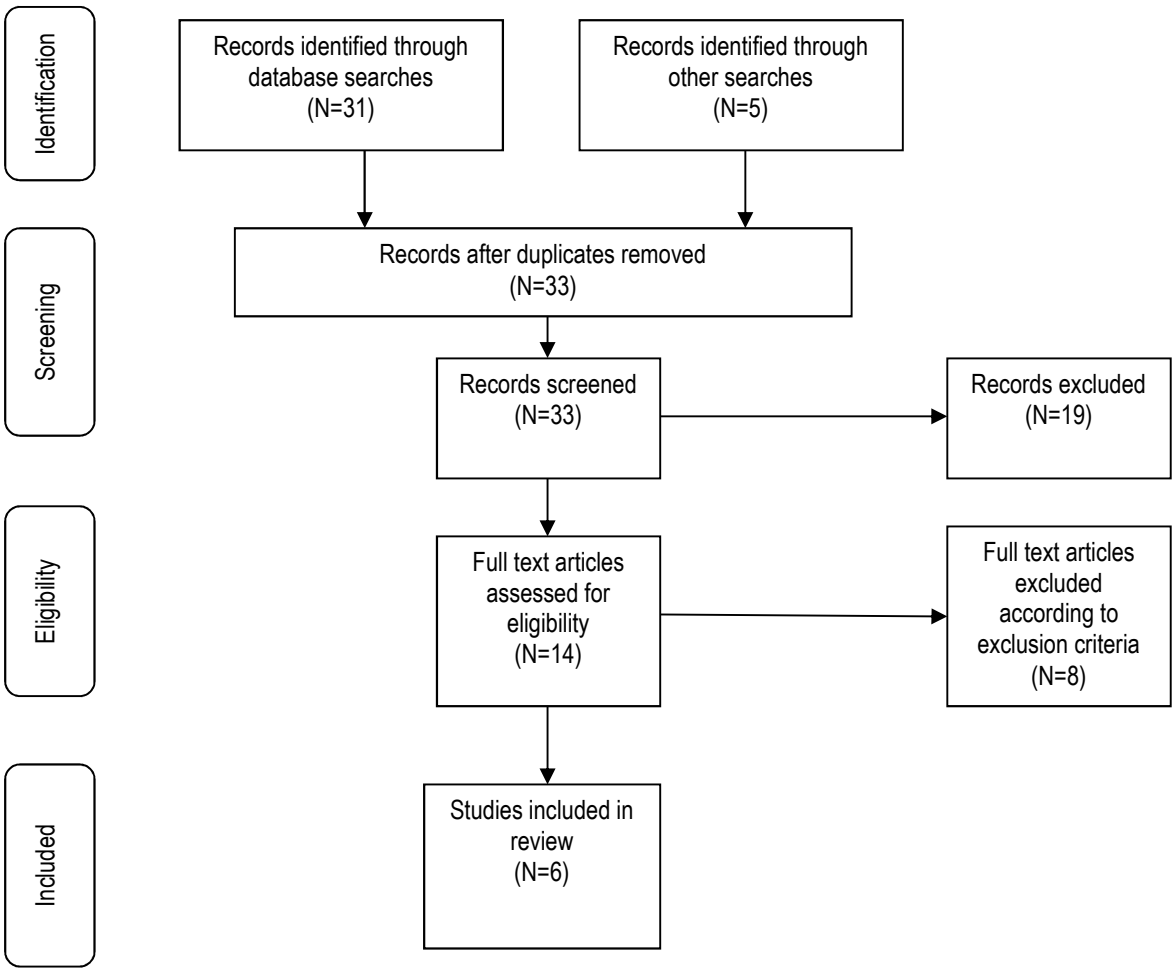


Figure 2.34.: Results of the literature search strategy on the various interventions implemented in the treatment of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Six (6) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, a prospective

observational study, a retrospective study and two (2) case series studies. Articles appraised are presented in Table 2.37.

Table 2.37.: Appraised articles on the various interventions for the treatment of VOR-gain dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=6)				
Level of Evidence				
I (N=3)	**II**	**III** (N=1)	**IV** (N=2)	**V**
Balci *et al* (2013:259)		Herron (2016:72)	Brown *et al* (2006:76)	
Dai *et al* (2013:477)			Suarez *et al* (2003:143)	
Rowe *et al* (2013:5)				

Findings of the literature appraised indicated that the clinical feature of VOR-gain dysfunction in post-stroke patients were treated using interventions that included; (a) (a) advice on adaptive strategies to optimise visual function related to gaze stabilisation (Rowe *et al* 2013:5); (b) occlusion of a spectacle lens (Rowe *et al* 2013:5); (c) use of fresnel prisms aimed to improve diplopia (Rowe *et al* 2013:5; Herron 2016:72); (d) refractive correction (Rowe *et al* 2013:5); and (e) vestibular adaptation exercises (gaze stabilisation exercises) (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477; Herron 2016:72).

Findings of the study by Rowe *et al* (2013:5) indicated that 5.0% (N=46) of the study sample presented with 'impaired gaze holding' (Section 2.3.1.2). Of the 5.0% of patients who presented with 'impaired gaze holding', 39.1% (N=18) received advice on adaptive strategies to optimise visual function related to 'impaired gaze holding'. Advice on adaptive strategies included compensatory head posture, visual field awareness, visual scanning, reading options and the use of appropriate task lighting (Rowe *et al* 2013:5). Two (2) patients (4.3%) received occlusion of a spectacle lens compared to four (4) patients (8.7%) who received fresnel prisms aimed to improve diplopia (double vision) (Rowe *et al* 2013:5). Eight (8) patients (17.4%) received refractive correction and none of the patients who presented with 'impaired gaze holding', received orthoptic exercises (Rowe *et al* 2013:5).

Although the stroke patients' (N=131) reflexive control of gaze that includes the VOR-gain or DVA (Section 2.4.1.2), were not quantified prior to the implementation of intervention, Herron (2016:72) provided gaze stabilisation exercises to 35.9% of the patients post-stroke. Herron (2016:72) described the gaze stabilisation exercises as follows: a patient has to fixate his/her eyes on a target at midline and eye level, where-after the patient rotates his/her head from left to right while maintaining visual fixation on the target. The gaze stabilisation exercises described by Herron (2016:72) are based upon the vestibular rehabilitation approach (Section 1.1.4) that specifically include the process of 'adaptation' (Section 2.5.1.2). The process of 'adaptation' for visual-vestibular interaction (gaze stabilisation) is achieved by repetitive and provocative movements of the head and/or eyes, aimed to produce an error signal that the CNS attempts to reduce by modifying the gain of the VOR (Herdman and Whitney 2007:315). Gaze stabilisation exercises to retrain VOR function are prescribed to stimulate retinal slip to optimise vision during head movement (Herdman and Whitney 2007:315). Although gaze stabilisation exercises are based upon the vestibular rehabilitation approach, Herron (2016:74) did not mention the role of the central vestibular system involved in the reflexive control of gaze that specifically include the VOR-gain post-stroke.

As gaze stabilisation exercises to retrain VOR function are considered as part of the vestibular rehabilitation approach, the studies by Suarez *et al* (2003:143), Brown *et al* (2006:76), Balci *et al* (2013:259) and Dai *et al* (2013:477) were included in the literature review as the authors investigated the effects of VRT in patients who presented with central vestibular dysfunction associated with a stroke (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). Although Brown *et al* (2006:76), Balci *et al* (2013:259) and Dai *et al* (2013:477) included vestibular adaptation exercises aimed to re-adjust the gain of the VOR, all three (3) studies posed several limitations. The first limitation is that neither of these authors quantified their study samples' VOR-gain dysfunction prior to the intervention delivered (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). Assessment on the level of body structure and function were limited to the assessment of higher vestibular function using the Rivermead Behavioural Inattention test to quantify visual-perceptual function (Dai *et al* 2013:477). Assessment on activity and participation level were limited to the assessment of impairment of sensorimotor control of balance, mobility

and gait performance using the ABC-scale (Brown *et al* 2006:76), DHI (Brown *et al* 2006:76; Balci *et al* 2013:259), DGI (Brown *et al* 2006:76; Balci *et al* 2013:259), TUG (Brown *et al* 2006:76; Balci *et al* 2013:259), FTSTS test (Brown *et al* 2006:76), BBS (Balci *et al* 2013:259) and the Postural Assessment Scale (PASS) (Dai *et al* 2013:477). Dai *et al* (2013:477) also assessed patients' functional ability using the Functional Independence Measure (FIM). Suarez *et al* (2003:143) assessed patients' VOR using electronystagmography (ENG) (N=12). Suarez *et al* (2003:143) also assessed the study samples' postural responses by determining the center of pressure (COP) distribution area using a confidence ellipse (CE) and sway velocity (SV) under two visual conditions. The two (2) visual conditions included (1) standing position, eyes open with a stable visual surrounding; and (2) standing position, eyes open with surrounding optokinetic (OK) stimulation (clockwise and counter clockwise) at an angular velocity of 65°/s (Suarez *et al* 2003:143). Patients' were also evaluated using the Dizziness Handicap Inventory (DHI) and the Test for Equilibrium Under Altered Sensory Conditions (TEUSAC) (Suarez *et al* 2003:143).

Findings of Suarez et al (2003:143) indicated that patients' parameters of postural control that include CE (stable visual surrounding: P=0.0159; OK stimulation: P=0.0019) and SV (stable visual surrounding: P=0.0037; OK stimulation: P=0.003) decreased significantly following VRT, indicating an improvement in their postural strategies. Results at long-term follow-up (12±5months post-VRT) indicated that patients (N=7) demonstrated an increase in CE and SV, indicating an impairment of postural control in the absence of any physical training. Suarez *et al* (2003:143) indicated that continuation of training may be necessary in order to maintain the improvement in postural control obtained with VRT.

Findings of Brown *et al* (2006:76) demonstrated statistically significant improvement (P<0.05) of sensorimotor control of balance, mobility and gait, specifically functional balance quantified by the FTSTS and the ability to modify gait in response to changing task demands quantified by the DGI in patients (N=10) that received VRT post-stroke (Brown *et al* 2006:76). In contrast, findings of the study by Balci *et al* (2013:259) indicated that although the sensorimotor control of balance, mobility and gait performance quantified by the BBS, TUG, DGI and DHI improved significantly in all patients (who sustained a posterior circulation stroke), no statistically significant differences were noted between the groups that received VRT (N=6), visual feedback

posturography training (N=6) or a home exercise programme (N=13). Balci *et al* (2013:259) hypothesised that improved balance and gait performance may be attributed to central compensation mechanisms due to active neuronal changes in the cerebellum and brainstem facilitated by VRT. The absence of statistically significant differences between the groups may be attributed to the small sample size (N=25). The authors recommended that: (1) a larger sample size may demonstrate differences between groups; and (2) a well-designed combination of different rehabilitation methods may improve the residual effects after the acute period in patients with central vestibular disorders post-stroke (Balci *et al* 2013:259).

Lastly, the findings of the study by Dai *et al* (2013:477) indicated although higher vestibular function, specifically visual-perceptual function, functional balance and functional ability, improved significantly ($P<0.000$) in patients who presented with visual-perceptual dysfunction following a right hemispheric stroke, no statistically significant difference were noted between the control group (N=24) that received 'conventional rehabilitation' and the experimental group (N=24) that received 'conventional rehabilitation' and VRT as an add-on intervention. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai et al (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training. The patients received VRT over a four-week intervention period. During the first two (2) weeks, a registered nurse treated the experimental group where-after patients' informal caregivers took over treatment for the last two (2) weeks of the intervention period. The informal caregivers received only twenty (20) to forty (40) minutes training in VRT from the registered nurse who delivered VRT during the initial two (2) weeks of the intervention period. After the brief training, the patients' informal caregivers were responsible for the supervision and guidance of the intervention received by patients in the experimental group.

The second feature of reflexive control of gaze to be considered is dynamic visual acuity.

(ii). Intervention for dynamic visual acuity impairment

To determine the various interventions implemented in the treatment of dynamic visual acuity impairment in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.35., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “dynamic visual acuity”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of dynamic visual acuity impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

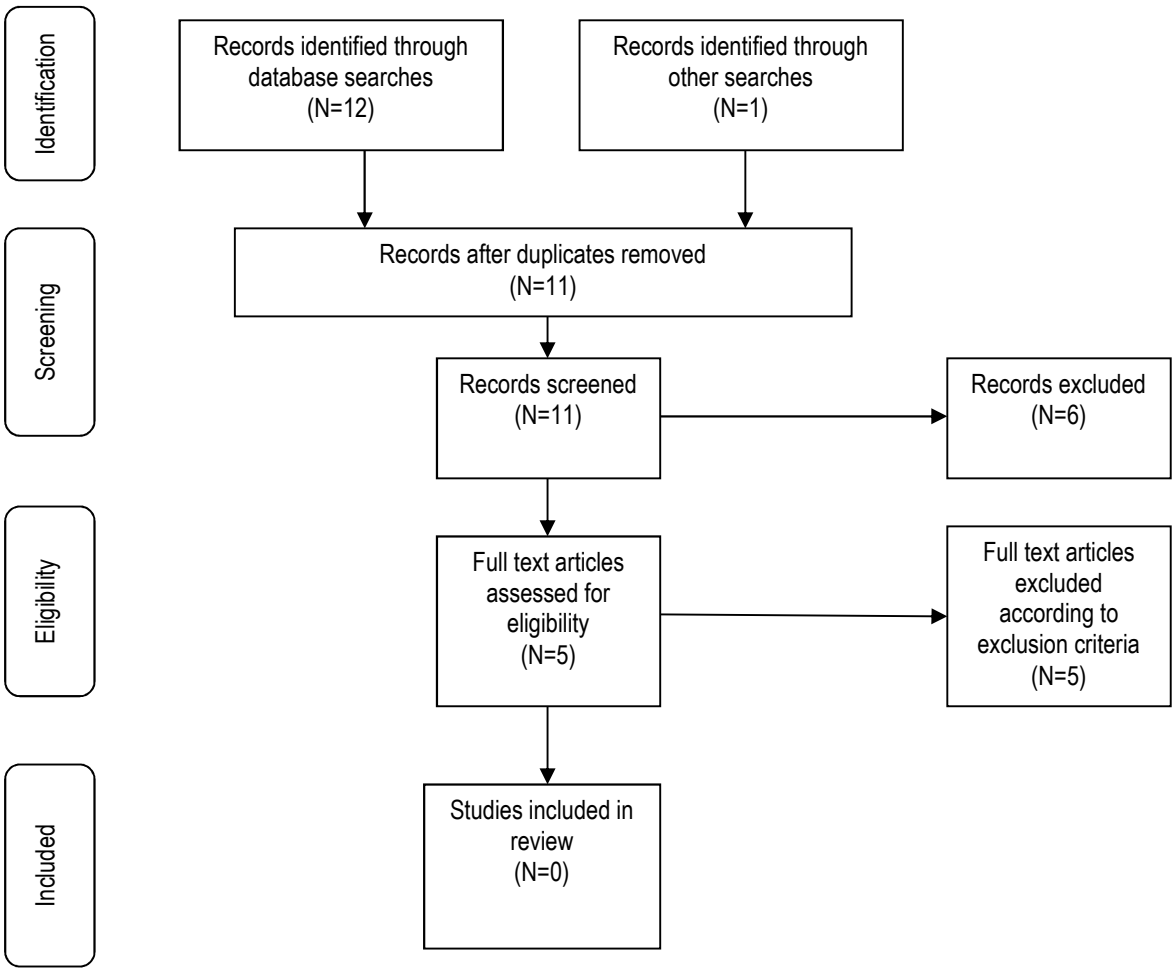


Figure 2.35.: Results of the literature search strategy on the various interventions implemented in the treatment of dynamic visual acuity impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

No studies were found that implemented interventions aimed to improve impaired dynamic visual acuity in patients post-stroke. The third clinical feature of central vestibular dysfunction on the level of body structure and function is saccule and inferior vestibular nerve function, discussed in in Section 2.5.1.3.

2.5.1.3. Saccule and inferior vestibular nerve function

To determine the various interventions implemented in the treatment of saccule and inferior vestibular nerve function impairment in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.36., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “saccule; “inferior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of saccule and inferior vestibular nerve function impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

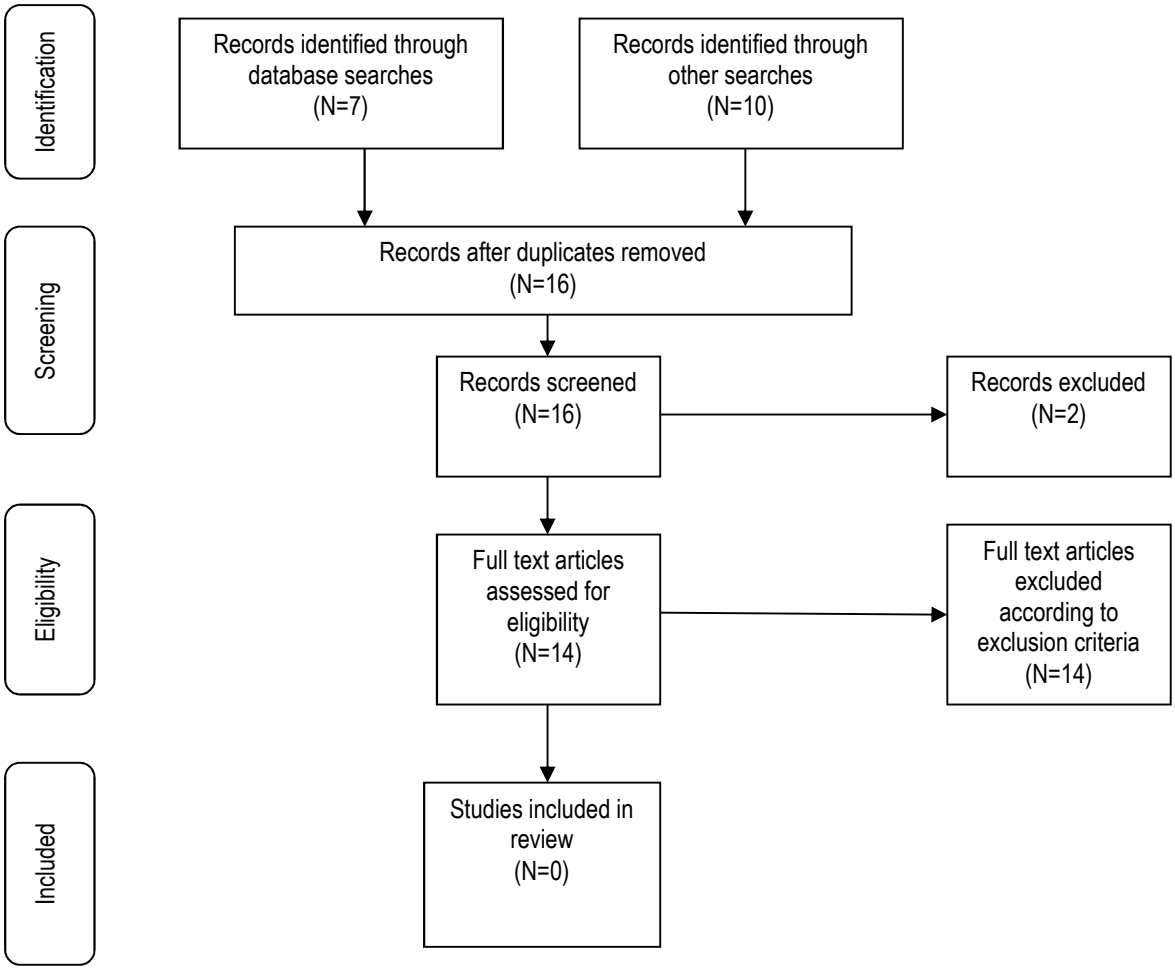


Figure 2.36.: Results of the literature search strategy on the various interventions implemented in the treatment of saccule and inferior vestibular nerve function impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

No studies were found that implemented interventions aimed to improve impaired saccule and inferior vestibular nerve function in patients post-stroke. The fourth clinical feature of central vestibular dysfunction on the level of body structure and function is the utricle and superior vestibular nerve function, discussed in Section 2.5.1.4.

2.5.1.4. Utricle and superior vestibular nerve function

To determine the various interventions implemented in the treatment of utricle and superior vestibular nerve function impairment in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.37., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”, “utricle; “superior vestibular nerve function”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of utricle and superior vestibular nerve function impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

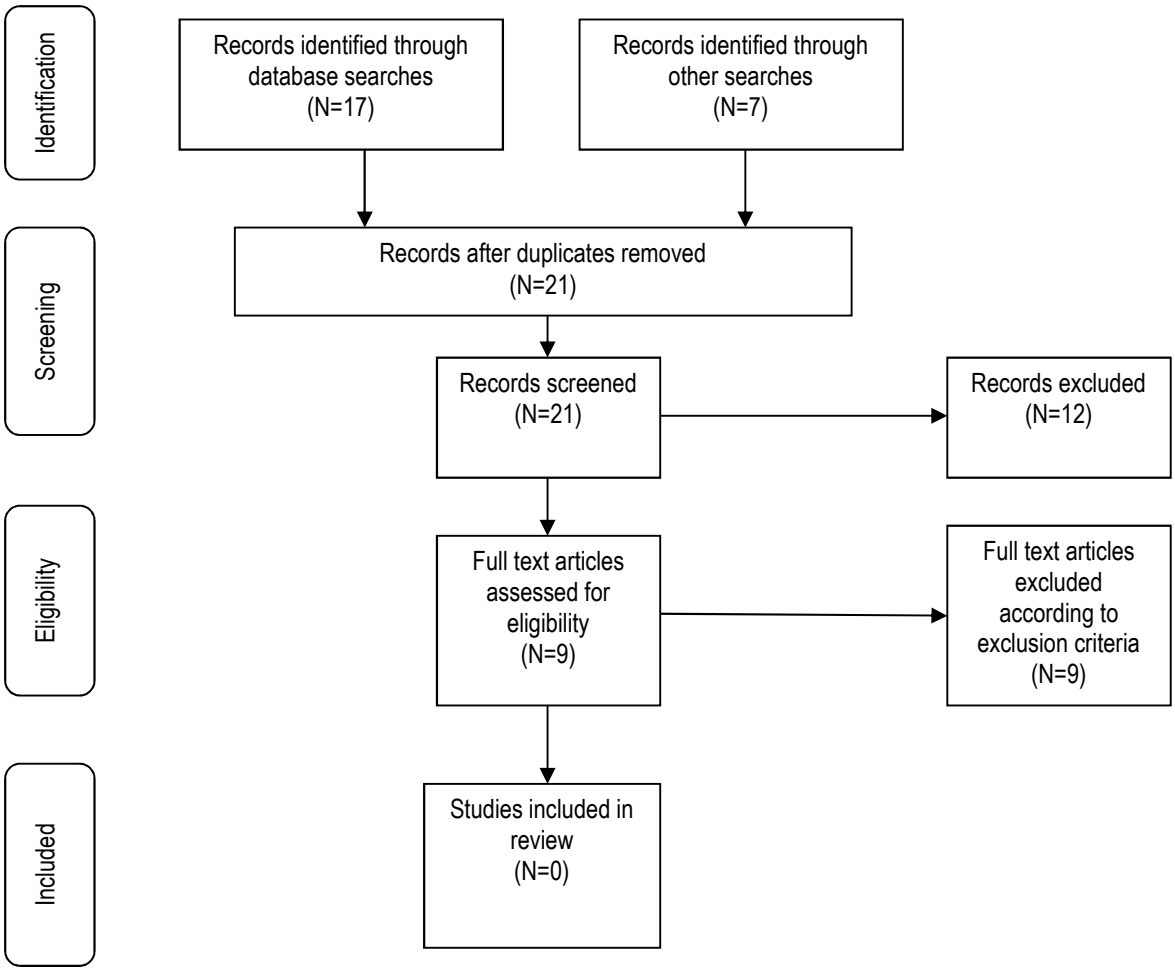


Figure 2.37.: Results of the literature search strategy on the various interventions implemented in the treatment of utricle and superior vestibular nerve function impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

No studies were found that implemented interventions aimed to improve impaired utricle and superior vestibular nerve function in patients post-stroke. The fifth (5^{th}) clinical feature of central vestibular dysfunction on the level of body structure and function to consider is higher vestibular function, discussed Section 2.5.1.5.

2.5.1.5. Higher vestibular function

In the current study, the management of impaired higher vestibular function is limited to the impairment of residual oculomotor visual performance, visual-perceptual function and cognitive function. The first feature of higher vestibular function to be discussed, is residual oculomotor visual performance.

(i). Intervention for residual oculomotor visual performance function impairment

To determine the various interventions implemented in the treatment of impaired residual oculomotor visual performance function in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.38., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”; “residual oculomotor visual performance”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

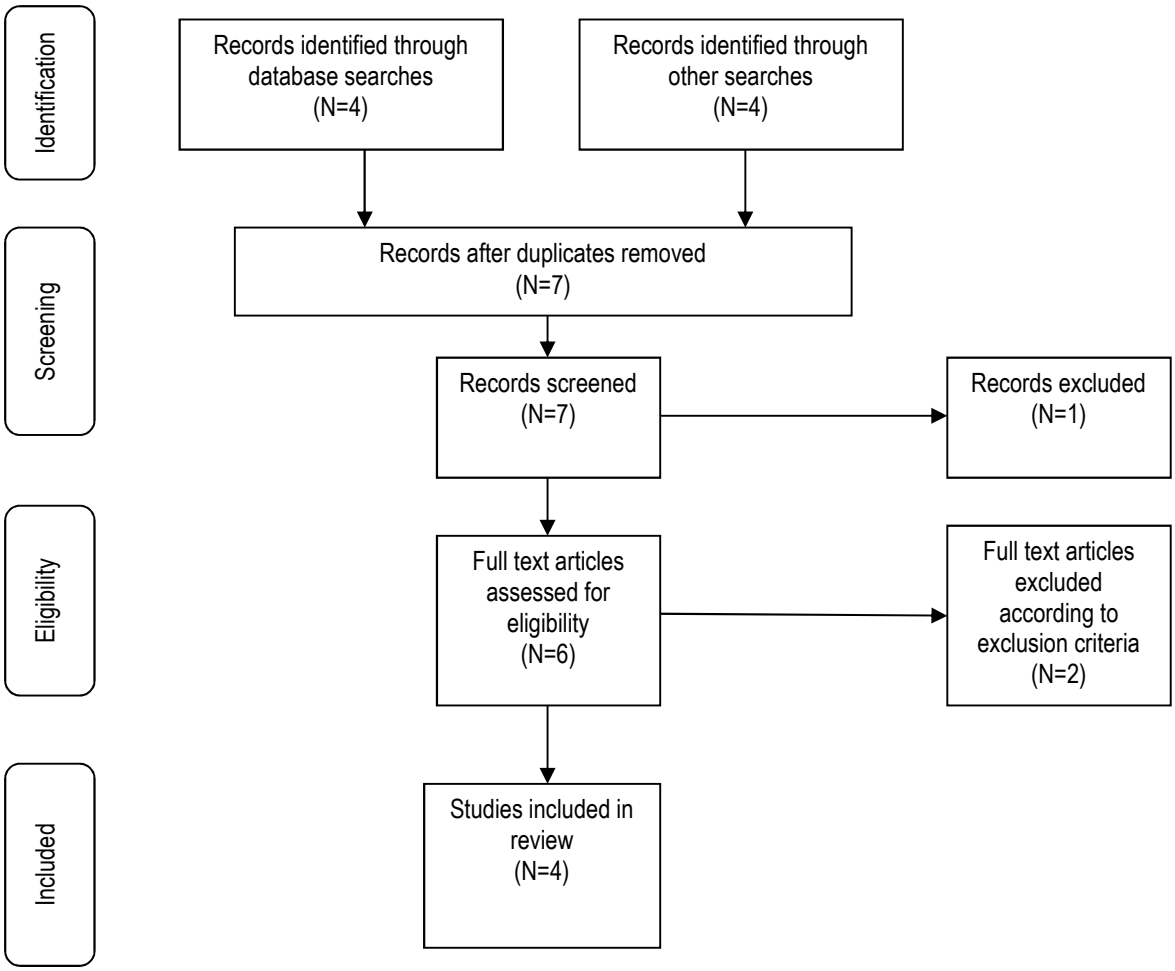


Figure 2.38.: Results of the literature search strategy on the various interventions implemented in the treatment of impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Four (4) articles were critically reviewed and an appraisal of the quality of evidence was completed. The articles appraised included an RCT, a prospective observational study, a case study and a case series. Articles appraised are presented in Table 2.38.

Table 2.38.: Appraised articles on the various interventions for the treatment of impaired residual oculomotor visual performance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=4)				
Level of Evidence				
I (N=2)	**II**	**III**	**IV** (N=2)	**V**
Rowe *et al* (2011:406)			Kapoor *et al* (2004:1667)	
Van Wyk *et al* (2014:856)			Ciuffreda *et al* (2006:9)	

Findings of the literature appraised, indicated that the clinical feature of impaired residual oculomotor visual performance function in post-stroke patients were treated using interventions that included; (a) single-line and multiple-line simulated reading (Kapoor *et al* 2004:1667; Ciuffreda *et al* 2006:9); (b) advice on adaptive strategies to optimise residual oculomotor visual performance function (Rowe *et al* 2011:408); (c) refractive correction (Rowe *et al* 2011:408); (d) typoscope reading guide (Rowe *et al* 2011:408); (e) use of prisms aimed to improve diplopia (Rowe *et al* 2011:408); (f) tracking exercises (Rowe *et al* 2011:408); (g) low vision aids (Rowe *et al* 2011:408); (h) occlusion of a spectacle lens (Rowe *et al* 2011:408); (i) use of Peli prisms aimed to improve diplopia (Rowe *et al* 2011:408); (j) convergence exercises (Rowe *et al* 2011:408); (k) cortical visual impairment registration (Rowe *et al* 2011:408); and (l) saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856).

Findings of the study by Rowe *et al* (2013:5) indicated that advice on adaptive strategies to optimise residual oculomotor visual performance function, included compensatory head posture, visual field awareness, visual inattention awareness, reading strategies and the use of appropriate lighting (Rowe *et al* 2011:408). Other visual rehabilitation options aimed to improve the residual oculomotor visual performance function provided by Rowe *et al* (2011:406), included refractive correction, typoscope, prisms, tracking exercises, low vision aids, occlusion of a spectacle lens, Peli prisms, convergence exercises and cortical visual impairment registration. Van Wyk *et al* (2014:856) implemented saccadic eye movement training

with visual scanning exercises (VSEs), integrated with task-specific activities in the treatment of patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) post-stroke. Findings of the study by Van Wyk *et al* (2014:856) demonstrated statistically significant improvement of residual oculomotor visual performance function (P=0.021) quantified by the King-Devick Test©, higher vestibular function, specifically visual-perceptual function (P=0.016), quantified by the Star Cancellation Test and functional ability (P=0.004) quantified by the BI. Van Wyk *et al* (2014:856) concluded that significant improved residual oculomotor visual performance function and visual-perceptual function translated to significantly improved ability to perform ADLs post-stroke.

As previously discussed (Section 2.5.1.1), Kapoor *et al* (2004:1667) and Ciuffreda *et al* (2006:9) implemented single-line and multiple-line simulated reading twice per week over an eight (8)-week intervention period. Both studies concluded that patients presented with improved basic ocular motility and reading ability following oculomotor rehabilitation that specifically included simulated reading. Although these studies demonstrated significant improvement of basic oculomotor and reading-related oculomotor parameters, the studies' sample sizes were limited to only one (1) stroke patient in the case study by Kapoor *et al* (2004:1667) and five (5) stroke patients in the case series by Ciuffreda *et al* (2006:9) (Section 2.5.1.1). The second feature of higher vestibular function to be discussed, is visual-perceptual function.

(ii). Intervention for visual-perceptual dysfunction

Published articles that have assessed various interventions in the management of visual–perceptual dysfunction post-stroke, includes the following treatment techniques; (a) neck-muscle vibration; (b) caloric vestibular stimulation; (c) galvanic stimulation; (d) prism adaptation aimed to improve diplopia ; (e) TMS; (f) transcranial direct current stimulation (TDCS); (g) visuomotor feedback training; (h) functional electric stimulation (FES); (i) combination of visual scanning training and FES; (j) eye-patching in combination with conventional occupational therapy; and (k) virtual reality training (Kerkhoff and Schenk, 2012). In this section, the literature review of interventions used in the treatment of the clinical feature of impaired higher vestibular function, specifically visual-perceptual dysfunction in post-stroke patients, are limited to articles previously reviewed (Section 2.2.5.2. and Section 2.3.5.2).

To determine the various interventions implemented in the treatment of visual–perceptual dysfunction in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.39., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”; “visual–perceptual dysfunction”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of visual–perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

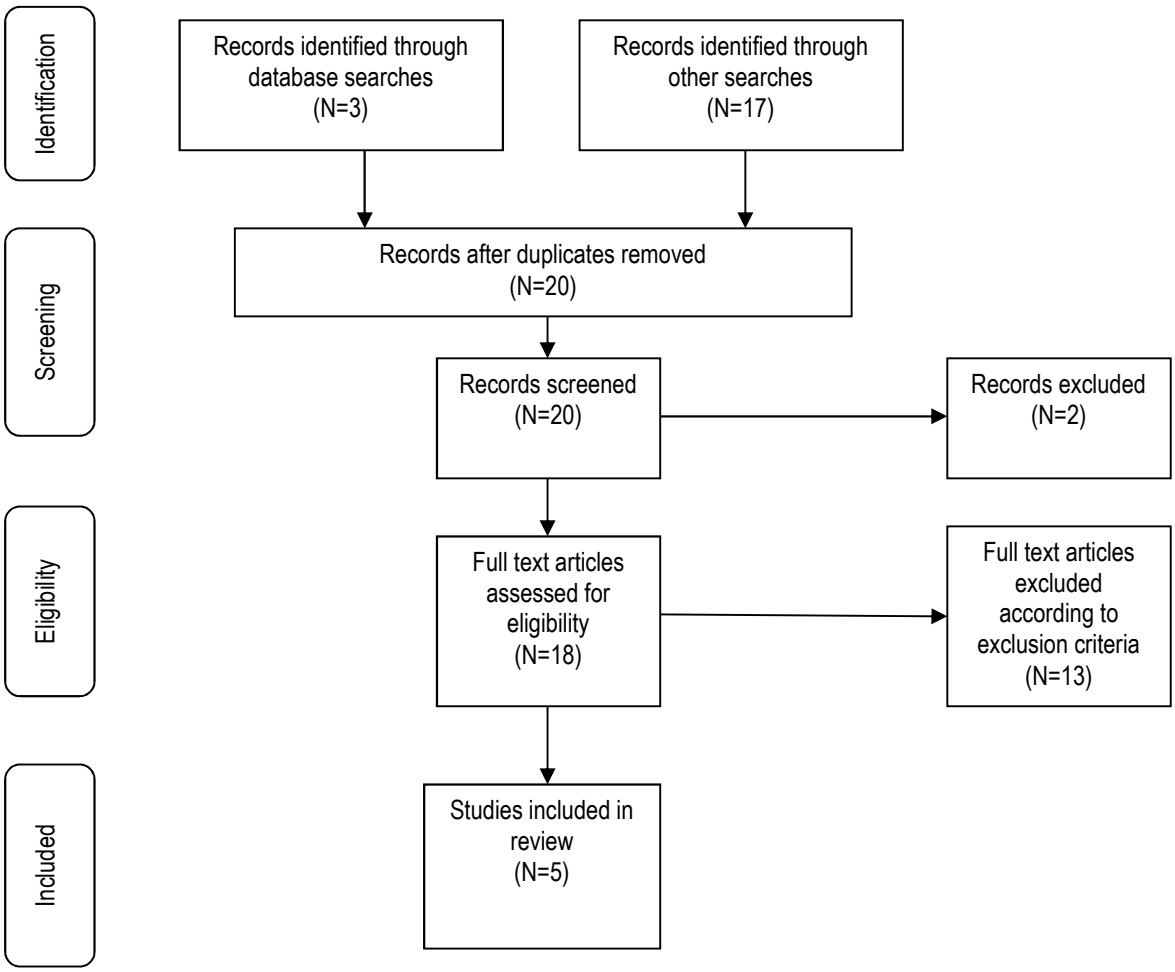


Figure 2.39.: Results of the literature search strategy on the various interventions implemented in the treatment of visual–perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Five (5) articles were critically reviewed and an assessment for the quality of evidence was completed. All five (5) articles appraised were RCTs (Kerkhoff *et al* 2012:1164; Dai *et al* 2013:477; Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856). Articles appraised are presented in Table 2.39.

Table 2.39.: Appraised articles on the various interventions for the treatment of visual-perceptual dysfunction due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=5)				
Level of Evidence				
I (N=5)	**II**	**III**	**IV**	**V**
Kerkhoff *et al* (2012:1164)				
Dai *et al* (2013:477)				
Kerkhoff *et al* (2013:789)				
Kerkhoff *et al* (2014:557)				
Van Wyk *et al* (2014:856)				

Findings of the literature appraised indicated that the clinical feature of impaired higher vestibular function, specifically visual-perceptual dysfunction in post-stroke patients, were treated using interventions that included; (a) optokinetic stimulation to elicit smooth pursuit eye movements (Kerkhoff *et al* 2012:1164); (b) vestibular rehabilitation therapy (Dai *et al* 2013:477); (c) smooth pursuit eye movement training (Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557); (d) saccadic eye movement training (Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557); and (e) saccadic eye movement training with visual scanning exercises (VSEs), integrated with task-specific activities (Van Wyk *et al* 2014:856).

Kerkhoff *et al* (2012:1164) implemented optokinetic stimulation that elicited smooth pursuit eye movements in the treatment of impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) and auditory neglect, in patients (Section 2.2.5.2). Kerkhoff *et al* (2012:1164) concluded that optokinetic stimulation therapy with smooth pursuit eye movements is a multimodal, effective and

easily applicable technique for the treatment of patients who present with auditory and visual neglect post-stroke. In two (2) follow-up studies, Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) implemented both smooth pursuit, as well as saccadic eye movement training, to compare the effect of these two (2) interventions in the treatment of visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.2.5.2). Findings of the study by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) demonstrated that repetitive contra-lesional smooth pursuit eye movement training was associated with superior, multimodal therapeutic effects compared to saccadic eye movement training in patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect). Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) concluded that smooth pursuit eye movement training is effective and feasible in the treatment of patients who present with higher vestibular function impairment, specifically visual-perceptual dysfunction, post-stroke. Saccadic eye movement training described by Kerkhoff *et al* (2013:789) and Kerkhoff *et al* (2014:557) included visual scanning training that consisted of visual scanning of an array of stationary horizontal and vertical target symbols on the display of a computer screen by starting at the top left corner and ending at the bottom right, without head movements (Kerkhoff *et al* 2013:789; Kerkhoff *et al* 2014:557; Hill *et al* 2015:410).

Dai *et al* (2013:477) implemented vestibular rehabilitation therapy in the treatment of patients who presented with visual-perceptual dysfunction following a right hemispheric stroke. The two groups were comparable prior to the invention period and did not differ significantly in age, gender, number of days post-stroke and cognitive function at baseline. Findings of the study by Dai *et al* (2013:477) indicated that no statistically significant difference were noted between the visual-perceptual function, functional balance and functional ability of the control group (N=24) that received 'conventional rehabilitation' and the experimental group (N=24) that received 'conventional rehabilitation' and VRT as an add-on intervention. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai et al (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training. Although no statistically significant difference in visual-perceptual function, functional balance and functional ability were noted between the groups, significant with-in group improvement ($P<0.000$) of visual-

perceptual function measured by the Rivermead Behavioural Inattention test, functional balance measured by the PASS and functional ability quantified by the FIM (Dai *et al* 2013:477), were observed. Although no statistically significant difference in visual-perceptual function, functional balance and functional ability were noted between the two groups, the experimental group demonstrated a higher post mean (88.71 vs. 68.83) (P=0.130) in visual-perceptual function, a higher post mean (76.21 vs. 65.17) (P=0.093) in functional ability and a higher post mean (21.54 vs. 18.04) (P=0.094) in functional balance after the four (4)-week intervention period, compared to the control group.

Lastly, Van Wyk *et al* (2014:856) implemented saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities in the treatment of patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect), post-stroke. Findings of the study by Van Wyk *et al* (2014:856) demonstrated statistically significant improvement of residual oculomotor visual performance function (P=0.021), quantified by the King-Devick Test©, higher vestibular function, specifically visual-perceptual function (P=0.016) quantified by the Star Cancellation Test and functional ability (P=0.004) quantified by the BI. Van Wyk *et al* (2014:856) concluded that saccadic eye movement training with visual scanning exercises as an intervention has an effect on the visual-perceptual function of patients post-stroke. Van Wyk *et al* (2014:856) further concluded that the significant improvement in patients' visual-perceptual function translated to significant improved ability to perform ADLs post-stroke. It is important to highlight that none of the articles appraised mentioned the role of the central vestibular system involved in impaired higher vestibular function, specifically visual-perceptual function post-stroke (Section 1.1.3.1). The third feature of higher vestibular function to be discussed is cognitive function.

(iii). Intervention for cognitive impairment

Published articles that have assessed various interventions for the management of cognitive impairment post-stroke, include attention, visual perception, apraxia, language and communication, memory, executive function, problem solving, awareness and comprehensive-holistic cognitive rehabilitation (Cicerone *et al* 2005:1681). In this section, the literature review of intervention strategies used in the

treatment of cognitive impairment in post-stroke patients, are limited to articles previously reviewed (Section 2.3.1.5. and Section 2.4.1.5).

To determine the various interventions implemented in the treatment of cognitive impairment in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.40., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”; “cognitive impairment”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

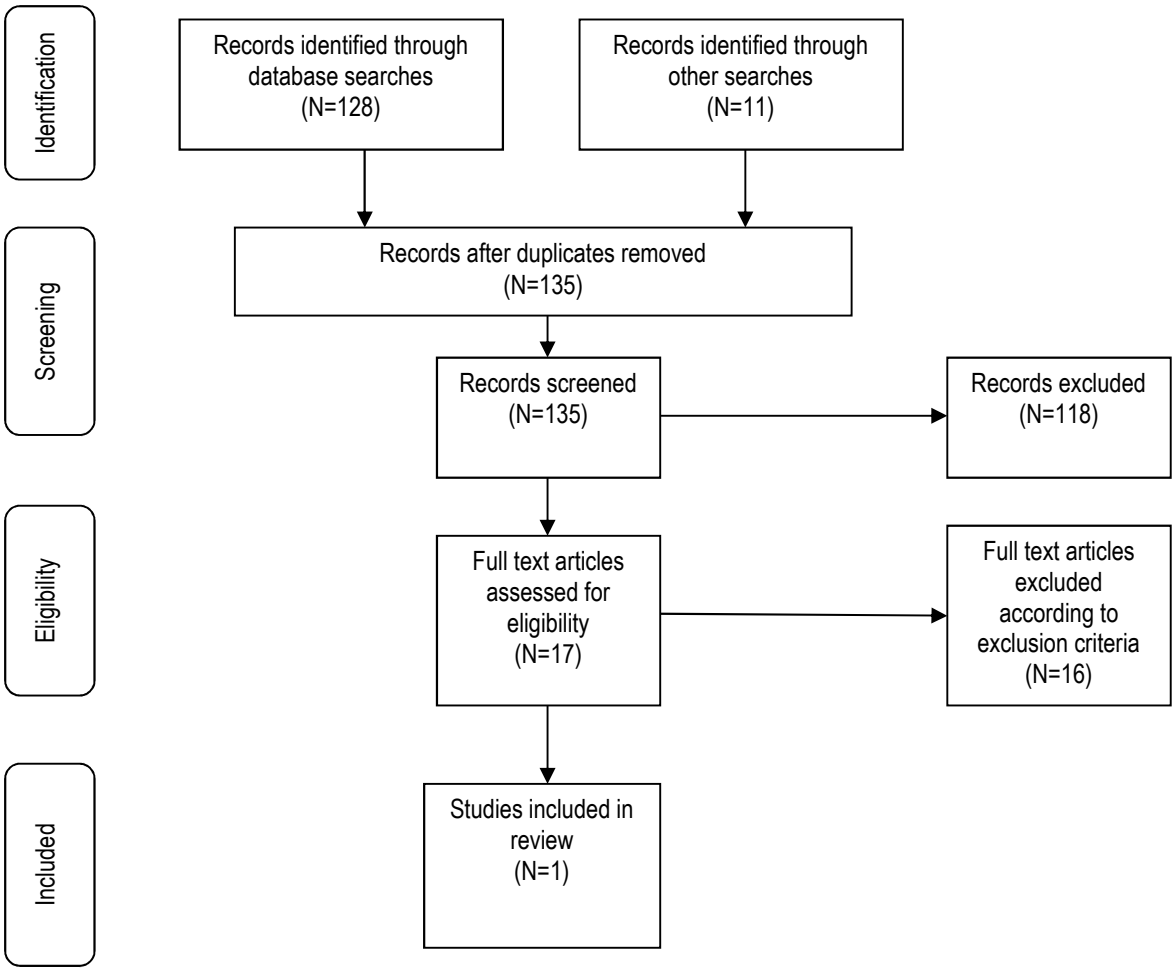


Figure 2.40.: Results of the literature search strategy on the various interventions implemented in the treatment of cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Only one (1) article was critically reviewed and an assessment of the quality of evidence was completed. The article appraised was a retrospective study (Ng *et al* 2005:2138). The article appraised is presented in Table 2.40.

Table 2.40.: Appraised article on the various interventions for the treatment of cognitive impairment due to central vestibular dysfunction in the sub-acute post-stroke population.

Article appraised for the quality of evidence (N=89)				
Level of Evidence				
I	**II**	**III** (N=89)	**IV**	**V**
		Ng *et al* (2005:2138)		

The aim of the retrospective study by Ng *et al* (2005:2138) was to describe the demographics, clinical profile and functional outcomes in patients with posterior cerebral artery (PCA) stroke and to identify the factors associated with functional change during rehabilitation and discharge planning. All patients (N=89) received a comprehensive rehabilitation program that included physiotherapy, occupational therapy and speech and language therapy for an average of three (3) hours per day. Findings of the study by Ng *et al* (2005:2138) indicated that comprehensive rehabilitation has a statistically significant effect ($P<0.001$) on motor impairments quantified by the FIM motor score, cognitive impairments quantified by the FIM cognitive score and functional ability quantified by the total FIM score in patients with PCA stroke. The results of the studies by Ng *et al* (2005:2138) limit the generalizability of the findings to patients who have suffered strokes in other vascular territories.

The sixth and final clinical feature of central vestibular dysfunction on the level of body structure and function to consider, is the presence of anxiety and/or depression in the sub-acute phase post-stroke. The level of anxiety and/or depression post-stroke is discussed in Section 2.5.1.6.

2.5.1.6. Level of anxiety and/ or depression post-stroke

To determine the various interventions described in the treatment of anxiety and/or depression in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.41., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases, using the following key words: “intervention”; “anxiety”; “depression”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

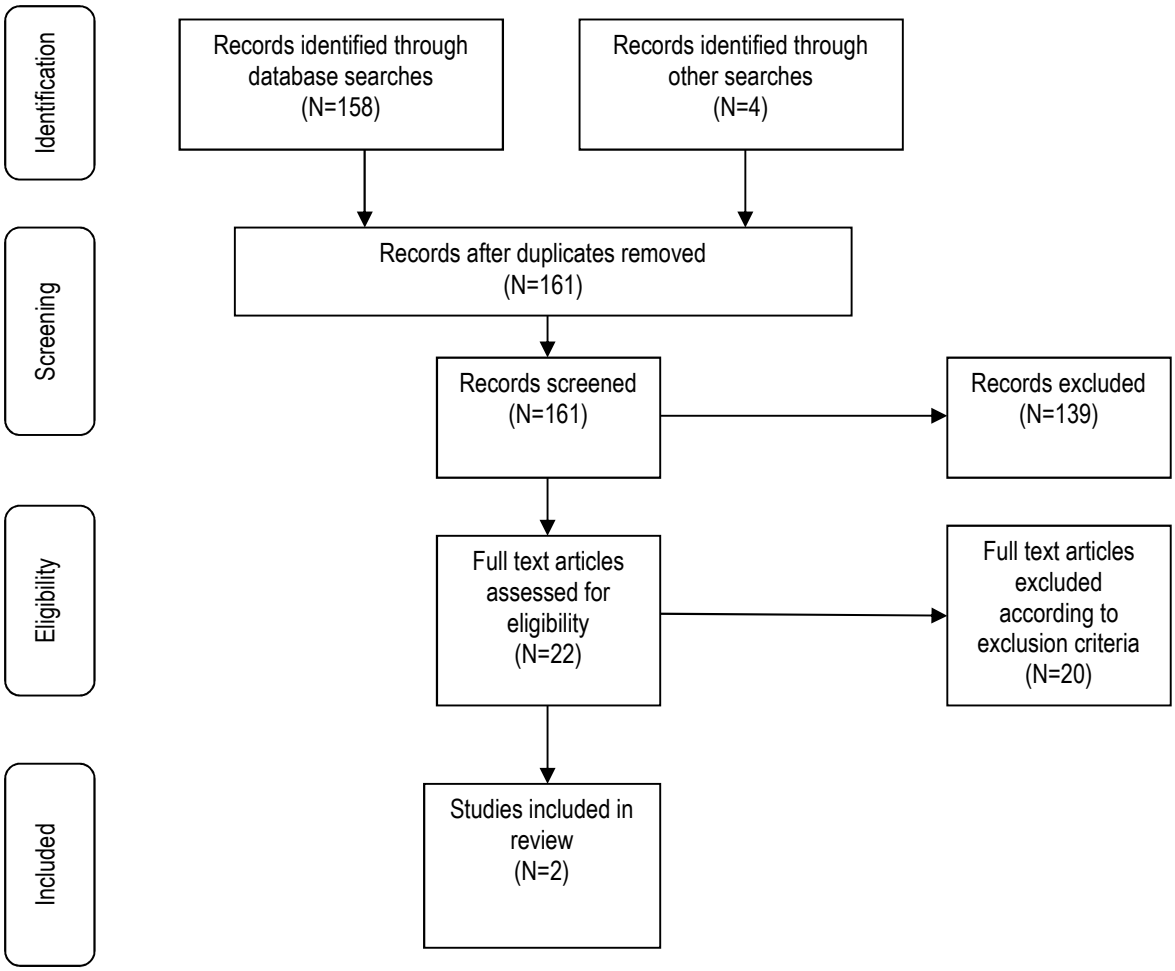


Figure 2.41.: Results of the literature search strategy on the various interventions implemented in the treatment of anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Two (2) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a RCT and case-study. Articles appraised are presented in Table 2.41.

Table 2.41.: Appraised articles on the various interventions for the treatment of anxiety and/or depression due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=2)				
Level of Evidence				
I	**II** (N=1)	**III**	**IV** (N=1)	**V**
	Meli *et al* (2007:185)		Nagaratnam *et al* (2005:253)	

Findings of the literature reviewed indicated that the clinical features of anxiety and/ or depression in post-stroke patients were treated using interventions that included a combination of pharmacological and rehabilitation therapy (Nagaratnam *et al* 2005:253) and VRT (Meli *et al* 2007:185).

The case series by Nagaratnam *et al* (2005:253) included one (1) patient with a history of longstanding intermittent vestibular symptoms, such as dizziness followed by bouts of nausea and vomiting, decreased balance, recurrent falls and anxiety. The patient had a history of a right lacunar stroke suffered several years prior to the case series research, which resulted in left-sided residual weakness. Nagaratnam *et al* (2005:253) indicated that the patient received a combination of pharmacological and rehabilitation therapy. Although Nagaratnam *et al* (2005:253) indicated that the patient returned home after a successful period of rehabilitation, the authors did not mention whether the patient's level of anxiety and/or depression improved after the intervention period. Nagaratnam *et al* (2005:253) also did not specify the duration of the intervention period nor the treatment principles of the rehabilitation therapy provided to the patient.

The aim of this study by Meli *et al* (2007:185) was to assess the effects of VRT (without behavioural or pharmacological therapy) in chronic vestibular patients. Only three (3) patients with central vestibular dysfunction were included in the study sample. The diagnosis of central vestibular dysfunction was based on positive magnetic resonance imaging (MRI) scans of vestibular pathway lesions and signs of the centrality of the electronystagmography and/or the auditory brain response. Patients received VRT that consisted of a programme of adaptation for visual-vestibular interaction (gaze

stabilisation), substitutional and/or habitual exercises aimed to readjust the gain of the VOR, habituate the patient to movement, facilitate sensory substitution and improve a person's balance and postural control (Alghadir *et al* 2013:1). Results of the study by Meli *et al* (2007:185) indicated that VRT has a statistically significant effect ($P<0.001$) on patients' anxiety assessed by the State-Trait Anxiety Inventory (STAI) and depression quantified by the Center for Epidemiological Studies Depression Scale (CES-D) in patients with chronic vestibular dysfunction. Within-group data analysis pertaining to only patients with central vestibular dysfunction, were not described.

Central vestibular dysfunction is also identified by impairment on activity and participation level because it includes; (1) impaired sensorimotor control of balance, mobility and gait; and (2) functional ability. The first impairment on activity and participation level to be discussed in Section 2.5.2., is impaired sensorimotor control of balance, mobility and gait.

2.5.2. Activity and participation level

2.5.2.1. Sensorimotor balance, mobility and gait

The first activity limitation of sensorimotor balance, mobility and gait to be discussed is functional balance.

(i). Intervention for functional balance impairment

The improvement of functional balance of a post-stroke patient is a major goal for rehabilitation interventions to improve a patient's ability to achieve and maintain a state of equilibrium during any posture or activity (Van Nes *et al* 2009:819; Påhlman *et al* 2011:1952). The restoration of balance in post-stroke patients is a prerequisite for independence in functional tasks such as transfers, walking and social participation (Påhlman *et al* 2011:1952). Improved functional balance are associated with a decreased risk of falling post-stroke and is an important prognostic indicator for length of stay in hospital and discharge placement following a stroke (Van Nes *et al* 2009:819; Påhlman *et al* 2011:1952).

To determine the various interventions implemented in the treatment of impaired functional balance in the sub-acute post-stroke population, the literature search

strategy indicated in Figure 2.42., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases using the following key words: “intervention”; “functional balance”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population were included in this section of the review.

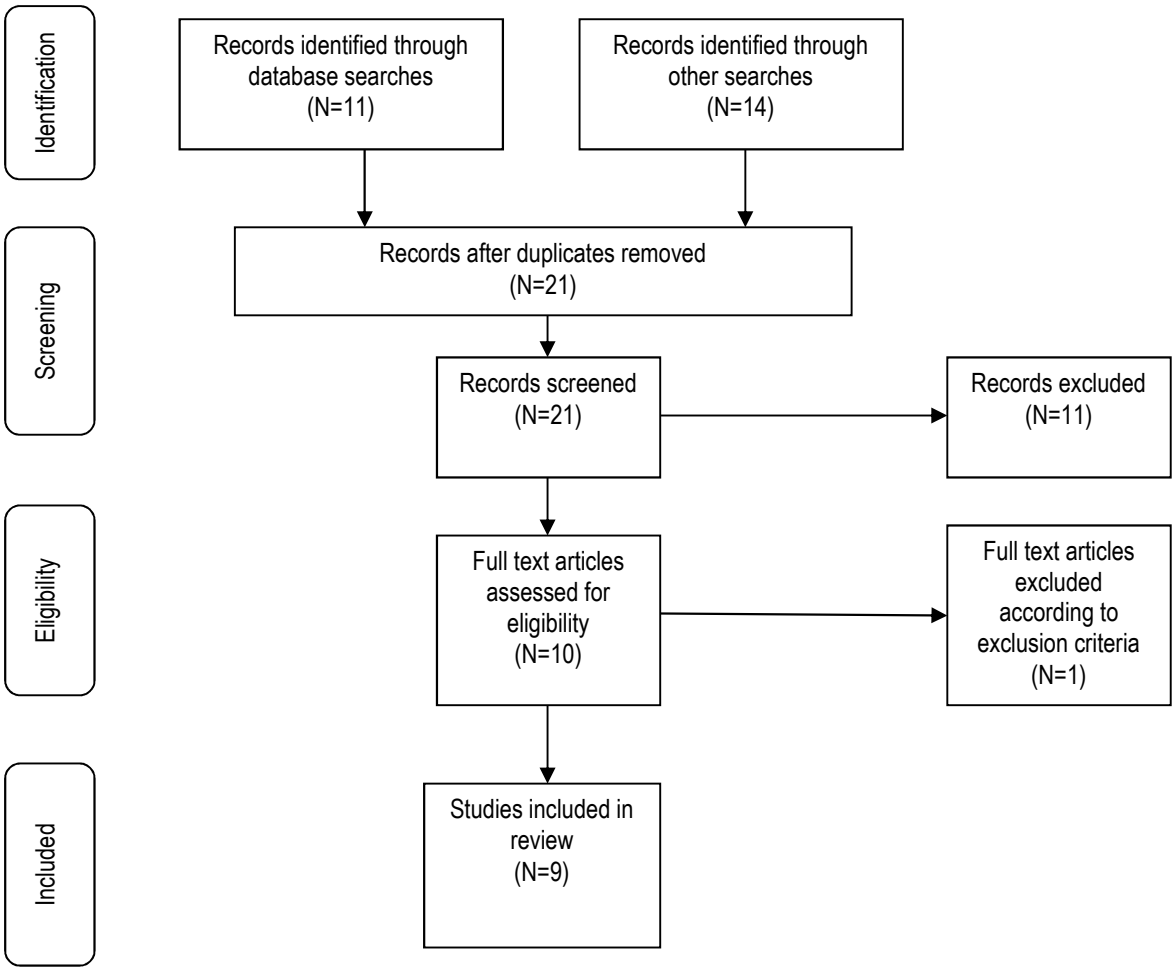


Figure 2.42.: Results of the literature search strategy on the various interventions implemented in the treatment of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Nine (9) articles were critically reviewed and an assessment for the quality of evidence was completed. The articles appraised included three (3) RCTs, a prospective observational study and five (5) case series studies. Articles appraised are presented in Table 2.42.

Table 2.42. Appraised articles on the various interventions for the treatment of impaired functional balance due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=9)				
Level of Evidence				
I (N=4)	**II**	**III**	**IV** (N=5)	**V**
Bonan *et al* (2004:274)			Suarez *et al* (2003:143)	
Van Nes *et al* (2009:819)			De Haart *et al* (2004:886)	
Balci *et al* (2013:259)			Brown *et al* (2006:76)	
Dai *et al* (2013:477)			Smania *et al* (2008:313)	
			Schow *et al* (2016:333)	

Findings of the literature reviewed indicated that the activity and participation limitation of impaired functional balance in post-stroke patients were treated using interventions that included; (a) exercises performed in supine or prone position (Bonan *et al* 2004:274); (b) exercises performed in a sitting position (Bonan *et al* 2004:274); (c) exercises performed in four point kneeling (Bonan *et al* 2004:274); (d) exercises performed in an upright position (Bonan *et al* 2004:274; Smania *et al* 2008:313); (e) balance training on a treadmill (Bonan *et al* 2004:274); (f) balance training on a stationary bicycle (Bonan *et al* 2004:274); (g) walking on a foam rubber track with obstacles (Bonan *et al* 2004:274); (h) individual physiotherapy sessions embedded in an extensive, individualized NDT rehabilitation program with a general emphasis on the optimal use of the paretic body side (De Haart *et al* 2004:886); (i) individualised physiotherapy sessions (Van Nes *et al* 2009:819); (j) group sessions of physiotherapy (Van Nes *et al* 2009:819); (k) vestibular rehabilitation therapy (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477); (l) visual feedback posturography training (VFPT) (Balci *et al* 2013:259); (m) basic balance and mobility

home exercise programme (Balci *et al* 2013:259; Dai *et al* 2013:477); and (n) a combination of balance training and visual therapy (Schow *et al* 2016:333).

Bonan *et al* (2004:274) randomly assigned patients to either a balance rehabilitation programme with visual cue deprivation or without visual cue deprivation. The rehabilitation program was exactly the same for the two groups (vision-deprived group vs. group without visual cue deprivation) except that the eyes of the vision-deprived group were blinded with a mask throughout the treatment sessions. The aim of the visual cue deprivation was to facilitate the patients' utilisation of somatosensory and vestibular inputs and to decrease their reliance on visual input during balance training. The program consisted of one-hour sessions for four consecutive weeks (total of twenty (20) therapy sessions). A therapy session commenced with five (5) minutes of spasticity inhibition followed by one (1)-hour dedicated to balance training. The hour of balance training included thirty (30) minutes of exercises performed in the supine or prone position, sitting position, four-point kneeling and exercises performed in an upright position. Each session then included twenty (20) minutes of balance training on a treadmill and stationary bicycle and ended with ten (10) minutes of walking on a foam rubber track with obstacles (Bonan *et al* 2004:274).

All patients who participated in the study by De Haart *et al* (2004:886) received a minimum of five (5) weekly 30-minute sessions of individual physiotherapy, three weekly 30-minute sessions of occupational therapy and daily 60-minute group therapy. Motor rehabilitation consisted of an extensive, individualised NDT programme with general emphasis placed upon the optimal use of the paretic side of the body.

Van Nes *et al* (2009:819) implemented an individualised treatment program that consisted of a minimum of five (5) 30-minute individual sessions of physiotherapy, five (5) 60-minute group sessions of physiotherapy and three (3) 30-minute individual sessions of occupational therapy. Smania *et al* (2008:313) implemented a sensory integration and balance training programme that consisted of twenty (20) 50-minute sessions over a four (4)-week period. The sensory integration and balance training programme consisted of weight transfer and balance exercises performed in an upright position without any support.

Suarez *et al* (2003:143) administered VRT that included training of the VOR, (eye–head coordination exercises), smooth pursuit and saccadic eye movements, OK

stimulation, habituation exercises and postural control training (COG training, stepping and gait training in different sensory circumstances). Brown *et al* (2006:76) and Balci *et al* (2013:259) implemented VRT that consisted of a programme of adaptation, substitutional and/or habituation exercises aimed to readjust the gain of the VOR, habituate the patient to movement, facilitate sensory substitution and improve patients' functional balance and postural control (Alghadir *et al* 2013:1). The VRT programme administered by Dai *et al* (2013:477) consisted of vestibular adaptation exercises aimed to improve patients' gaze stability post-stroke. The VRT programme did not include substitutional and/or habitual exercises aimed to facilitate sensory substitution, habituate patients to movement and/or improve their functional balance and postural control (Alghadir *et al* 2013:1).

Alternatively, Schow *et al* (2016:333) implemented approximately forty (40) sessions of 1.5 hours duration over a four (4)-month intervention period. The rehabilitation programme consisted of a combination of balance training and visual therapy. Balance training incorporated individualised vestibular and proprioceptive exercises aimed to improve sensory integration of patients post-stroke. Visual therapy included training of binocularity, visual fixation, visual tracking, convergence, divergence, visual attention, accommodation, eye-hand coordination and binocularity. It is important to highlight that although Schow *et al* (2016:333) incorporated processes of the vestibular rehabilitation approach into the delivered intervention, Schow *et al* (2016:333) did not specify the delivered intervention as VRT.

Apart from the VRT group, Balci *et al* (2013:259) also randomly assigned patients to either a visual feedback posturography training (VFPT) group or a home exercise group. The home exercise programme consisted of basic balance and mobility exercises that included weight shifting to the left and right when sitting on the bed, sit to stand activity, weight shifting in standing with hip abduction and extension, gait training (marching on the spot, walking forward and backward, side to side walking, walking with normal and narrowed base of support). Apart from the patients who were randomly assigned to the 'conventional rehabilitation' and VRT group (experimental group), Dai *et al* (2013:477) also randomly assigned patients to 'conventional rehabilitation' (without the add-on of VRT) (control group). Both the experimental and control groups received the same 'conventional rehabilitation'. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour

of occupational therapy for five (5) days per week. Dai *et al* (2013:477) indicated that the physiotherapy sessions included active and passive exercises, resistance exercises and ambulation training. Occupational therapy included activities to improve patients' endurance, balance and independence in ADLs such as bathing, toileting and dressing (Dai *et al* 2013:477).

The second feature of sensorimotor balance, mobility and gait to be discussed is the ability to modify gait in response to changing task demands.

(ii). Intervention for impaired ability to modify gait in response to changing task demands

Findings from the study by Gimmon *et al* (2017:3347) demonstrated that central vestibular processing is a control parameter regulating gait. Central vestibular dysfunction may thus result in impaired bilateral coordination of gait (Gimmon *et al* 2017:3347) and decreased ability to modify gait in response to changing task demands. To determine the various interventions implemented in the treatment of impaired ability to modify gait in response to changing task demands in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.43., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases using the following key words: "intervention"; "ability to modify gait in response to changing task demands"; "gait modification"; "central vestibular dysfunction"; "stroke" OR "post-stroke", in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

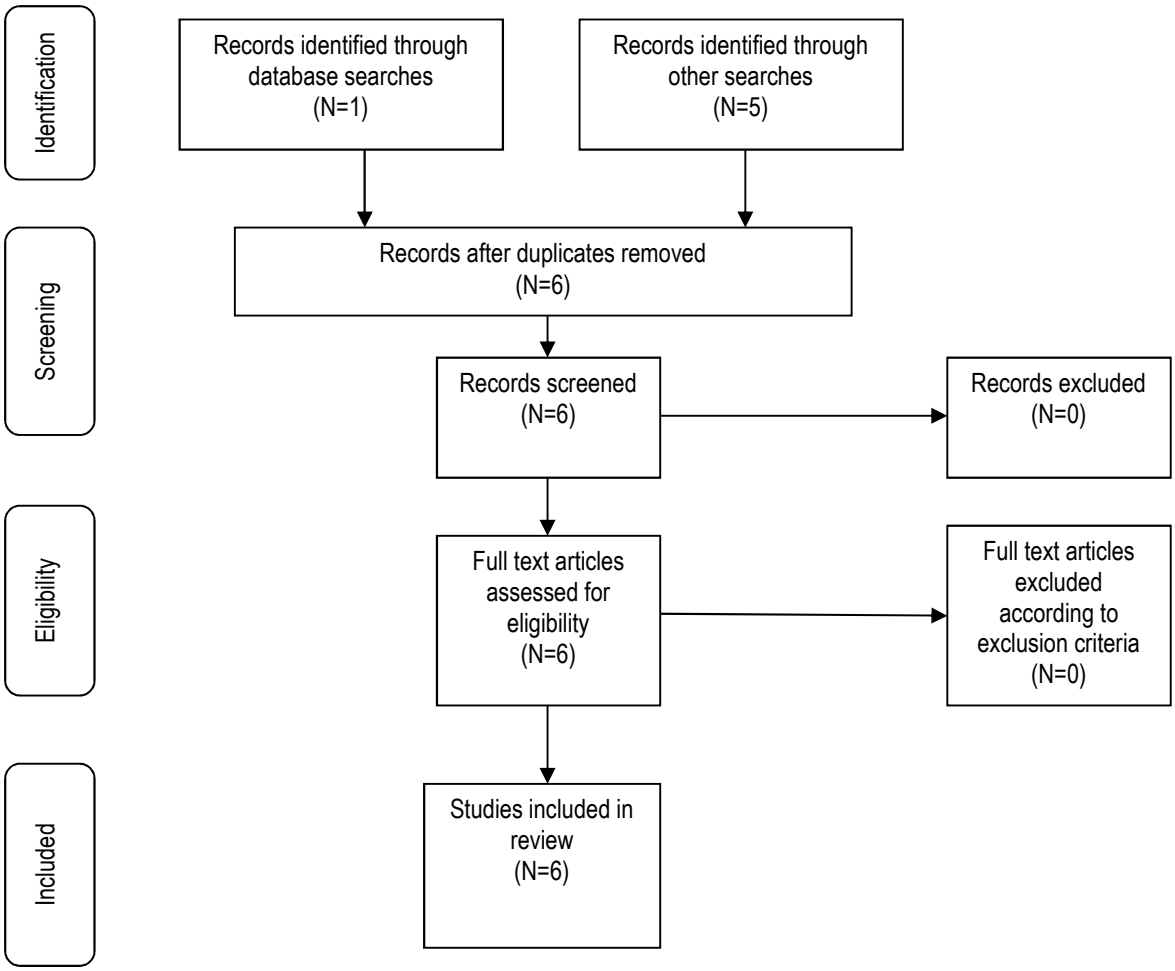


Figure 2.43.: Results of the literature search strategy on the various interventions implemented in the treatment of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Six (6) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included two (2) RCTs, a prospective observational study and three (3) case series studies. Articles appraised are presented in Table 2.43.

Table 2.43.: Appraised articles on the various interventions for the treatment of impaired ability to modify gait in response to changing task demands due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=6)				
Level of Evidence				
I (N=3)	**II**	**III**	**IV** (N=3)	**V**
Bonan *et al* (2004:274)			De Haart *et al* (2004:886)	
Van Nes *et al* (2009:819)			Brown *et al* (2006:76)	
Balci *et al* (2013:259)			Schow *et al* (2016:333)	

Findings of the literature appraised indicated that the activity and participation limitation of impaired ability to modify gait in response to changing task demands in post-stroke patients were treated using interventions that included; (a) exercises performed in supine or prone position (Bonan *et al* 2004:274); (b) exercises performed in a sitting position (Bonan *et al* 2004:274); (c) exercises performed in four point kneeling (Bonan *et al* 2004:274); (d) exercises performed in an upright position (Bonan *et al* 2004:274); (e) balance training on a treadmill (Bonan *et al* 2004:274); (f) balance training on a stationary bicycle (Bonan *et al* 2004:274); (g) walking on a foam rubber track with obstacles (Bonan *et al* 2004:274); (h) individual physiotherapy sessions embedded in an extensive, individualized NDT rehabilitation program with a general emphasis on the optimal use of the paretic body side (De Haart *et al* 2004:886); (i) individualised 'physiotherapy' sessions (Van Nes *et al* 2009:819); (j) group sessions of 'physiotherapy' (Van Nes *et al* 2009:819); (k) vestibular rehabilitation therapy (Brown *et al* 2006:76; Balci *et al* 2013:259); (l) visual feedback posturography training (VFPT) (Balci *et al* 2013:259); (m) basic balance and mobility home exercise programme (Balci *et al* 2013:259); and (n) a combination of balance training and visual therapy (Schow *et al* 2016:333).

As previously discussed, Bonan *et al* (2004:274) randomly assigned patients to either a balance rehabilitation programme with visual cue deprivation or without visual cue deprivation. The rehabilitation program was exactly the same for the two groups (vision-deprived group vs. group without visual cue deprivation) except that the eyes

of the vision-deprived group were blinded with a mask throughout the treatment sessions. The aim of the visual cue deprivation was to facilitate the patients' utilisation of somatosensory and vestibular inputs and to decrease their reliance on visual input during balance training. A therapy session consisted of inhibition of spasticity followed by exercises performed in the supine or prone position, sitting position, four-point kneeling and in the upright position followed by balance training on a treadmill, stationary bicycle and walking on a foam rubber track with obstacles (Bonan *et al* 2004:274). Also previously discussed, De Haart *et al* (2004:886) implemented an extensive individualised NDT programme with general emphasis placed on the optimal use of the paretic body side. In contrast, Van Nes *et al* (2009:819) also implemented an individualised treatment program that consisted of a both individual and group sessions of physiotherapy. Van Nes *et al* (2009:819) did not specify the treatment approach used during the individual or group sessions of physiotherapy.

Balci *et al* (2013:259) randomly assigned twenty-five patients (N=25) to either a VRT group (N=6), visual feedback posturography training (VFPT) (N=6) or home exercises group (N=13). Patients assigned to the VRT group received a programme of adaptation (gaze stabilisation), substitutional and/or habitual exercises aimed to readjust the gain of the VOR, habituate the patient to movement, facilitate sensory substitution and improve patients' functional balance and postural control (Alghadir *et al* 2013:1). Patients within the VFPT group received postural stability exercises performed on two (2) force plates that provided continuous visual feedback of patients' position of center of gravity. Patients within the home exercise programme group received basic balance and mobility exercises that included weight shifting to the left and right when sitting on the bed, sit to stand activity, weight shifting in standing with hip abduction and extension, gait training (marching on the spot, walking forward and backward, side to side walking, walking with normal and narrowed base of support).

Schow *et al* (2016:333) implemented a rehabilitation programme that consisted of a combination of balance training and visual therapy. Balance training incorporated individualised vestibular and proprioceptive exercises aimed to improve sensory integration of patients post-stroke. Visual therapy included training of binocularity, visual fixation, visual tracking, convergence, divergence, visual attention, accommodation, eye-hand coordination and binocularity.

The second activity limitation on activity and participation level as result of central vestibular dysfunction to consider is functional ability discussed in detail in Section 2.5.2.2.

2.5.2.2. Functional ability

A stroke patient may present with complex combinations of sensory, motor, cognitive and emotional impairments (Bonan *et al* 2013:713) that may result in the inability to respond efficiently upon the sensory input from the environment and demands of a specific task. Decreased ability to respond efficiently on visual, vestibular and somatosensory information results in decreased postural control that leads to increased functional dependence during ADL and disability (Bonan *et al* 2013:713; Chaikin 2013:867; Lacour and Bernard-Demanze 2015:285). In this section, the literature review on interventions used in the treatment of the activity and participation limitation of impaired functional ability in post-stroke patients include articles previously reviewed (Section 2.3.2.2. and Section 2.4.2.2). To determine the various interventions implemented in the treatment of impaired functional ability in the sub-acute post-stroke population, the literature search strategy indicated in Figure 2.44., was used. The search was conducted on Medline, EbscoHost, Google Scholar, OVID and CINAHL databases using the following key words: “intervention”; “functional ability”; “central vestibular dysfunction”; “stroke” OR “post-stroke”, in all possible combinations. The search limitations that were applied, included: articles published between 1997 and 2017; in the English language; and conducted on human subjects. Results of the literature search strategy on the various interventions implemented in the treatment of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population, were included in this section of the review.

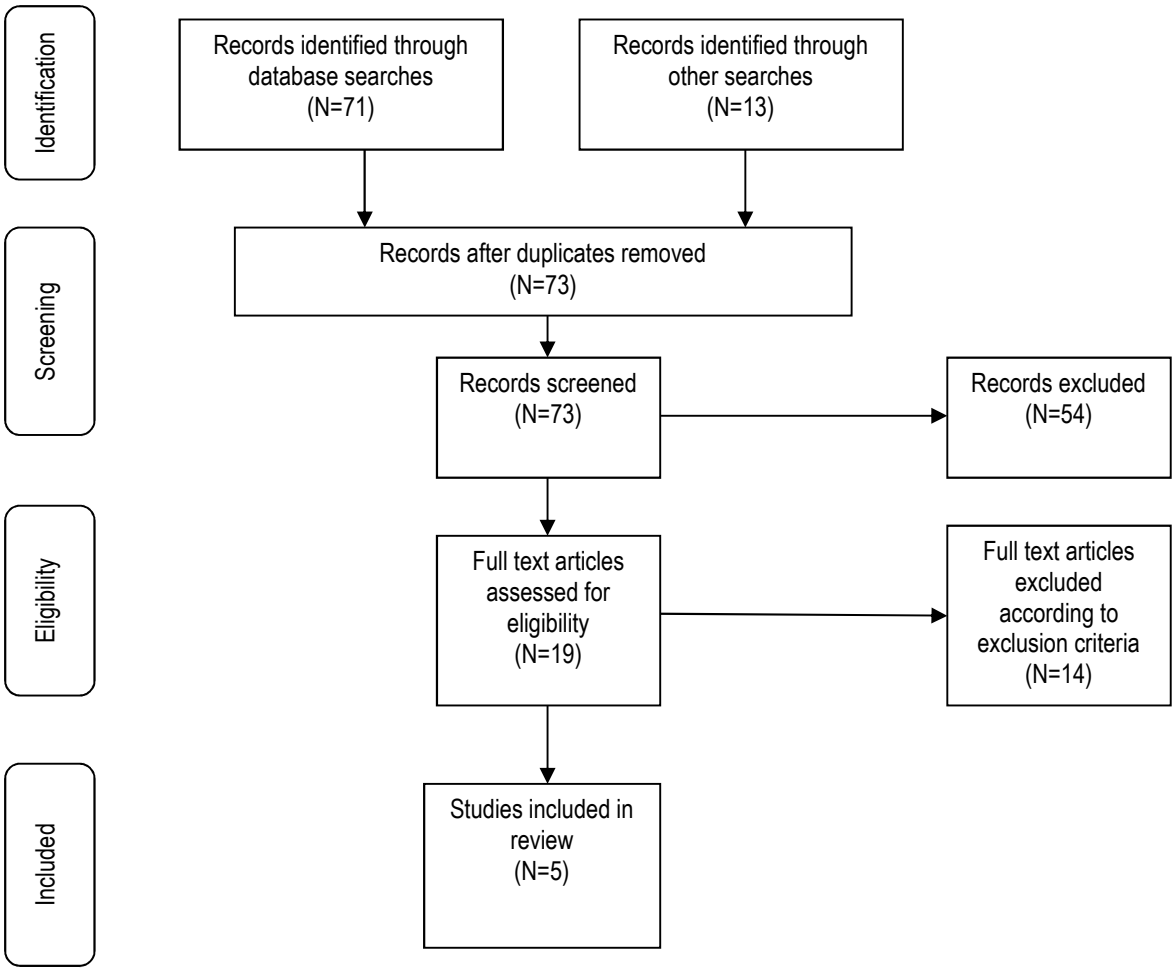


Figure 2.44.: Results of the literature search strategy on the various interventions implemented in the treatment of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population (based on the PRISMA flow diagram, Moher *et al* 2015:1).

Five (5) articles were critically reviewed and an assessment of the quality of evidence was completed. The articles appraised included a systematic review, three (3) RCTs, and a retrospective study. Articles appraised are presented in Table 2.44.

Table 2.44.: Appraised articles on the various interventions for the treatment of impaired functional ability due to central vestibular dysfunction in the sub-acute post-stroke population.

Articles appraised for the quality of evidence (N=5)				
Level of Evidence				
I (N=4)	**II**	**III** (N=1)	**IV**	**V**
Pollock *et al* (2011:2)		Ng *et al* (2005:2138)		
Dai *et al* (2013:477)				
Kerkhoff *et al* (2014:557)				
Van Wyk *et al* (2014:856)				

Findings of the literature appraised indicated that the activity and participation limitation of impaired functional ability in post-stroke patients were treated using interventions that included; (a) comprehensive rehabilitation programme (Ng *et al* 2005:2138); (b) vestibular rehabilitation therapy (Dai *et al* 2013:477); (c) active and passive exercises, resistance exercises and ambulation training (Dai *et al* 2013:477); (d) saccadic eye movement training (Kerkhoff *et al* 2014:557); (e) smooth pursuit eye movement training (Kerkhoff *et al* 2014:557); and (f) saccadic eye movement training with visual scanning exercises (VSEs) integrated with task-specific activities (Van Wyk *et al* 2014:856).

All patients (N=89) that participated in the study by Ng *et al* (2005:2138) received a comprehensive rehabilitation programme that included physiotherapy, occupational therapy and speech and language therapy for an average of three (3) hours per day. Findings of the study by Ng *et al* (2005:2138) indicated that comprehensive rehabilitation has a statistically significant effect ($P<0.001$) on the patients' functional ability quantified by a total FIM score following a PCA stroke.

The study by Pollock *et al* (2011:2) was included in the literature review as the aim of the Cochrane review was to determine the effects of interventions for eye movement disorders on functional ability following stroke. Pollock *et al* (2011:2) considered interventions for eye movement disorders that included; (1) restitutive intervention that

included saccadic eye movement, smooth pursuit eye movement, and convergence training; and (2) compensative intervention that consists of training of eye movements for reading, compensatory head movements and training in ADL. Although Pollock *et al* (2011:2) found no trials that investigated the effectiveness of restitutive, compensative or substitutive interventions for oculomotor control impairment post-stroke aimed to improve functional ability post-stroke, the authors did include two (2) randomised controlled trials (RCTs) (Strupp *et al* 2003:165; Leigh, Burnstine, Ruff and Kasmer 1991:1737) that investigated the effect of pharmacological intervention on eye movement disorders. Neither Strupp *et al* (2003:165) nor Leigh *et al* (1991:1737) determined the effect of rehabilitation on oculomotor impairment. Strupp *et al* (2003:165) and Leigh *et al* (1991:1737) measured aspects of eye movements: Strupp *et al* (2003:165) utilised two-dimensional videooculography to record eye movements in horizontal and vertical directions. Leigh *et al* (1991:1737) used the magnetic search coil technique to measure horizontal and vertical rotations, and an Amsler grid and video recording to measure eye movement (Pollock *et al* 2011:2). Pollock *et al* (2011:2) concluded that there is insufficient evidence to reach a conclusion about the effectiveness of interventions for patients with oculomotor impairment post-stroke and that further high-quality research trials are urgently required (Pollock *et al* 2011:2).

Dai *et al* (2013:477) randomly assigned patients to either a 'conventional rehabilitation' and VRT group (experimental group) or 'conventional rehabilitation group' (without the add-on of VRT) (control group). The VRT programme administered by Dai *et al* (2013:477) consisted of vestibular adaptation exercises aimed to improve patients' gaze stability post-stroke. The VRT programme did not include substitutional and/or habitual exercises aimed to facilitate sensory substitution, habituate patients to movement and/or improve their functional balance and postural control (Alghadir *et al* 2013:1). Both the experimental and control groups received the same 'conventional rehabilitation'. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai *et al* (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training. Occupational therapy included improving or maintaining endurance and balance aimed to improve independence in ADLs such as bathing, toileting and dressing (Dai *et al* 2013:477).

The study by Kerkhoff *et al* (2014:557) was included in the literature review as the authors randomly assigned patients to either saccadic eye movement training or smooth pursuit eye movement training to compare the effects of these two (2) interventions in the treatment of impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) in post-stroke patients (Section 2.2.5.2). The study by Van Wyk *et al* (2014:856) was also included in the review as the authors implemented saccadic eye movement training with VSEs integrated with task-specific activities in the treatment of patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect) post-stroke. Both studies (Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856) quantified patients' functional ability with the Barthel Index to determine whether the effect of the interventions translated to improved functional ability in post-stroke patients. Findings of the study by Kerkhoff *et al* (2014:557) demonstrated that repetitive contra-lesional smooth pursuit eye movement training was associated with superior, multimodal therapeutic effects compared to saccadic eye movement training in patients with impaired higher vestibular function, specifically visual-perceptual dysfunction (visual neglect). Kerkhoff *et al* (2014:557) concluded that smooth pursuit eye movement training is effective and feasible in the treatment of patients who present with higher vestibular function impairment, specifically visual-perceptual dysfunction post-stroke. Saccadic eye movement training described by Kerkhoff *et al* (2014:557) included visual scanning training that consisted of visual scanning of an array of stationary horizontal and vertical target symbols on the display of a computer screen by starting at the top left corner and ending at the bottom right without head movements (Kerkhoff *et al* 2014:557). In contrast to Kerkhoff *et al* (2014:557), findings of the study by Van Wyk *et al* (2014:856) indicated that the effect of saccadic eye movement training with visual scanning exercises as an intervention has a significant effect on the visual-perceptual function of patients post-stroke. Van Wyk *et al* (2014:856) concluded that the significant improved visual-perceptual function translated to significantly improved functional ability post-stroke. It is important to highlight that none of the articles reviewed mentioned the role of the central vestibular system involved in impaired functional ability post-stroke. The treatment approach for the rehabilitation of post-stroke patients who present with central vestibular dysfunction based on the outcome of the literature study, is discussed in Section 2.5.3.

2.5.3. Treatment approach for the rehabilitation of post-stroke patients presenting with central vestibular dysfunction

In the current study, the VRT approach was selected in the treatment of the clinical features and activity and participation limitations in patients with central vestibular dysfunction in the sub-acute phase post-stroke based upon the outcome of the literature study (Section 2.5.1. and 2.5.2). Vestibular rehabilitation therapy facilitates the use of sensory input such as visual and/or somatosensory (including proprioceptive) information to facilitate vestibular compensation through the process of sensory re-weighting in the sub-acute phase post-stroke (McDonnell and Hillier, 2015:3). A stroke may result in central vestibular system impairment due to the interruption of the brainstem and cerebellar processing circuits, the thalamic pathways, and the vestibular cerebral cortical network (Allen, Ribeiro, Arshad and Seemungal 2017:1). Due to the central vestibular dysfunction following a stroke, primary visual and motion-sensitive visual cortical areas are downregulated in both cortical hemispheres (Becker-Bense *et al* 2013:1103). The findings of Becker-Bense *et al* (2013:1103) are supported by findings of Roberts *et al* (2018:1010) that top-down modulation of the primary visual cortex might be a key component of effective vestibular adaptation and compensation following vestibular impairment. Previous published literature indicated that patients demonstrate better clinical outcomes when visual stimulation aimed to facilitate vestibular adaptation and substitution is added to rehabilitation programs (Whitney *et al* 2016:13; Roberts *et al* 2018:1010).

The first treatment principle of VRT implemented in the treatment of the clinical features and activity limitations of central vestibular dysfunction was saccadic eye movement training integrated with task-specific activities (Van Wyk *et al* 2014:856). Progression of these exercises is discussed in Table 3.2. Due to the structural neural connectivity between the vestibular nuclei and the cerebellum, oculomotor nucleus, trochlear nucleus, abducens nucleus, thalamus, and reticular formation (Section 1.1.2), saccadic eye movement training may activate the superior and inferior rectus, medial and lateral rectus, inferior and superior oblique extraocular muscles that have reflexogenic connections to the cerebellum (Carrick *et al* 2016:3). As Becker-Bense *et al* (2013:1103) indicated that central vestibular compensation and recovery processes post-stroke, occur mainly in the brainstem-cerebellar loops, the researcher hypothesised that improved functional outcome might be achieved through the

process of sensory substitution (sensory re-weighting) facilitated by VRT. Sensory substitution entails the process of sensory re-weighting of the multiple sensory modalities that include vestibular, visual and somatosensory (including proprioceptive) information involved in balance to ultimately improve functional outcome in patients with central vestibular dysfunction post-stroke (Balaban *et al* 2012:101; Lacour *et al* 2016:54).

The second treatment principle of VRT implemented in the treatment of the clinical features and activity limitations associated with central vestibular dysfunction was the implementation of VOR adaptation exercises aimed to recalibrate the VOR through the concept of retinal slip (Section 1.1.5.2). Progression of these exercises is discussed in Table 3.2. Adaptation as a process of recovery also includes the process of behavioural substitution (Lacour *et al* 2016:54). Behavioural substitution is based on the ability of the CNS to reorganize functionally by the processes of learning and to mimic lost or diminished vestibular functions such as impaired reflexive control of gaze post-stroke. Behavioural substitution following vestibular impairment entails the generation of saccadic eye movements during fast head movement to prevent oscillopsia during head rotation due to impaired VOR post-stroke (Lacour *et al* 2016:54). The researcher hypothesised that increased latency, velocity and accuracy of saccadic eye movements facilitated by VRT, might result in improve gaze stability, by generating a ballistic eye movement that reduced the smeared retinal image that may occur during head movements as result of an inadequate VOR due to central vestibular dysfunction (MacDougall and Curthoys 2012:1).

The third treatment principle of VRT implemented in the treatment of the clinical features and activity limitations associated with central vestibular dysfunction, is the implementation of standing and walking balance exercises (Whitney and Sparto 2011:157). As post-stroke patients may be over-reliant on one sensory system (vision, vestibular or somatosensation), the process of sensory re-weighting through the manipulation of the visual, somatosensory, or vestibular sensory systems were facilitated by VRT in order to reduce influence of the one dominant sensory system. Sensory re-weighting was facilitated through changes in the size of the base of support and modifications in the surface compliance (level vs. foam) incorporated in the treatment program to progress balance activities. Progression of these exercises is discussed in Table 3.2. Based on the findings of Balci *et al* (2013:259), the researcher

hypothesised that VRT might result in improved functional capacity measured by postural and balance outcomes that might have been attributed to central compensation mechanisms due to active neuronal changes in the cerebellum and brainstem in response to sensory conflict produced by vestibular pathology (Balci *et al* 2013:259).

2.6. SUMMARY

In this chapter, the existing research evidence that assessed the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in the post-stroke population, were critically appraised. Based on the extensive literature review, it may be summarised that a large difference in the reported prevalence of the clinical features of central vestibular disorders on the level of body structure and function in post-stroke patients, exist. The large difference in the reported prevalence of the clinical features categories may be attributed to the respective assessment methods used in the studies.

Assessment methods used to quantify central vestibular disorders in the post-stroke population ranged from conventional paper-and-pencil tests to expensive, complicated and semi-invasive techniques that limited translation from research to practice. Only four (4) studies were found that assessed the clinical features and activity limitations associated with central vestibular dysfunction prior to the testing of VRT in the treatment of post-stroke patients (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). All four (4) studies posed several limitations in the assessment of clinical features and activity limitations associated with central vestibular dysfunction in their study samples (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477).

Assessment of clinical features on the level of body structure and function were limited to the assessment of higher vestibular function using the Rivermead Behavioural Inattention test to quantify visual-perceptual function (Dai *et al* 2013:477). Neither of these authors (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477) quantified their study samples' oculomotor control (smooth pursuit eye movements, saccadic eye movements and visual acuity), reflexive control of gaze (VOR-gain dysfunction and

dynamic visual acuity), saccule, inferior vestibular nerve function, utricle and superior vestibular nerve function, higher vestibular function (residual oculomotor visual performance and cognition), level anxiety and/or depression (Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477). Suarez *et al* (2003:143) assessed the study samples' spontaneous and positional nystagmus, smooth pursuit and saccadic eye movements, optokinetic nystagmus, VOR and visual suppression using ENG.

Assessment of activity limitations on activity and participation level were limited to the assessment of impairment of sensorimotor control of balance, mobility and gait performance using the ABC-scale (Brown *et al* 2006:76), DHI (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259), TEUSAC (Suarez et al 2003:143), DGI (Brown *et al* 2006:76; Balci *et al* 2013:259), TUG (Brown *et al* 2006:76; Balci *et al* 2013:259), FTSTS test (Brown *et al* 2006:76), BBS (Balci *et al* 2013:259) and the Postural Assessment Scale (PASS) (Dai *et al* 2013:477). Only Dai *et al* (2013:477) quantified patients' functional ability using the Functional Independence Measure (FIM).

Based on the extensive literature review, it may be summarised that various interventions were tested in the treatment of clinical features and activity limitations associated with central vestibular dysfunction in the post-stroke population. These interventions included restitutive, compensative or substitutive interventions to address the various clinical features and activity limitations associated with central vestibular dysfunction. Four (4) studies were found that tested VRT in the treatment of post-stroke patients (Suarez *et al* 2003:143; Brown *et al* 2006:76; Balci *et al* 2013:259; Dai *et al* 2013:477).

Although findings by Brown *et al* (2006:76) demonstrated statistically significant improvement ($P<0.05$) of functional balance quantified by the FTSTS and the ability to modify gait in response to changing task demands quantified by the DGI following VRT; the sample size was limited to a case series of ten (10) patients (Level of evidence: IV). In contrast, findings of the study by Balci *et al* (2013:259) indicated that although the sensorimotor control of balance, mobility and gait performance quantified by the BBS, TUG, DGI and DHI improved significantly in all patients who sustained a posterior stroke, no statistically significant differences were noted between the groups that received VRT (N=6) versus visual feedback posturography training (N=6) or a

home exercise programme (N=13). The group that received VRT was limited to only six (6) patients with posterior stroke. Lastly, the findings of the study by Dai *et al* (2013:477) indicated that although higher vestibular function, specifically visual-perceptual function, functional balance and functional ability, improved significantly (P<0.000) in patients who presented with impaired visual-perceptual dysfunction following a right hemispheric stroke, no statistically significant difference were noted between the control group (N=24) that received 'conventional rehabilitation' and the experimental group (N=24) that received 'conventional rehabilitation' and VRT as an add-on intervention. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai et al (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training. The patients received VRT over a four (4)-week intervention period. During the first two (2) weeks, a registered nurse treated the experimental group where after patients' informal caregivers took over treatment for the last two (2) weeks of the intervention period. The informal caregivers received twenty (20) to forty (40) minutes training in VRT from the registered nurse that delivered VRT during the initial two (2) weeks of the intervention period. After the brief training, the patients' informal caregivers were responsible for the supervision and guidance of the intervention received by patients in the experimental group.

In Chapter 3, a detailed description of the methodological procedures that were implemented in the study to address the limitations identified in the literature, are presented. The research process that includes the study design, research setting, study population, sample size, eligibility criteria, data collection procedure, interventions, assessment battery, quality control, pilot study, data management and analysis, ethics and legal considerations for phase 1 and 2 of the study, are discussed in Chapter 3.

CHAPTER 3

RESEARCH METHODOLOGY

3.1. INTRODUCTION

A detailed description of the methodological procedures that were implemented in the study to address the limitations identified in the literature (Chapter 2), are presented in Chapter 3. The account of the research methodology includes the study design, research setting, study population, sample size, eligibility criteria, data collection procedure, interventions, battery of objective measures, quality control, pilot study, data management and analysis, ethics and legal considerations for phases 1 and 2 of the study. Ethics approval was obtained from the Ethics Committee of the Faculty of Health Sciences at the University of Pretoria (UP) (374/2015) after approval of the research protocol by the post-graduate committee of the School of Healthcare Sciences, UP (Addendum A). The study was also registered at the Pan African Clinical Trials Registry (PACTR201509001223262) (Addendum B). The study designs of phases 1 and 2 are discussed in Section 3.1.1.

3.1.1. Introduction to the study design

Due to the fact that the prevalence of all the facets of the clinical features and activity limitations in patients with central vestibular dysfunction have not been determined holistically, the prevalence of the clinical features on body structure and function, as well as the activity limitations associated with central vestibular dysfunction, has been determined as phase 1 of the current study. The clinical features associated with central vestibular dysfunction on the level of body structure and function, include the impairment of: (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4) utricle and superior vestibular nerve function; (5) higher vestibular function; and (6) anxiety and/or depression. The activity limitations associated with central vestibular dysfunction on the levels of activity and participation, include the impairment of: (1) sensorimotor control of balance, mobility and gait; (2) functional ability; and (3) participation in physical activity post-stroke. The second main problem identified was the fact that the assessment and intervention methods used in the management of these clinical features and activity limitations associated with

central vestibular dysfunction in post-stroke patients have not been standardised (Section 2.4.3). The study design was therefore planned in two phases. The study design of phase 1 of this study is discussed in Section 3.1.1.1.

3.1.1.1. Study design of phase 1 of the study

Phase 1 of the study entailed a cross-sectional survey to determine the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke (Table 1.5). A cross-sectional design is categorised as an observational study design that is used in a population-based survey to determine the prevalence of disease in a selected study population based on the inclusion and exclusion criteria set for the study (Setia 2016:261). The study design of phase 2 of this study is discussed in Section 3.1.1.2.

3.1.1.2. Study design of phase 2 of the study

Phase 2 of the study entailed a single-blind cluster randomised controlled trial to determine the treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction for patients in the sub-acute phase post-stroke. The research setting of the study is discussed in Section 3.1.2.

3.1.2. Research setting of the study

Phases 1 and 2 of the study were conducted at seven public and private rehabilitation centers in Pretoria and Johannesburg, Gauteng Province, South Africa. These rehabilitation centers are associated with academic institutions where research is being conducted in different fields of healthcare. Rehabilitation of patients with neurological impairments at these facilities were and are conducted by a multidisciplinary team. The multidisciplinary teams consisted of physiotherapists, occupational therapists, speech-and language therapists, audiologists, dieticians, social workers, nursing staff and medical doctors. These facilities accommodate all patients with neurological impairments in need of rehabilitation services, including

post-stroke patients, multiple sclerosis, Guillain-Barré Syndrome, neuropathies, spinal cord injuries, as well as head injuries. Stroke patients admitted to these facilities are within the sub-acute phase post-stroke, which ranges between seven (7) days to six (6) months post-stroke (Bernhardt *et al* 2017:444) (Section 1.1.4). Patients are referred to these rehabilitation centres by multiple private and public acute healthcare facilities.

3.1.3. Study population of the study

All patients who sustained a cerebral vascular incident (CVI), who were in the sub-acute phase post-stroke and admitted at a public or private rehabilitation centre in Pretoria and Johannesburg, Gauteng Province, South Africa, were eligible to participate in the study.

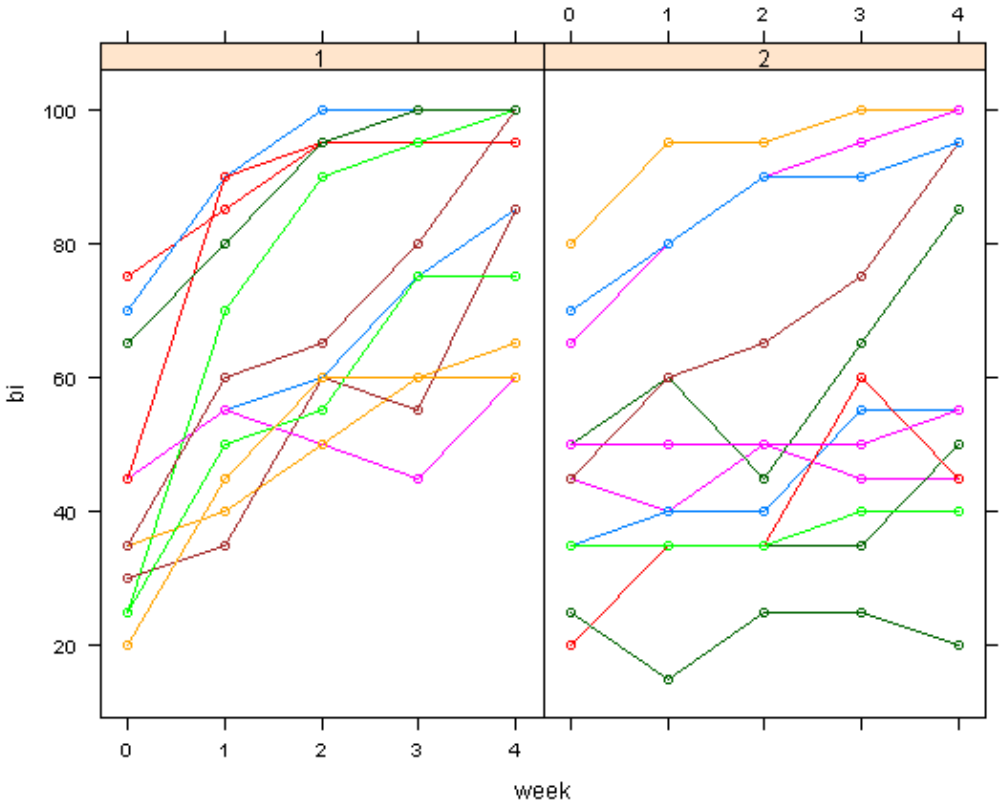
3.1.3.1. Sample sizes of phase 1 and phase 2 the study

The sample size of phases 1 and 2 were interrelated and was calculated simultaneously with the assistance of a statistician. An adequate and representative sample size required for phase 1 of the study was calculated based on a study by Van Wyk *et al* (2014:856). Findings of Van Wyk *et al* (2014:856) indicated that the mean and 95% confidence interval (CI) at baseline and at the end of each week of a four-week treatment period. The expected mean of the Barthel Index value at onset was 45/100 and the improvement in the change from baseline at two weeks for both groups was 36 which is 0.214 on the logarithmic (base 10) scale. From the reported 95% CI for the geometric mean, a standard deviation (SD) of 0.179 on the log scale was calculated. Since a change from baseline is of interest, this SD was inflated by a factor $\sqrt{2}$ to 0.249. Results of the BI of patients from the experimental group and control group over the four-week intervention period of the matched-pair randomised controlled trial (Van Wyk *et al* 2014:856) are presented in Table 3.1.

Table 3.1.: Results of the Barthel Index of the experimental group and control group over the four-week intervention period (Van Wyk *et al* 2014:856).

Barthel Index	All patients N=24	Experimental Group N=12	Control Group N=12	P-value[1]
Baseline	45.0 [33.8; 53.8]	40.0 [28.8; 50.0]	45.0 [35.0; 53.8]	0.54
Week 1	55.0 [40.0; 80.0]	57.5 [48.8; 81.2]	45.0 [35.0; 65.0]	0.20
Week 2	60.0 [48.8; 90.0]	62.5 [58.8; 95.0]	47.5 [35.0; 71.2]	0.02*
Week 3	70.0 [53.8; 95.0]	77.5 [60.0; 96.2]	57.5 [43.8; 78.8]	0.07
Week 4	85.0 [55.0; 100.0]	90.0 [72.5; 100.0]	55.0 [45.0; 95.0]	0.04*
[1] = P-value: Exceedance probability				
* = Significant at the 5% level				

Individual profiles of the BI of the experimental group and control group over the four-week intervention period (Van Wyk *et al* 2014:856) are presented in Graph 3.1.



Experimental group **Control group**

Graph 3.1.: Individual profiles of the Barthel Index of the experimental group and control group over the four-week intervention period (Van Wyk *et al* 2014:856).

Based on this information, a sample of a minimum of thirty (30) patients per group would have 90% power to detect the clinically relevant change when testing at the 0.05 level of significance for phase 2. If testing was one-sided (VRT integrated with task-specific activities), based on the published results of the previous study (Van Wyk *et al* 2014:856), a sample of thirty (30) patients per group were required for phase 2 of the study. Hence, to achieve a sample size of thirty (30) patients per group, phase 1 (cross-sectional survey) had to include a minimum of a hundred (100) post-stroke patients in the sub-acute phase.

The association between central vestibular dysfunction and the clinical feature of impairment of oculomotor control post-stroke are well-documented in the literature (Section 1.1.3.1). A Cochrane review by Pollock *et al* (2011:3) reported that over 70% of stroke patients may present with impaired oculomotor control as a result of central vestibular dysfunction post-stroke. Because the prevalence of impaired oculomotor control as result of central vestibular dysfunction post-stroke was expected to be in excess of 70% (Pollock *et al* 2011:3), a sample size of a minimum of a hundred (100) patients was adequate to estimate the prevalence's to an accuracy within 10%. Recruitment of patients to participate in this study was done in each of the seven public and private rehabilitation centers (Section 3.1.2) in consecutive sequence as patients were admitted to the particular center, until an adequate and representative sample group of at least N=100, was reached. The eligibility criteria for participation in the study are discussed in Section 3.1.4.

3.1.4. Eligibility criteria for participation in the study

The eligibility criteria for participants in phases 1 and 2 were different due to the different research designs of the two phases.

3.1.4.1. Eligibility criteria of phase 1 of the study

(i) Inclusion criteria of phase 1 of the study

a) Patients who suffered either an ischaemic or haemorrhagic stroke (Blanton *et al* 2006:1520) which was clinically diagnosed by a medical specialist. Information on the type of stroke was obtained from the patients' medical records.

b) Male and female patients in the age group 19 years – 84 years (The SASPI Project Team 2004:627).

c) Patients who were in the sub-acute phase following a stroke, able to follow instructions (Lennon, Ashburn and Baxter 2006:873) and had the capacity to provide informed consent (Loetscher *et al* 2015:64).

(ii) Exclusion criteria of phase 1 of the study

a) Severe cognitive impairment identified by the MMSE<7 (Hafsteinsdóttir, Algra, Kappelle, Grypdonck and Dutch NDT Study Group 2005:788). A MMSE-score of less than seven (7) is an indication of the presence of severe cognitive impairment.

b) History of an organic disorder or major psychiatric impairment (Blanton *et al* 2006:1520).

c) Other co-morbid diseases or disabilities such as cancer or amputation, that would have prevented or limited the functional assessment of the patients and their participation or follow-up over a period of twenty (20) weeks (Robertson, McMillan, MacLeod, Edgeworth and Brock 2002: 439; Blanton *et al* 2006:1520; Lennon, Ashburn and Baxter 2006:873).

d) Positive Dix-Hallpike test to exclude BPPV. Patients with a history of neck surgery, recent neck trauma, severe rheumatoid arthritis, atlanto-axial and occipito-atlantal instability, cervical myelopathy or radiculopathy, carotid sinus syncope, Chiari malformation and vascular dissection syndromes, were also excluded from the study (Herdman and Tusa 2007:255). The Dix-Hallpike test requires head rotation of 45° and extension of 20° to 30° for the assessment of BPPV (Figure 1.1) which may be contraindicated in patients with the latter conditions.

e) Participation in other pharmacological or rehabilitation intervention studies which could lead to confounding of the results of the current study (Blanton *et al* 2006:1520).

The eligibility criteria of phase 2 of the study are discussed in Section 3.1.4.2.

3.1.4.2. Eligibility criteria of phase 2 of the study

(i) Inclusion criteria of phase 2 of the study

(a) The same inclusion criteria that were applicable to patients in phase 1 of the study (Section 3.1.4.1) were applicable for phase 2 of the study.

(b) All patients in phase 1 of the study who were diagnosed with central vestibular dysfunction based on the outcome of the assessment if one or more of the following criteria were fulfilled, which included impaired smooth pursuit and/or saccadic eye movements using VNG (Section 3.1.7) and/or increased (hyperactive) horizontal VOR-gains using vHIT (Section 3.1.7) during phase 1 of the study.

(ii) Exclusion criteria of phase 2 of the study

The same exclusion criteria were applicable in phase 1 of the study (Section 3.1.4.1) since patients who were diagnosed with central vestibular dysfunction during phase 1 were randomly recruited for phase 2 of the study.

3.1.5. Data collection procedure of phase 1 and phase 2 of the study

The data collection procedure of phases 1 and 2 were different due to the different research designs of the two phases.

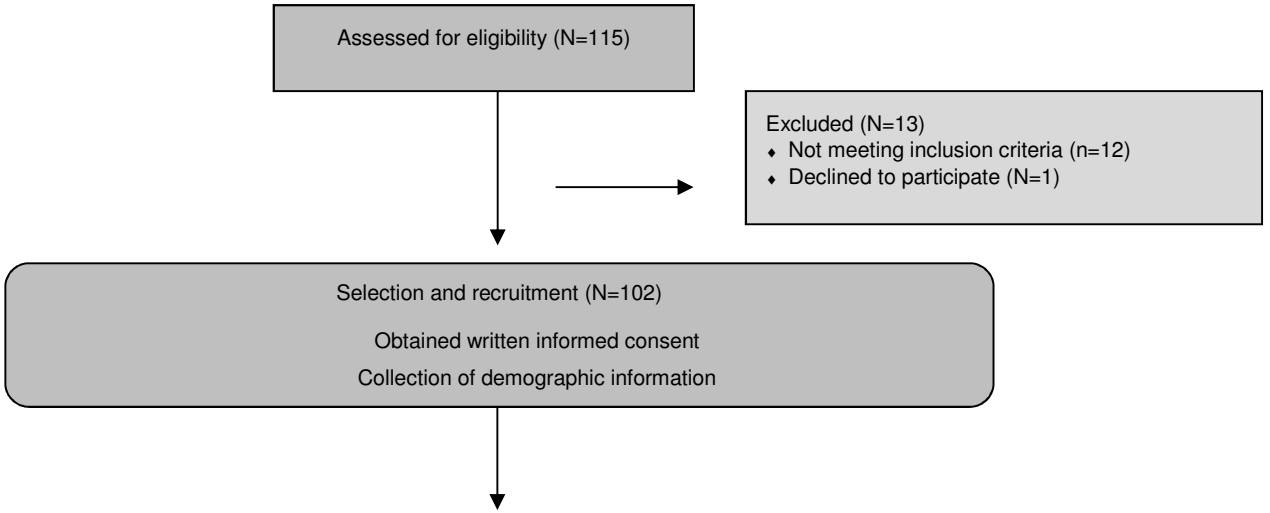
3.1.5.1. Data collection procedure of phase 1 of the study

In phase 1 of the study, one hundred and two (N=102) patients, who met the eligibility criteria (Section 3.1.4.1), in the seven research settings (Section 3.1.2) were recruited for participation in the study. After the patients were recruited in a particular

rehabilitation setting, the purpose and procedures of the study were explained to them in detail. The eligible patients were informed that participation in the trial was voluntary and they were free from undue coercion. Patients who voluntarily agreed to participate in the study, were asked to give their written informed consent and were included into the study.

Demographic information was collected from the participating patients after which they were subject to a battery of objective measures for the measurement of the clinical features associated with central vestibular dysfunction on the level of body structure and function, as well as activity limitations on activity and participation level. The battery of objective measures was completed by the principle investigator and an independent assessor (a qualified physiotherapist). The principle investigator, under guidance of an audiologist, completed all assessments of smooth pursuit and saccadic eye movements using VNG, as well as the assessment of VOR-gain using the EyeSeeCam vHIT throughout the study. The principal investigator also completed the assessment of saccule and inferior vestibular nerve function using cVEMP, as well as utricle and superior vestibular nerve function using oVEMP (Section 3.1.7.1). The independent assessor conducted the assessments of static and dynamic visual acuity using the LogMAR chart. The assessor also completed assessments of higher vestibular function using the King-Devick Test©, Star Cancellation Test and MMSE. The same independent assessor assessed the level of anxiety and/or depression using the HADS, functional balance using the BBS and the ability to modify gait using the DGI. Lastly, 20 weeks after rehabilitation was terminated, the independent assessor also contacted all patients who participated in phase 2, to complete the telephonic-administered IPAQ to assess their participation in physical activity post-stroke (Section 3.1.7.1). The same independent assessor conducted all the assessments across all sites (Section 3.1.2). The same conceptual framework based on the ICF-model (Lazaro *et al* 2013:187) within which the battery of objective measures for the current study were determined (Table 2.32) was used in phase 1 of the study. The battery of outcome measures used in the assessment of participants during phase 1, were selected to assess the clinical features on body structure and function, as well as the activity limitations associated with central vestibular

dysfunction in post-stroke patients which were described in the literature study. The flow chart of phase 1 of the study is presented in Figure 3.1.



Battery of objective measures used in phase 1 of the study					
Level of body structure and function			**Activity and participation level**		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	Video nystagmography (VNG)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	Berg Balance Scale
	Saccadic eye movements	Video nystagmography (VNG)		**Ability to modify gait in response to changing task demands**	Dynamic Gait Index
	Static visual acuity	LogMAR chart			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	video Head Impulse Test (vHIT)	**FUNCTIONAL ABILITY**	**Functional ability**	Barthel Index
	Dynamic visual acuity	LogMAR chart			
SACCULE, INFERIOR VESTIBULAR NERVE FUNCTION	**Cervical vestibular-evoked myogenic potential (cVEMP)**	cVEMP			
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**Ocular vestibular-evoked myogenic potential (oVEMP)**	oVEMP			

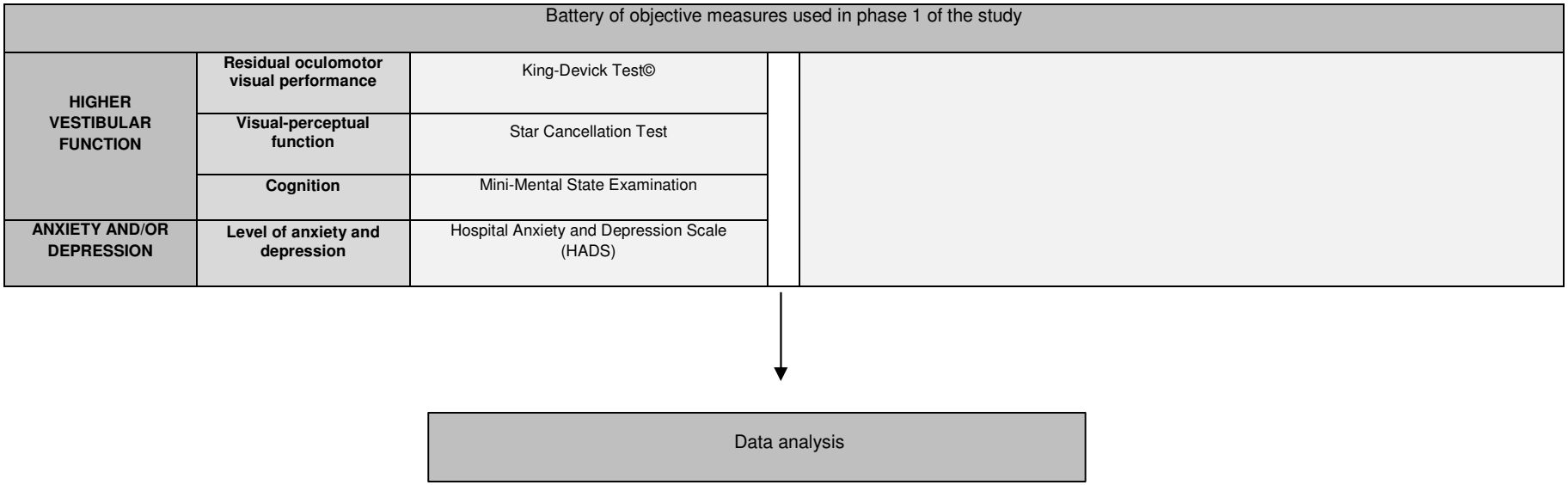


Figure 3.1.: Flow chart of phase 1 of the study.

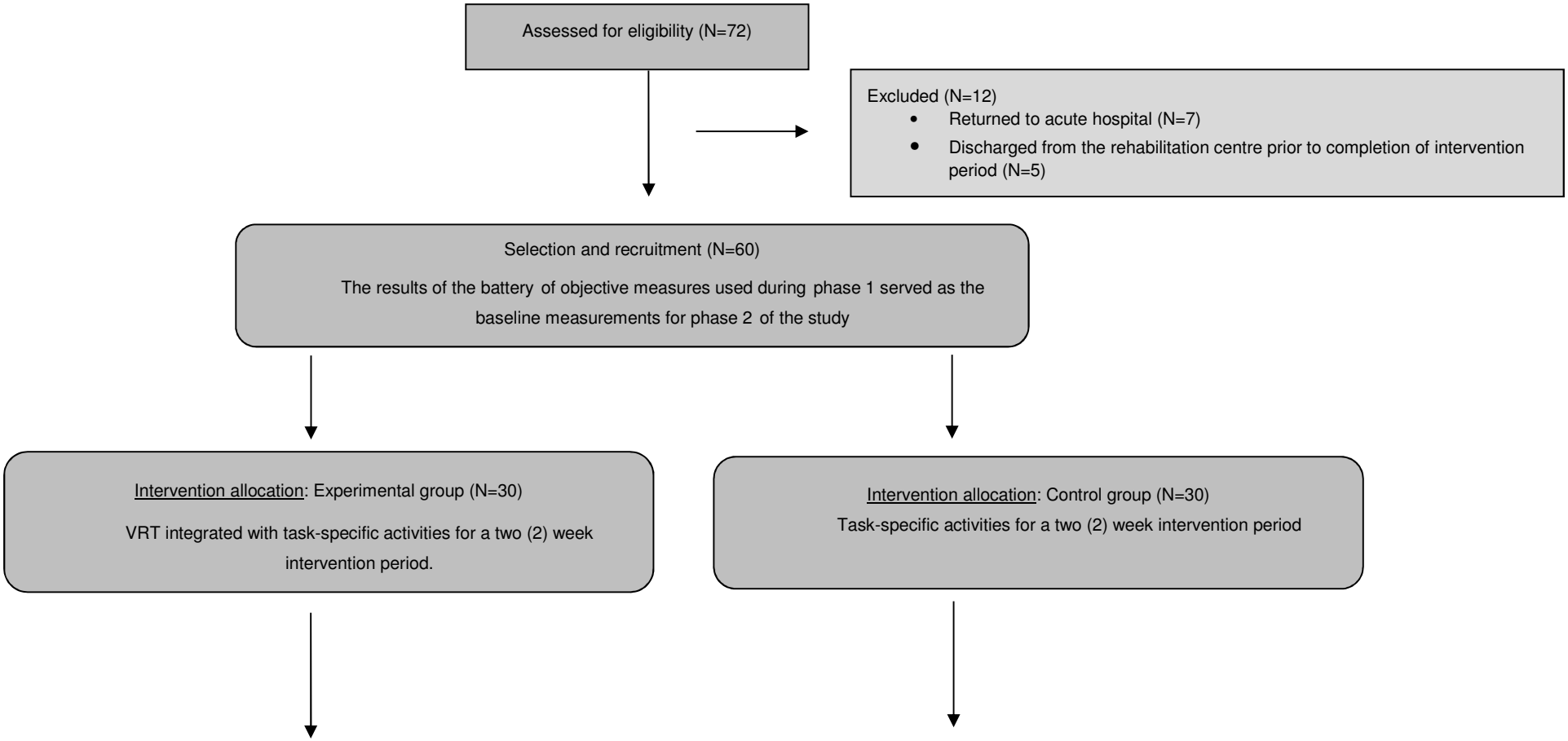
The validity, reliability and normative values of the battery of objective measures used in the measurement of the clinical features and activity limitations associated with central vestibular dysfunction in phase 1 of the study are discussed in Section 3.1.7. After the completion of the battery of objective measures, the data obtained in phase 1 were analysed to determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who were in the sub-acute phase post-stroke. The data analysis of phase 1 are summarised in Section 3.1.10. The results of phase 1 are presented in Chapter 4.

3.1.5.2. Data collection procedure of phase 2 of the study

In phase 2, patients who had been assessed as part of phase 1 to determine the prevalence of the clinical features associated with central vestibular dysfunction, and who were diagnosed with central vestibular dysfunction based on the outcome of the assessment if one or more of the following criteria were fulfilled, which included impaired smooth pursuit and/or saccadic eye movements using VNG (Section 3.1.7). Patients who presented with increased (hyperactive) horizontal VOR-gains using vHIT (Section 3.1.7) were also recruited to participate in phase 2 of the study. Sixty (N=60) patients that were diagnosed with central vestibular dysfunction based on the above-mentioned criteria, were recruited to participate in phase 2 of the study. After the purpose and procedures of phase 2 were explained to them in detail, the sixty (N=60) patients were randomly allocated to either an experimental group (N=30) or a control group (N=30) using a formula on a Microsoft Excel program to randomly allocate patients (Van Wyk *et al* 2014:857). If patients dropped out of phase 2 for any reason, another patient was recruited to replace them. The patients from the experimental group and the control group were blinded to the group they were assigned to (Blanton *et al* 2006:1520).

Patients in the experimental group received VRT integrated with task-specific activities as an intervention approach, compared to the control group that received only task-specific activities as an intervention approach for a two (2) week intervention period. The interventions received by patients in the experimental and control groups are discussed in Section 3.1.6. After the two (2) week intervention period, the battery of

objective measures were repeated. Twenty (20) weeks after they had been discharged from their two weeks of rehabilitation, the independent assessor contacted all patients who participated in the experimental group and control group, to complete the telephonically administered IPAQ to determine the long-term effect of the interventions on the two groups of patients. The validity, reliability and normative values of the battery of objective measures used in the measurement of the clinical features and activity limitations associated with central vestibular dysfunction in phases 1 and 2 are discussed in Section 3.1.7. After the results of the battery of objective measures were obtained in phase 2, the data were analysed. The data analysis procedures of phase 2 are summarised in Section 3.1.10. The results of phase 2 are presented in Chapter 5. The flow chart of the data-collection procedure of phase 2 of the study is presented in Figure 3.2.


Assessed for eligibility (N=72)
Excluded (N=12)
Returned to acute hospital (N=7)
Discharged from the rehabilitation centre prior to completion of intervention period (N=5)
Selection and recruitment (N=60)
The results of the battery of objective measures used during phase 1 served as the baseline measurements for phase 2 of the study
Intervention allocation: Experimental group (N=30)
VRT integrated with task-specific activities for a two (2) week intervention period.
Intervention allocation: Control group (N=30)
Task-specific activities for a two (2) week intervention period

Battery of objective measures used in phase 2 of the study					
Level of body structure and function			Activity and participation level		
Clinical features associated with central vestibular dysfunction		**Objective measure(s)**	**Activity limitations associated with central vestibular dysfunction**		**Objective measure(s)**
OCULOMOTOR CONTROL	**Smooth pursuit eye movements**	Video nystagmography (VNG)	**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	Berg Balance Scale
	Saccadic eye movements	Video nystagmography (VNG)		**Ability to modify gait in response to changing task demands**	Dynamic Gait Index
	Static visual acuity	LogMAR chart			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	video Head Impulse Test (vHIT)	**FUNCTIONAL ABILITY**	**Functional ability**	Barthel Index
	Dynamic visual acuity	LogMAR chart			
SACCULE, INFERIOR VESTIBULAR NERVE FUNCTION	**Cervical vestibular-evoked myogenic potential (cVEMP)**	cVEMP			
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**Ocular vestibular-evoked myogenic potential (oVEMP)**	oVEMP			
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	King-Devick Test©			
	Visual-perceptual function	Star Cancellation Test			
	Cognition	Mini-Mental State Examination			
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	Hospital Anxiety and Depression Scale (HADS)			

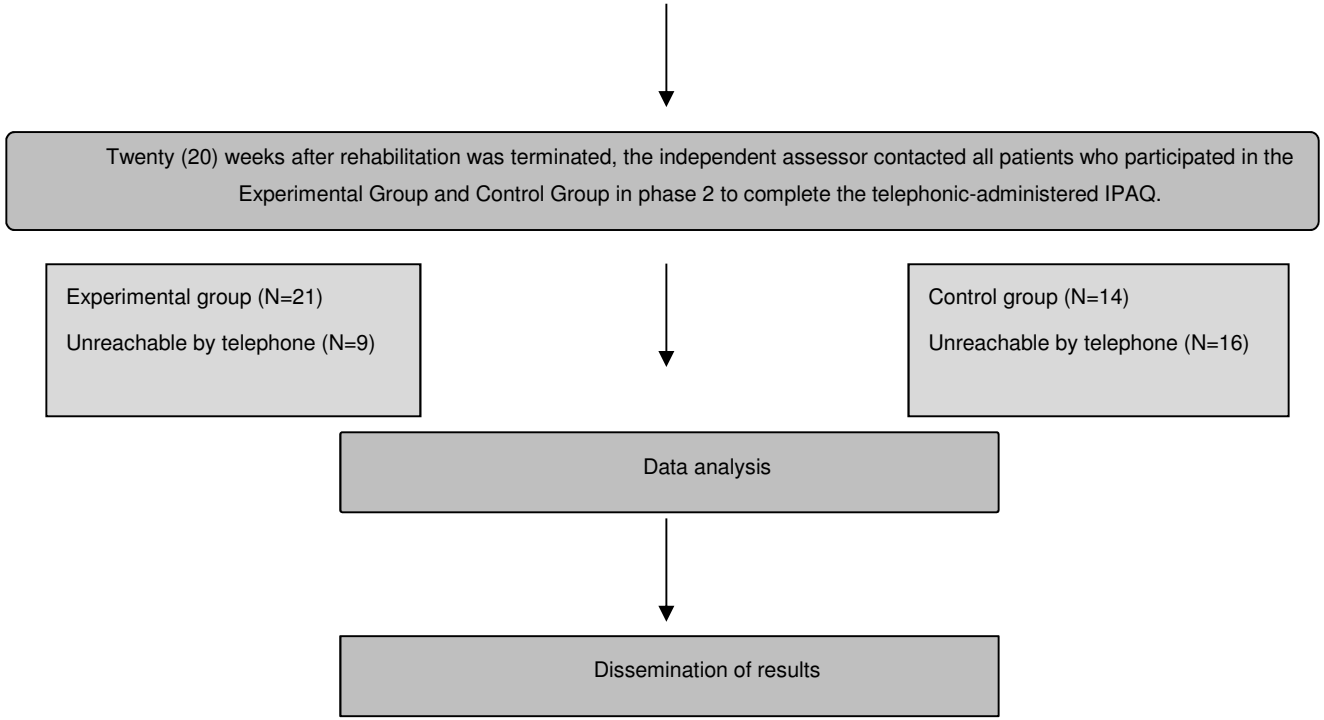


Figure 3.2.: Flow chart of phase 2 of the study.

The intervention received by patients in the experimental group and control group in phase 2 of the study are discussed in Section 3.1.6.

3.1.6. Intervention received by patients in phase 2 of the study

Patients in the experimental group were treated by the principal investigator with VRT integrated with task-specific activities as an “add-on” intervention. The treatment approach for the rehabilitation of the experimental group was selected based upon the outcome of the literature study (Section 2.5.1. and 2.5.2.). Patients in the control group within the rehabilitation centers were treated by qualified physiotherapists who used the same task-specific principles during the rehabilitation of post-stroke patients as the principal investigator. The principal investigator ensured that the physiotherapists that were recruited to participate in the treatment of patients in the control group, were trained in the implementation of task-specific principles in the rehabilitation of post-stroke patients and had a minimum of three (3) years’ experience in the rehabilitation of post-stroke patients in the sub-acute phase. The task-specific approach is the standard of care (intervention) in post-stroke rehabilitation (Rensink, Lindeman and Hafsteinsdóttir 2009:737). The treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction received by patients in the experimental group and control group are presented in Table 3.2.

Table 3.2.: The treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction received by patients in the experimental group and control group.

Task-specific activities	Progression of task-specific activities	"Add-on" intervention: Vestibular rehabilitation therapy[1] integrated with task-specific activities[2]
1.1. Symmetrical static *sitting* with bilateral upper limbs and feet supported on a hard (level) surface within a closed kinetic chain (CKC) position (Kim and Yoo 2017:846).	1.1. Incorporate *upper extremity movement* (open kinetic chain movement) (Kim and Yoo 2017:846) and *reaching* (Dean, Channon and Hall 2007:97) in *sitting*. Bilateral and unilateral shoulder flexion, with and without weight such as soccer ball, medicine ball and large exercise ball (throwing and bouncing).	1.1. Commence with *saccadic eye movement substitution* by implementing *visual scanning exercises (VSEs)* with saccadic eye movement training (using a HART-chart) integrated with task-specific activities (Van Wyk *et al* 2014:859)[3].
1.2. Weight-shifting (anterior / posterior / lateral) while in symmetrical *sitting* on hard (level) surface to modify center of gravity (COG).		1.2. Place the HART-chart in the *centre* of the patient's visual field.
1.3. *Sit to stand* training (Cheng, Wu, Liaw, Wong and Tang 2001:1650).	1.2. Alternate between lighter and heavier objects during upper extremity movement and reaching to modify COG in *sitting*.	1.3. Progress the activity by placing the HART-chart in the *outer* left *and* right visual field of the patient. The patient performs 90° left and right horizontal head rotations to read the HART-chart in both visual fields.
1.4. Symmetrical static *standing* (Cheng *et al* 2001:1650) on a hard (level) surface with upper limbs symmetrically supported on a hard surface within a closed kinetic chain (CKC) position (Kim and Yoo 2017:846).	1.3. Reaching tasks beyond arm's length in *sitting*. Vary reach distance, direction, thigh support, seat height and task (Dean *et al* 2007:97).	1.4. As the patient habituate to the head motion, *increase velocity* of head motion while continuing to perform VSEs using the HART-chart.
1.5. Weight-shifting (anterior / posterior / lateral) while in symmetrical *standing* on hard (level) surface to modify center of gravity (COG).	1.4. Standing with feet apart (increased base of support [BOS]), eyes open → eyes closed.	1.5. Progress to the process of adaptation by performing *gaze stabilization* and/or *VOR training* to produce an error signal that the CNS attempts to reduce retinal slip and visual blurring by modifying the gain of the VOR[4].
1.6. Symmetrical static standing on soft (foam) surface with upper limbs symmetrically supported on a hard surface within a closed kinetic chain (CKC) position (Kim and Yoo 2017:846).	1.5. Standing with feet touching (decreased BOS), eyes open → eyes closed.	1.6. *Gaze stabilization and/or VOR training*: Horizontal and vertical head movements while eyes remain on target placed in the *centre* of the patient's visual field. Place the target on a mirror to enable the physiotherapist to monitor gaze of the patient.
	1.6. Standing with one foot ahead by a half-foot length (semi-tandem Romberg), eyes open → eyes closed.	

Table 3.2.: (continued) The treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction received by patients in the experimental- and control group.

Task-specific activities	Vestibular rehabilitation therapy integrated with task-specific activities	"Add-on" intervention: Vestibular rehabilitation therapy integrated with task-specific activities
1.7. Weight-shifting (anterior / posterior / lateral) while in symmetrical static standing on soft (foam) surface to modify center of gravity (COG). 1.8. Weight-shifting activities in the medial-lateral and anterior-posterior direction by *stepping* / *alternated stepping* in the anterior-posterior and medial-lateral direction. 1.9. Commence *walking* with or without an assistive device under supervision to ensure safety during gait. 1.10. *Stair climbing* with or without an assistive device under supervision to ensure safety.	1.7. Standing in a tandem position with the feet touching in a straight line (tandem Romberg), eyes open → eyes closed. 1.8. Half-standing (one foot supported on a step), eyes open → eyes closed. 1.9. Single leg stance (one foot unsupported), eyes open → eyes closed. 1.10. Standing on various surfaces to facilitate weight-shift (anterior / posterior / lateral) and to modify COG using a firm surface with incline, firm surface with decline, soft surface (foam proprioception mat), BOSU-ball and trampoline. 1.11. Incorporate *upper extremity movement* (open kinetic chain movement) (Kim and Yoo 2017:846) and *reaching* in *standing*. Bilateral and unilateral shoulder flexion, with and without weight such as a soccer ball, medicine ball and large exercise ball (throwing and bouncing). 1.12. Alternate between lighter and heavier objects during upper extremity movement and reaching to modify COG in *standing*.	1.7. If the patient presents with difficulty to initiate head movement or maintain velocity of head movement, the physiotherapist *facilitates head movement* while the patient engages in gaze stability exercise. The ability of the patient to keep his/her eyes on the target should determine the velocity of the head movement; start with slow head movement and increase speed of head movement to reach target velocity of ≥ 2Hz[5]. 1.8. Progress to *active assisted* head movement and finally independent head movement produced by the patient while maintaining gaze stability on a target. 1.9. Progress gaze stabilization and/or VOR training by placing the target in different locations *within* the 180° visual field of the patient. 1.10. Incorporate horizontal and vertical head movements in *all sitting, sit to stand, standing* and *gait activities* (Whitney and Sparto 2011:157)[6].

Table 3.2.: (continued) The treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction received by patients in the experimental- and control group.

Task-specific activities	Vestibular rehabilitation therapy integrated with task-specific activities	"Add-on" intervention: Vestibular rehabilitation therapy integrated with task-specific activities
	1.13. Reaching tasks beyond arm's length in *standing*. Vary reach distance, direction and task. 1.14. Alter speed of upper extremity movement (open kinetic chain movement). 1.15. Alter *speed* of stepping activities. 1.16. *Stepping* (marching) on various surfaces. 1.17. *Walking* on uneven surfaces, change of directions and stepping over/around objects of different sizes. 1.18. Alternating *gait speed* from self-selected gait speed to fast and slower gait speed, quick stops/starts and walking backwards. 1.19. *Walking* while carrying an object / throwing / bouncing / kicking a ball.	1.11. *Process of 'habituation'*: Positions and movements used during the process of 'habituation' may include moving from sitting to lying in supine, rolling from supine to left side lying, rolling from supine to right side lying, moving from supine to sitting, left and right Dix-Hallpike position; return to sitting from the Dix-Hallpike position; horizontal and vertical movement of the head and turning 180° to the left and right (Herdman and Whitney 2007:312)[7].
[1] = Vestibular rehabilitation therapy (VRT) for treatment (rehabilitation) of central vestibular dysfunction consist of a programme of exercises designed to facilitate adaptation of the vestibular system, habituate the person to movement, teach sensory substitution and improve a patient's balance and postural control (Alghadir *et al* 2013:1).		
[2] = The process of substitution facilitates the use of individual or combinations of sensory input such as somatosensory (including proprioceptive) or visual[3] information to facilitate vestibular compensation through the process of sensory re-weighting due to dysfunctional vestibular input (McDonnell and Hillier 2015:3).		

Table 3.2.: (continued) The treatment principles for the clinical features and activity limitations associated with central vestibular dysfunction received by patients in the experimental- and control group.

[3] = Saccadic eye movement substitution may be achieved by the implementation of VSEs integrated with task-specific activities (Van Wyk *et al* 2014:856). Progression of these exercises is guided by the patient's ability to allocate information-processing resources between two (2) tasks and to maintain sufficient attention on the visual scanning task during the dual-task performance of horizontal and vertical saccadic eye movements, as well as head movement while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856). ** Perform VSEs using a HART-chart (Van Wyk et al 2014:859) in all sitting, sit to stand, standing and gait activities.*
[4] = The process of 'adaptation' for visual-vestibular interaction (gaze stabilisation) and eye/hand co-ordination uses repetitive and provocative movements of the head and/or eyes aimed to reduce error and restore VOR-gain (Cullen *et al* 2009:171; Balaban *et al* 2012:101; McDonnell and Hillier 2015:3). The best stimulus to induce 'adaptation' is to produce an error signal that the CNS attempts to reduce by modifying the gain of the VOR (Herdman and Whitney 2007:311). Gaze stabilisation exercises to retrain VOR function are prescribed to stimulate retinal slip to optimise vision during head movement (Herdman and Whitney 2007:311). ** Perform gaze stabilisation and/or VOR training in all sitting, sit to stand, standing and gait activities.*
[5] = Target velocity <2Hz produces smooth pursuit eye movement.
[6] = Horizontal and vertical head movements are emphasised during all activities to increase SCC stimulation, facilitate dissociation between the head and trunk and to improve coordination of axial segments and pelvic rotations during head rotation.
[7] = The process of 'habituation' is aimed to 'habituate' or reduce a patient's responsiveness to repetitive stimuli aimed to re-balance tonic activity within the vestibular nuclei (Gans 2002:149; McDonnell and Hillier, 2015:3). 'Habituation' is based on the inherent plasticity of the CNS and is more likely to be a compensatory or neuroplastic process (Han *et al* 2011:184; McDonnell and Hillier, 2015:3), rather than a physiological synaptic habituation response.

The principal investigator and physiotherapists who provided treatment to patients in the experimental and control group respectively, implemented an individualized exercise programme based on the treatment principles described in Table 3.2. The average duration of physiotherapy sessions was approximately 45 minutes. Time spent on report writing and discussions with other members of the multidisciplinary team were not included in these 45 minutes. Patients in the experimental group and control group received intervention daily for a period of two (2) weeks. The two (2) week period of intervention was selected due to the fact that patients are, on average, admitted to a rehabilitation centre post-stroke for a period of two (2) weeks. The intervention period of two (2) weeks was further decided upon because results from a previous study (Van Wyk *et al* 2014:856) demonstrated a statistically significant (P=0.02) difference between the experimental group and control group after two (2) weeks' intervention (Van Wyk *et al* 2014:856) (Table 3.1. and Graph 3.1.). Due to the fact that rehabilitation is a multidisciplinary team approach, all the patients who participated in the single-blind cluster randomised controlled trial continued to be treated by other members of the multidisciplinary team, namely the occupational therapist, the speech and language therapist and social worker as it is customary in all the rehabilitation centres.

The battery of objective measures used in the assessment of the clinical features and activity limitations associated with central vestibular dysfunction in phases 1 and 2 are discussed in Section 3.1.7.

3.1.7. Battery of objective measures used in phase 1 and phase 2 of the study

The battery of outcome measures implemented in phases 1 and 2 in the current study were selected to quantify the clinical features & activity and participation limitations associated with central vestibular dysfunction in post-stroke patients, were critically reviewed and appraised (Section 2.4). The summary of the battery of objective measures is presented in Table 2.32. The measurement of the clinical features associated with central vestibular dysfunction on the level of body structure and function are discussed in Section 3.1.7.1.

3.1.7.1. Measurement of the clinical features associated with central vestibular dysfunction on the level of body structure and function

The first clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phases 1 and 2 was oculomotor control (Section 1.1.3.1).

(1). Oculomotor control

In this study, the assessment of oculomotor control consisted of the measurement of smooth pursuit and saccadic eye movements using VNG and static visual acuity using the LogMAR chart.

(i) Measurement of smooth pursuit and saccadic eye movements using video nystagmography

Smooth pursuit eye movements and saccadic eye movements of all patients in the study were measured using VNG. Video nystagmography was used to record patients' eye movements using digital video image technology to measure the (a) *gain* of *smooth pursuit eye movements* of the left and right eyes into the left and right visual field; (b) the *latency* of *saccadic eye movements* of the left and right eyes into the left and right visual field; (c) the *velocity* of *saccadic eye movements* of the left and right eyes into the left and right visual field; and (d) the *accuracy* of *saccadic eye movements* of the left and right eyes into the left and right visual field (Section 2.4.1.1).

All patients' smooth pursuit eye movements and saccadic eye movements of the left and right eyes into the left and right visual fields measured by VNG are presented within the context of the visual pathway. The visual pathway is presented in Figure 2.3. (Coren *et al* 2003:608). As demonstrated in Figure 2.3., the left and right visual fields of a person are represented in the hemisphere that is contralateral to the stimulated visual field (Si, Zhang, Zhang and Jiang 2017:2018). It is therefore essential to present the results of the measurement of smooth pursuit eye movements and saccadic eye movements of both eyes into both visual fields separately to identify possible differences in oculomotor function and visual activation between the two

hemispheres (Hougaard, Jensen, Amin, Rostrup, Hoffmann and Ashina 2015:2) of post-stroke patients. Normative values for smooth pursuit eye movements (gain) and saccadic eye movements (latency, velocity and accuracy) of the left and right eyes into the left and right visual fields by age group are presented in Table 3.3.

Table 3.3.: Normative values for smooth pursuit and saccadic eye movements by age group (Interacoustics® American Institute of Balance; Seminole, Florida) (https://www.dizzy.com/aib-technology-partners/).

NORMATIVE VALUES FOR SMOOTH PURSUIT AND SACCADIC EYE MOVEMENTS OF BOTH EYES INTO BOTH VISUAL FIELDS BY AGE GROUP									
SMOOTH PURSUIT EYE MOVEMENT: GAIN									
Smooth pursuit eye movement		**Patient Age: 20–49 years**		**Patient Age: 50–69 years**		**Patient Age: 70-79 years**		**Patient Age: 80-98 years**	
		Mean (%)	**Standard deviation**	**Mean (%)**	**Standard deviation**	**Mean (%)**	**Standard deviation**	**Mean (%)**	**Standard deviation**
Left Visual field	Gain of the Right Eye	≥94	14	≥96	8	≥92	9	≥95	6
	Gain of the Left Eye	≥95	5	≥95	7	≥88	18	≥92	13
Right Visual field	Gain of the Right Eye	≥93	9	≥91	18	≥90	9	≥91	13
	Gain of the Left Eye	≥95	8	≥96	4	≥91	14	≥91	13
SACCADIC EYE MOVEMENT: LATENCY									
Saccadic eye movement		**Patient Age: 20–49 years**		**Patient Age: 50–69 years**		**Patient Age: 70-79 years**		**Patient Age: 80-98 years**	
		Mean (ms)	**Standard deviation**	**Mean (ms)**	**Standard deviation**	**Mean (ms)**	**Standard deviation**	**Mean (ms)**	**Standard deviation**
Left Visual field	Latency of the Left Eye	≤215	36	≤246	21	≤239	28	≤244	29
	Latency of the Right Eye	≤214	36	≤239	46	≤234	30	≤232	39
Right Visual field	Latency of the Left Eye	≤221	39	≤241	51	≤228	65	≤251	30
	Latency of the Right Eye	≤218	48	≤244	35	≤230	60	≤249	45

Table 3.3.: (continued) Normative values for smooth pursuit and saccadic eye movements by age group (Interacoustics® American Institute of Balance; Seminole, Florida) (https://www.dizzy.com/aib-technology-partners/).

NORMATIVE VALUES FOR SMOOTH PURSUIT AND SACCADIC EYE MOVEMENTS OF BOTH EYES INTO BOTH VISUAL FIELDS BY AGE GROUP									
SACCADIC EYE MOVEMENT: VELOCITY									
Saccadic eye movement		**Patient Age: 20–49 years**		**Patient Age: 50–69 years**		**Patient Age: 70-79 years**		**Patient Age: 80-98 years**	
		Mean (°/s)	**Standard deviation**	**Mean (°/s)**	**Standard deviation**	**Mean (°/s)**	**Standard deviation**	**Mean (°/s)**	**Standard deviation**
Left Visual field	Velocity of the Left Eye	≥333	62	≥303	77	≥276	74	≥260	50
	Velocity of the Right Eye	≥336	52	≥320	73	≥292	59	≥276	60
Right Visual field	Velocity of the Left Eye	≥302	62	≥309	63	≥294	118	≥286	70
	Velocity of the Right Eye	≥293	69	≥274	88	≥223	69	≥238	81
SACCADIC EYE MOVEMENT: ACCURACY									
Saccadic eye movement		**Patient Age: 20–49 years**		**Patient Age: 50–69 years**		**Patient Age: 70-79 years**		**Patient Age: 80-98 years**	
		Mean (%)	**Standard deviation**	**Mean (%)**	**Standard deviation**	**Mean (%)**	**Standard deviation**	**Mean (%)**	**Standard deviation**
Left Visual field	Accuracy of the Left Eye	≥95	11	≥90	9	≥89	10	≥85	17
	Accuracy of the Right Eye	≥94	8	≥91	18	≥92	8	≥86	20
Right Visual field	Accuracy of the Left Eye	≥93	14	≥88	23	≥91	24	≥98	14
	Accuracy of the Right Eye	≥93	7	≥83	24	≥90	41	≥89	19

(a). Validity and reliability of the measurement of smooth pursuit and saccadic eye movements using video nystagmography

Mohamed (2016:202) indicated that measurement of smooth pursuit and saccadic eye movements using VNG has a moderate sensitivity (55%) and high specificity (90%) as a predictor of central vestibular dysfunction (N=51). Bargary, Bosten, Goodbourn, Lawrance-Owen, Hogg and Mollon (2017:157) indicated good test–retest reliability in the measurement of the *gain* of *smooth pursuit eye movement* (N=1058) (Pearson's correlation coefficient = 0.88; Spearman's correlation coefficient = 0.86; and intra-class correlation coefficient (ICC) = 0.86). Bargary *et al* (2017:157) also indicated good test–retest reliability in the measurement of the *latency* of saccadic eye movement (N=1058) (Pearson's correlation coefficient = 0.83; Spearman's correlation coefficient = 0.84; and ICC = 0.84) and *accuracy* of saccadic eye movement (N=1058) (Pearson's correlation coefficient = 0.82; Spearman's correlation coefficient = 0.83; and ICC = 0.82). Findings of Bargary *et al* (2017:157) demonstrated good test–retest reliability in the measurement of the relationship between the amplitude and the *peak velocity* of saccadic eye movement (N=1058) (Pearson's correlation coefficient = 0.86; Spearman's correlation coefficient = 0.88; and ICC = 0.88).

(ii) Measurement of static visual acuity using the LogMAR chart

The static visual acuity of all patients in the study was measured using the LogMAR chart. Reduced static visual acuity is defined as visual acuity worse than 0.5 LogMAR according to the World Health Organisation (WHO) (Rowe *et al* 2011:406). The LogMar chart follows the principle of logarithmic size progression and is considered the gold standard for the measurement of static visual acuity (Noushad *et al* 2012:87). The normative values for the LogMAR chart are presented in Table 3.4.

Table 3.4.: Normative values for the LogMAR chart (Rowe *et al* 2011:406).

LogMAR chart	Interpretation of the LogMAR chart
> 1.3 LogMAR	Blindness
> 0.5-1.3 LogMAR	Reduced static visual acuity
≤ 0.5 LogMAR	Normal static visual acuity

(a). Validity and reliability of the measurement of static visual acuity using the LogMAR chart

The LogMar chart is regarded as the gold standard for the measurement of static visual acuity (Lotery *et al* 2000:221; Rowe *et al* 2009:188; Rowe *et al* 2011:406; Noushad *et al* 2012:87). Rosser, Cousens, Murdoch, Fitzke and Laidlaw (2003:3278) indicated that measurement of static visual acuity using the LogMAR chart to determine a test–retest variability change criterion of 0.11 logMAR. The LogMar chart has a high sensitivity (100%, 95% confidence interval [CI] 93%–100%) and high specificity (96%, 95% CI 86%–99.5%) in the measurement of changes of 0.2 to 0.3 logMAR (N=50). Rosser *et al* (2003:3278) also indicated in the measurement of change of 0.1 logMAR, the LogMAR chart has a sensitivity (38%, 95% CI 25%–53%) and high specificity (96%, 95% CI 86%–99.5%). Findings of Arditi and Cagenello (1993:120) indicated that the LogMar chart has good test-retest reliability for the measurement of static visual acuity (correlation coefficient = 0.895) (N=78).

The second clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phases 1 and 2 was reflexive control of gaze (Section 1.1.3.1).

(2). Reflexive control of gaze

In this study, the assessment of reflexive control of gaze consisted of the measurement of the VOR-gain using vHIT and DVA using the LogMAR chart. The measurement of VOR-gain using vHIT are firstly discussed.

(i) Measurement of the vestibulo-ocular reflex-gain using the video Head Impulse Test

The VOR-gain of all patients in the study was measured using the EyeSeeCam vHIT (Leigh and Zee 2006:5; Petersen, Straumann and Weber 2013:41). The vHIT is a small, light-weight and fast head-mounted video camera system that allows accurate measurement of eye movements during passive head rotation at a peak angular velocity of ± 200°/s and a peak angular acceleration of 2500-3000°/s. The vHIT specifically quantifies the VOR-gain which is the ratio of the corrective eye movement response to the passive head movement stimulus. The perfect VOR gain is thus 1.0, which means the corrective eye movement is exactly equal to and opposite of the head movement. A VOR-gain of 1.0 suggests that the corrective eye movement exactly corrects for the head movement and thus the retinal image remains stable during the head movement (MacDougall and Curthoys 2012:1). The normative values for the vHIT is presented in Table 3.5.

Table 3.5.: Normative values for the video Head Impulse Test (MacDougall and Curthoys 2012:1; Choi *et al* 2018:90).

Vestibulo-ocular reflex-gain	**Interpretation of the video Head Impulse Test**
< 0.68	Vestibular hypofunction
0.68–1.2	Absence of vestibular impairment
> 1.2	Vestibular hyperfunction

Findings of a recent study by Choi *et al* (2018:90) demonstrated the use of vHIT in patients with central vestibular dysfunction. Patients with lesions that involve the vestibular nucleus, nucleus prepositus hypoglossi or flocculus, may present with vestibular hypofunction as result of significantly reduced unilateral or bilateral horizontal VOR-gains measured with vHIT. In contrast, patients with diffuse cerebellar lesions may present with vestibular hyperfunction as result of increased (hyperactive) horizontal VOR-gains (Choi *et al* 2018:90). Choi *et al* (2018:90) remarked that the identification and definition of differences in patterns observed during the assessment of the VOR may aid therapists to localise the lesions in the central vestibular system to facilitate the management of patients with impaired reflexive control of gaze post-stroke.

(a). Validity and reliability of the measurement of the vestibulo-ocular reflex-gain using the video Head Impulse Test

MacDougall, Weber, McGarvie, Halmagyi and Curthoys (2009:1134) demonstrated that simultaneous video and search coil recordings of eye movements were closely comparable (average concordance correlation coefficient rc=0.930) in healthy subjects (N=8) and patients with vestibular dysfunction (N=8). No statistically significant difference in mean VOR-gain measured with vHIT compared to search coils, were observed in healthy subjects (P=0.107) and patients with vestibular dysfunction (P=0.073) (MacDougall *et al* 2009:1134). Findings of MacDougall *et al* (2009:1134) also indicated that the vHIT has a high sensitivity and specificity of 1.0 (95% CI 0.69–1.0). These findings of MacDougall *et al* (2009:1134) are supported by Singh, Govindaswamy and Jagadish (2019:744) who indicated that the vHIT has good test-retest reliability for the measurement of VOR-gain (ICC ≥ 0.76) (N=40).

The second feature of reflexive control of gaze that was assessed was DVA.

(ii) Measurement of dynamic visual acuity using the LogMAR chart

Dynamic visual acuity assesses the VOR by evaluating the patient's ability to stabilise their gaze during head movements. The DVA of all patients in the study was measured using the LogMAR chart. Similar to the assessment of static visual acuity, DVA is also measured as the logarithm of the minimal angle of resolution (LogMAR) (Tusa 2007:131). The assessment of DVA was performed while the patient was seated in front of the LogMAR chart. Firstly, the examiner asked the patient to read the LogMAR chart without head movement. Thereafter, the examiner oscillated the patient's head horizontally at 2 Hz while the patient was asked to continue reading the LogMAR chart. A metronome was used to standardise the frequency of head rotations at 2 Hz to improve the reliability of the test and to facilitate an adequate visual stimulus intensity during the testing of DVA (Dannenbaum, Paquet, Hakim-Zadeh and Feldman 2005:13). Visual acuity with and without head movement were compared by assessing the number of lines the patient was unable to complete during DVA testing. The normative values of the DVA test using the LogMAR chart is presented in Table 3.6.

Table 3.6.: Normative values for the LogMAR chart used in the measurement of dynamic visual acuity (Tusa 2007:118).

LogMAR chart	Interpretation of the LogMAR chart
> 1.3 LogMAR	Blindness
> 0.5-1.3 LogMAR	Reduced static visual acuity
≤ 0.5 LogMAR	Normal static visual acuity
Dynamic visual acuity minus static visual acuity: Decrease of >0.2 LogMAR	VOR-impairment that results in decreased dynamic visual acuity
Dynamic visual acuity minus static visual acuity: Decrease of ≤0.2 LogMAR	Absence of dynamic visual acuity impairment

(a). Validity and reliability of the measurement of dynamic visual acuity using the LogMAR chart

Vital *et al* (2010:686) demonstrated that dynamic visual acuity testing by using passive horizontal head rotations (movements) at a velocity higher than 150°/s has a high sensitivity (100%), specificity (94%) and accuracy (95%) in comparison to horizontal head impulse testing with scleral search coils (N=115). Riska and Hall (2016:545) indicated that the dynamic visual acuity test expressed as LogMAR has good test-retest reliability for horizontal head movements (ICC = 0.832 - 0.856) (N=42). Findings by Riska and Hall (2016:545) also indicated that the dynamic visual acuity test expressed as dynamic visual acuity loss (dynamic visual acuity minus static visual acuity: decrease of ≤0.2 LogMAR) has a test-retest reliability for horizontal head movements (ICC = 0.154 - 0.371) (N=42). Dynamic visual acuity expressed as LogMAR (raw scores) has a higher test-retest reliability compared to dynamic visual acuity expressed as dynamic visual acuity loss (dynamic visual acuity minus static visual acuity: decrease of ≤0.2 LogMAR) (Riska and Hall 2016:545).

The third and fourth clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phases 1 and 2 was the saccule, inferior vestibular nerve function and utricle, as well as superior vestibular nerve function of patients in the sub-acute phase post-stroke (Section 1.1.3.1).

(3). Saccule, inferior vestibular nerve function and utricle, superior vestibular nerve function

The saccule, inferior vestibular nerve function and its central projections of all patients in the study were measured using the cVEMP test (Tusa 2007:132). The cVEMP is generated via a pathway that commences in the saccule and proceeds along the vestibular afferent fibres to the vestibular nuclei, where-after it proceeds through rapid conducting projections that synapse with the sternomastoid nuclei (Chen and Young 2003:990). The cVEMP is thus a sound-evoked muscle response from the sternocleidomastoid muscle generated by the patient's response on an acoustical stimulation of the saccule. The response to the stimulus is an inhibitory response of the tone in the sternocleidomastoid muscle detected by a surface electromyography (EMG) recording (Tusa 2007:132). Diagnostic information about the function of the saccule and inferior vestibular nerve is provided by the presence or absence of the muscle response (Tusa 2007:132; Kim *et al* 2011:1).

The utricle and superior vestibular nerve function of all patients in phases 1 and 2 were measured using the oVEMP test (Curthoys *et al* 2012:41). The oVEMP is generated via the crossed excitatory vestibulo(otolith)-ocular reflex (Oh *et al* 2013). The oVEMP is detected by surface EMG electrodes placed close to the eyes (Colebatch, Rosengren and Welgampola 2016:133) to detect and record myogenic potentials in response to sound. The oVEMP is thus a sound-evoked muscle response from the inferior oblique extraocular muscles generated by the patient's response on an acoustical stimulation of the utricle. Diagnostic information about the function of the utricle and superior vestibular nerve is provided by the presence or absence of the

muscle response. Normative values for the cVEMP and oVEMP are presented in Table 3.7.

Table 3.7.: Normative values for the cervical vestibular-evoked myogenic potential and ocular vestibular-evoked myogenic potential (Kim *et al* 2011:1; Colebatch *et al* 2016:133).

VESTIBULAR EVOKED MYOGENIC POTENTIALS	
Cervical vestibular-evoked myogenic potential	**Normative value**
cVEMP P1	≤ 19 ms
cVEMP N1	≤ 28 ms
Ocular vestibular-evoked myogenic potential	**Normative value**
oVEMP N1	≤ 11.1 ms
oVEMP P1	≤ 17.6 ms
cVEMP = Cervical vestibular-evoked myogenic potential	
oVEMP = Ocular vestibular-evoked myogenic potential	
N1 = First negative deflection on wave form	
P1 = First positive peak on wave form	

Patients with a lesion at/ or below the vestibular nucleus in the MVST (Section 2.3.2.1), or spinal accessory nucleus would present with an isolated absent cVEMP. Patients with a lesion at or above the vestibular nucleus in the MLF (Section 1.1.1.2) or oculomotor nucleus would present with an absent oVEMP. It is important to highlight that patients who present with a combined cVEMP and oVEMP abnormality would suggest a lesion in the vestibular nucleus or root entry zone (Rosengren and Colebatch 2018:481). Although recovery of otolith function and VEMPs may occur following a peripheral vestibular nerve disorder such as vestibular neuritis (Figure 1.1), VEMPs in patients with central vestibular dysfunction may remain abnormal or absent even after central vestibular compensation has occurred (Rosengren and Colebatch 2018:481).

(a). Validity and reliability of the measurement of saccule, inferior vestibular nerve function and utricle, superior vestibular nerve function using cervical and ocular vestibular-evoked myogenic potentials

Bush, Jones and Shinn (2010:170) demonstrated that P1 (first positive peak on wave form) and N1 (first negative deflection on wave form) components of the cVEMP have a specificity of 86.25% and 70.50% respectively (N=8). Findings by Maes *et al* (2009:594) indicated that the P1 and N1 components of cVEMP has good test-retest reliability (ICC = 0.78 - 0.96) (N=61). Agrawal, Bremova, Kremmyda, Strupp and Macneilage (2013:905) demonstrated that the N1 amplitude component of the oVEMP were significantly associated with horizontal plane perceptual thresholds along the inter-aural (IA) axis (left or right) (P=0.0093) and naso-occipital (NO) (forward or backward) (P=0.0285) axis using a multi-axis motion platform (N=75). The N1 amplitude component of the oVEMP were not statistically significantly associated with head-vertical (HV) axis (up or down) perceptual thresholds (P=0.2000). Findings of Agrawal *et al* (2013:905) suggest that the tests of horizontal perceptual thresholds and oVEMP measure the same underlying physiological construct of utricular function. Özdek, Keseroğlu, Er, Ünsal and Gündüz (2017:26) indicated that the combination of oVEMP and vHIT have a sensitivity (77.3%) and specificity (80.1%) as an indicator of vestibular dysfunction (N=30). Findings by Piker, Jacobson, McCaslin and Hood (2011:222) indicated that the N1 and P1 components of oVEMP has a test–retest reliability (ICCs = 0.53 to 0.65).

The fifth clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phases 1 and 2, was higher vestibular function of patients in the sub-acute phase post-stroke (Section 1.1.3.1).

(4). Higher vestibular function

In the current study, the assessment of higher vestibular function consisted of the measurement of residual oculomotor visual performance using the King-Devick Test©, visual-perceptual function using the Star Cancellation Test and cognitive function using the Mini-Mental State Examination. The measurement of residual oculomotor visual performance is firstly discussed.

(i) Measurement of residual oculomotor visual performance using the King-Devick Test©

The residual oculomotor visual performance of all patients in the study was assessed using the King-Devick Test© (Zoltan 1996:27). The King-Devick Test© consists of three (3) sub-tests (Sub-test 1 to Sub-test 3). Interpretation of the King-Devick Test© includes; (i) the time taken to complete the test (the time indicated the speed with which the test was completed); and (ii) the average errors made during the completion of the sub-tests. Normative values for the King-Devick Test© are presented in Table 3.8.

Table 3.8.: Normative values for the King-Devick Test© (Zoltan 1996:27).

King-Devick Test©	**Interpretation of the King-Devick Test©**		
	King-Devick Sub-test 1	**King-Devick Sub-test 2**	**King-Devick Sub-test 3**
Time (seconds) taken to complete the sub-test	14.86	16.87	18.73
Average errors made in completion of the sub-test	0.07	0.07	0.33

(a). Validity and reliability of the measurement of residual oculomotor visual performance using the King-Devick Test©

Heick, Bay and Valovich McLeod (2018:808) demonstrated acceptable correlation ($r=0.67$, $P<0.001$) between the King-Devick Test© and Developmental Eye Movement (DEM) test that assesses both horizontal and vertical saccadic eye movements (N=42). Findings by Heick *et al* (2018:808) suggest that the King-Devick Test© and DEM test measure the same underlying physiological process of residual oculomotor visual performance through the assessment of horizontal saccadic eye movements. Heick *et al* (2018:808) also indicated that the King-Devick Test© has good test-retest reliability (ICC = 0.98, 95% CI 0.97-0.99) (N=42). The second feature of higher vestibular function that was assessed was visual-perceptual function.

(ii) Measurement of visual-perceptual function using the Star Cancellation Test

The visual-perceptual function of all patients in the study was assessed using the Star Cancellation Test (Wilson *et al* 1987:98; Van Wyk *et al* 2014:856). Interpretation of the Star Cancellation Test includes; (i) the number of errors made during the completion of the test; and (ii) the time taken to complete the test (speed). Normative values for the Star Cancellation Test are presented in Table 3.9.

Table 3.9.: Normative values for the Star Cancellation Test (Van Kessel *et al* 2010:603).

Star Cancellation Test Score	**Interpretation of the Star Cancellation Test**
Number of errors made during the completion of the test: ≤ 51	Presence of visual-perceptual dysfunction
Number of errors made during the completion of the test: > 51	Absence of visual-perceptual dysfunction

(a). Validity and reliability of the measurement of visual-perceptual function using the Star Cancellation Test

Agrell, Dehlin, and Dahlgren (1997:295) indicated that the Star Cancellation Test demonstrated moderate correlation with other conventional paper-and-pencil tests such as the Clock-drawing Test (r=-0.47) and the Copy a cross Test (r=-0.47). The Star Cancellation Test correlated moderately with the Barthel Index (r=0.48) (Agrell *et al* 1997:295). Marsh and Kersel (1993:245) indicated that the Star Cancellation Test demonstrated acceptable correlation with the Line Crossing Test (r=0.68) and with the Indented Paragraph Test (r=-0.60). Marsh and Kersel (1993:245) found that the Star Cancellation Test was the most sensitive measure of visual-perceptual function, specifically unilateral spatial neglect (100%), when compared with the other conventional paper-and-pencil tests. Bailey *et al* (2000:146) indicated that the Star Cancellation Test scored 76.4% for relative test sensitivity for visual-perceptual function compared to other conventional paper-and-pencil tests such as the Copy a Daisy Test (57.5%). The third feature of higher vestibular function that was assessed was cognitive function.

(iii) Measurement of cognitive function using the Mini-Mental State Examination

The cognitive function of all patients in the study was assessed using the Mini-Mental State Examination (MMSE) (Folstein *et al* 1975:189). The MMSE consists of eleven (11) questions or tasks that assess seven (7) cognitive domains, which include; (i) orientation to time; (ii) orientation to place; (iii) registration of three (3) words; (iv) attention and calculation; (v) recall of three (3) words; (vi) language; and (vii) visual construction. Normative values for the MMSE (Folstein, Folstein, McHugh and Fanjiang 2001:1) are presented in Table 3.10.

Table 3.10.: Normative values for the level of cognitive impairment on the Mini-Mental State Examination (Folstein *et al* 2001:1).

Mini-Mental State Examination Score	Level of impairment
≥ 27	No cognitive impairment
21–26	Mild cognitive impairment
11–20	Moderate cognitive impairment
≤ 10	Severe cognitive impairment

(a). Validity and reliability of the measurement of cognitive function using the Mini-Mental State Examination

Folstein *et al* (1975:189) indicated that the MMSE showed acceptable correlation with the Wechsler Adult Intelligence Scale (WAIS) verbal IQ (r=0.78) and the WAIS performance IQ (r=0.66). Dick *et al* (1984:496) indicated that the MMSE demonstrated moderate correlation with the WAIS verbal IQ (r=0.55) and the WAIS performance IQ (r=0.56). Findings from Folstein *et al* (1975:189) are supported by findings of Snowden *et al* (1999:1000) that indicated that the MMSE showed acceptable correlation with the WAIS verbal IQ (r=0.78) and WAIS performance IQ (r=0.66). The sixth clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phases 1 and 2 was the level of anxiety and/or depression of patients in the sub-acute phase post-stroke (Section 1.1.3.1).

(5). Level of anxiety and/or depression post-stroke

The level of anxiety and/or depression of all patients in the study were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983:361). The HADS consists of two sub-scales namely the HADS–Anxiety Sub-scale for measurement of anxiety and the HADS–Depression Sub-scale for measurement of depression. The HADS comprises of fourteen (14) questions that includes seven (7) questions to identify anxiety (HADS–Anxiety Sub-scale) and seven (7) questions to

identify depression (HADS–Depression Sub-scale) (Stern 2014:393). Normative values for the HADS is presented in Table 3.11.

Table 3.11.: Normative values for the Hospital Anxiety and Depression Scale (Stern 2014:393).

HADS – Anxiety Sub-scale	HADS – Depression Sub-scale	Level of impairment
0-7	0-7	Normal
8-10	8-10	Mild
11-21	11-21	Moderate to severe

(a). Validity and reliability of the measurement of anxiety and/or depression using the Hospital Anxiety and Depression Scale

Clark and Steer (1994:1089) indicated that the HADS demonstrated acceptable correlation with the 13-item Cognitive-Affective Subscale of the Beck Depression Inventory (BDI) (r=0.73). Findings by Clark and Steer (1994:1089) are supported by findings from Bjelland, Dahl, Haug and Neckelmann (2002:69) that the HADS showed acceptable to good correlation with the BDI (r=0.61-0.83). The HADS also demonstrated acceptable correlation with the Clinical Anxiety Scale (r=0.69-0.75) and acceptable to good correlation with the Spielberger's State-Trait Anxiety Inventory (r=0.64-0.81) and the Montgomery Asberg Depression Rating Scale (r=0.62-0.81) (Bjelland *et al* 2002:69). The measurement of clinical features associated with central vestibular dysfunction on the level of activity and participation are discussed in Section 3.1.7.2.

3.1.7.2. Measurement of activity limitations associated with central vestibular dysfunction on the level of activity and participation

The first activity limitation associated with central vestibular dysfunction on the levels of activity and participation assessed in phases 1 and 2 was sensorimotor balance, mobility and gait (Section 1.1.3.2).

(1). Sensorimotor balance, mobility and gait

In the current study, the assessment of sensorimotor balance, mobility and gait consisted of the measurement of functional balance using the BBS and the ability to modify gait in response to changing task demands using the DGI. The measurement of functional balance is firstly discussed.

(i) Measurement of functional balance using the Berg Balance Scale

The functional balance of all patients in the study were assessed using the BBS. The BBS consists of fourteen (14) items that are scored on a scale of zero (0) to four (4). The maximum total score on the test is 56. The items on the BBS include simple mobility tasks that include transfers, standing unsupported, sit-to-stand, tandem standing, turning 360° and single-leg stance. Normative values for the BBS are presented in Table 3.12.

Table 3.12.: Normative values for the Berg Balance Scale (Berg, Wood-Dauphinee, Williams and Maki 1992:7).

Berg Balance Score	Fall risk
41 – 56	Low fall risk
21 – 40	Medium fall risk
0 – 20	High fall risk

(a). Validity and reliability of the measurement of functional balance using the Berg Balance Scale

Berg *et al* (1992:7) indicated that the BBS showed a good correlation (Jonsdottir and Cattaneo 2007:1410) with the Barthel Index (r=0.80-0.94) and acceptable to good correlation (Jonsdottir and Cattaneo 2007:1410) with the balance subscale of the Fugl-Meyer Assessment (r=0.62-0.94). Findings by Berg *et al* (1992:7) are supported by findings from other published literature that indicated that the BBS demonstrated an acceptable correlation (Jonsdottir and Cattaneo 2007:1410) with the Single-Leg

Stance (SLS) (r=0.65–0.79) (Flansbjer *et al*2012:165) and a good correlation (Jonsdottir and Cattaneo 2007:1410) with the Postural Assessment Scale (r=0.92-0.95) (Mao, Hsueh, Tang, Sheu and Hsieh 2002:1022) and the balance subscale of the Fugl-Meyer Assessment (r=0.90-0.92) (Mao *et al* 2002:1022). Results of the retrospective study by Whitney, Wrisley and Furman (2003:178) demonstrated a moderate correlation between the BBS and DGI (r=0.71; P<01) in patients with vestibular dysfunction (N=70). Findings of Whitney *et al* (2003:178) indicated that the BBS provides valuable information of the functional balance abilities specifically in patients with vestibular dysfunction. The second feature of sensorimotor balance, mobility and gait that was assessed was a patient's ability to modify gait in response to changing task demands using the DGI.

(ii) Measurement of the ability to modify gait in response to changing task demands using the Dynamic Gait Index

The ability to modify gait in response to changing task demands and risk of falling of all patients that participated in the study were assessed using the DGI (Shumway-Cook *et al* 1997:812). The DGI assessed walking while changing speed, performing head turns while walking, gait with pivot turn, walking over and around obstacles and stair climbing (Jonsdottir and Cattaneo 2007:1410). The DGI has been used to determine the fall risk specifically in patients with vestibular dysfunction (Whitney *et al* 2000:99). Normative values for the DGI are presented in Table 3.13.

Table 3.13.: Normative values for the Dynamic Gait Index (Whitney *et al* 2000:99).

Dynamic Gait Index Score	Fall risk
19-24	Low fall risk
0-18	High fall risk

(a). Validity and reliability of the measurement of the ability to modify gait in response to changing task demands using the Dynamic Gait Index

Jonsdottir and Cattaneo (2007:1410) indicated that the DGI showed a good correlation (Jonsdottir and Cattaneo 2007:1410) with the BBS (r=0.83) and an acceptable correlation (Jonsdottir and Cattaneo 2007:1413) with the ABC scale. The DGI also demonstrated an acceptable correlation with the timed walking test (r=0.73) and the TUG (r=0.77) (Jonsdottir and Cattaneo 2007:1410). The second activity limitation associated with central vestibular dysfunction on the levels of activity and participation assessed in phases 1 and 2 was functional ability (Section 1.1.3.2).

(2). Functional ability

The functional ability of all patients in the study was assessed using the Barthel Index (Mahoney and Barthel 1965:61). The Barthel Index assesses the performance on ten (10) basic ADLs regarding feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing, as well as the assistance required to perform these activities (Mahoney and Barthel 1965:61). Normative values for the Barthel Index are presented in Table 3.14.

Table 3.14.: Normative values for the Barthel Index (Mahoney and Barthel 1965:61).

Barthel Index Score	Level of dependence
0-20	Total dependence
21–60	Severe dependence
61–90	Moderate dependence
91–99	Minimal dependence
100	Independent

(a). Validity and reliability of the measurement of functional ability using the Barthel Index

Hsueh, Lee and Hsieh (2001:526) indicated that the BI showed an acceptable to good correlation with the Fugl-Meyer motor assessment at 14 days post-stroke (r=0.80), 30

days post-stroke (r=0.81), 90 days post-stroke (r=0.78) and 180 days post-stroke (r=0.80). The BI demonstrated a good correlation with the BBS at 14 days post-stroke (r=0.89), 30 days post-stroke (r=0.94), 90 days post-stroke (r=0.90) and 180 days post-stroke (r=0.91) (Hsueh *et al* 2001:526). Patients' participation in physical activity post-stroke was assessed in this study using the telephonic-administered IPAQ.

(3) Participation in physical activity post-stroke

The patients' participation in physical activity post-stroke was assessed using the telephonic-administered IPAQ. The telephonic-administered IPAQ was developed by the International Consensus Group in 1997 to establish a standardised and culturally adaptable instrument across various populations in the world to monitor physical activity and inactivity in patients' home environment (Craig *et al* 2003:1381).

(a). Validity and reliability of the measurement of patients' participation in physical activity post-stroke using the International Physical Activity Questionnaire

Hallal *et al* (2010:402) indicated that the telephonic-administered IPAQ showed a good correlation (r=0.94) with the face-to-face administered IPAQ. Hagströmer, Oja and Sjöström (2006:755) indicated that the telephonic-administered IPAQ demonstrated a moderate correlation with total time spent in physical activity (r=0.55) and an acceptable correlation with time spent in vigorous physical activity (r=0.71) measured with an activity monitor (accelerometer).

3.1.8. Quality control (bias protection)

The study was conducted at seven (7) public and private rehabilitation centres for post-stroke patients in Pretoria and Johannesburg, Gauteng, South Africa (Section 3.1.2) (Van Wyk *et al* 2016:140). Patients were referred to these rehabilitation centres by multiple private and public acute healthcare facilities. Recruitment of post-stroke patients from these multiple rehabilitation centres minimised inclusion bias (Smith and

Noble 2014:101) as the sample group selected in phases 1 and 2 were representative of the study population (Section 3.1.3). Stroke patients admitted to these facilities were within the sub-acute phase post-stroke that ranged between seven (7) days to six (6) months post-stroke (Bernhardt *et al* 2017:444) (Section 1.1.4). Therefore, all patients that participated in phases 1 and 2 were representative of the study population (Section 3.1.3) of post-stroke patients in the sub-acute phase in Pretoria and Johannesburg, Gauteng, South Africa (Section 3.1.2). To further minimise inclusion bias, patients who had been assessed as part of phase 1 which aimed to determine the prevalence of the clinical features associated with central vestibular dysfunction, and who were diagnosed with central vestibular dysfunction based on the outcome of the assessment, were recruited to participate in phase 2 of the study. Thereafter, patients in phase 2 were randomly allocated to either an experimental group or a control group using a formula on a Microsoft Excel program to randomly allocate patients to either intervention group (Van Wyk *et al* 2014:857).

To prevent data-collection bias and measurement bias (Smith and Noble 2014:101), the principle investigator under guidance of an audiologist, completed all assessments of smooth pursuit and saccadic eye movements using VNG, as well as the assessment of VOR-gain using the EyeSeeCam vHIT throughout the study. The principal investigator also completed the assessment of saccule and inferior vestibular nerve function using cVEMP, as well as utricle and superior vestibular nerve function using oVEMP (Section 3.1.7.1). The VNG, EyeSeeCam vHIT, cVEMP and oVEMP are highly sophisticated apparatus that objectively quantifies smooth pursuit eye movements, saccadic eye movements, VOR-gain, saccule and inferior vestibular nerve function, as well as utricle and superior vestibular nerve function. Due to the use of highly sophisticated technology, the principal investigator could not manipulate the outcome of these assessments. The validity or reliability of the assessment methods using VNG, EyeSeeCam vHIT, cVEMP and oVEMP had been developed and/or administered and/or tested by researchers for validity, reliability or correlation with other assessment methods / outcomes measures (MacDougall *et al* 2009:1134; Maes *et al* 2009:594; Bush *et al* 2010:170; Piker *et al* 2011:222; Agrawal *et al* 2013:905; Mohamed 2016:202; Bargary *et al* 2017:157; Özdek *et al* 2017:26; Singh *et al* 2019:744).

The independent assessor conducted the assessments of static and dynamic visual acuity using the LogMAR chart. The assessor also completed assessments of higher vestibular function using the King-Devick Test©, Star Cancellation Test and MMSE. The same independent assessor assessed the level of anxiety and/or depression using the HADS, functional balance using the BBS and the ability to modify gait using the DGI. Lastly, 20 weeks after rehabilitation was terminated, the independent assessor contacted all patients who participated in phase 2, to complete the telephonic-administered IPAQ to assess their participation in physical activity post-stroke (Section 3.1.7.1). The validity or reliability of the assessment methods and objective measures that include the LogMAR chart, King-Devick Test©, Star Cancellation Test, MMSE, HADS, BBS, DGI and IPAQ had been developed and/or administered and/or tested by researchers for validity, reliability or correlation with other assessment methods / outcomes measures (Folstein *et al* 1975:189; Dick *et al* 1984:496; Berg *et al* 1992:7; Arditi and Cagenello 1993:120; Marsh and Kersel 1993:245; Clark and Steer 1994:1089; Agrell *et al* 1997:295; Snowden *et al* 1999:1000; Bailey *et al* 2000:146; Hsueh *et al* 2001:526; Bjelland *et al* 2002:69; Mao *et al* 2002:1022; Rosser *et al* 2003:3278; Hagströmer *et al* 2006:755; Jonsdottir and Cattaneo 2007:1410; Hallal *et al* 2010:402; Vital *et al* 2010:686; Flansbjer *et al* 2012:165; Riska and Hall 2016:545; Heick *et al* 2018:808) (Section 3.1.7.1).

All assessment methods and objective measures completed by the principle investigator and independent assessor are internationally recognized. The validity or reliability of the assessment methods and objective measures used within the study had been developed and/or administered and/or tested by researchers for validity, reliability or correlation with other assessment methods / outcomes measures (Section 3.1.7.1). The results of the current study may therefore be compared to the results of similar studies in which the same data capturing methods or outcomes measures have been implemented / tested / correlated.

Data-collection and measurement bias were also limited because the independent assessor was blinded regarding the group that the patients were assigned to. The principal investigator treated patients in the experimental group based on the treatment principles suggested / described in the literature for the treatment of the clinical features and activity limitations associated with central vestibular dysfunction

(Table 3.2). The principal investigator ensured that the qualified physiotherapists who treated patients in the control group in the various rehabilitation centers, were trained in the implementation of the treatment principles of the task-specific approach (Table 3.2) (Rensink *et al* 2009:737). The principal investigator ensured that these physiotherapists had a minimum of three (3) years' experience of using the task-specific approach in the rehabilitation of post-stroke patients in the sub-acute phase. To prevent data-analysis bias (Smith and Noble 2014:101), the data analysis of the study was completed by an independent statistician. The principal investigator also attended a course on Good Clinical Practice Guidelines (GCP 2015/07-002).

3.1.9. Pilot study

A pilot study was performed prior to commencement of the study to test the study procedure and techniques of data-gathering. The number of patients that were included in the pilot study was 10% of the calculated sample size of phases 1 and 2 of the study. In phase 1 of the pilot study, ten (10) patients who met the eligibility criteria (Section 3.1.4.1) were recruited for participation in the study and were assessed to determine the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients in the sub-acute phase.

After the patients were recruited, the purpose and procedures of the study were explained to them in detail. The eligible patients were informed that participation in the trial was voluntary and they were free from undue coercion. Patients who voluntary agreed to participate in the study, were asked to give written informed consent and were included in the study. Demographic information was collected from the participating patients after which they were subject to a battery of objective measures (Section 3.1.7.1) for the measurement of the clinical features and activity limitations associated with central vestibular dysfunction on the level of body structure and function, as well as activity and participation level.

The battery of objective measures was completed by the independent assessor and the principal investigator under guidance of an audiologist. The independent assessor

completed the measurement of: (a) static and dynamic visual acuity using the LogMAR chart; (b) residual oculomotor visual performance using the King-Devick Test©; (c) visual-perceptual function using the Star Cancellation Test; (d) cognitive function using the MMSE; (e) anxiety and/or depression using the HADS; (f) functional balance using the BBS; (g) the ability to modify gait in response to changing task demands using the DGI; (h) functional ability using the BI; and (i) patients' participation in physical activity post-stroke using the IPAQ. The principal investigator completed the measurement of; (a) smooth pursuit eye movement (gain) of the left and right eyes into the left and right visual fields using VNG; (b) saccadic eye movement (latency, velocity and accuracy) of the left and right eyes into the left and right visual fields using VNG; (c) VOR-gain using the vHIT; (d) saccule and inferior vestibular nerve function using the cVEMP test; and (e) utricle and superior vestibular nerve function using the oVEMP test. After the completion of the battery of objective measures, the data obtained in phase 1 of the pilot study were analysed. The duration of the battery assessment was between sixty (60) and ninety (90) minutes. When patients felt tired, they had the opportunity to take a break until they felt rested enough to continue, or the assessment was continued the following day. During the duration of the current study, the data collection did not exceed more than two (2) days.

After phase 1 of the pilot study was completed, the pilot study of phase 2 commenced. Patients who had been assessed during phase 1 of the study and who were diagnosed with central vestibular dysfunction based on the outcome of the assessment, (discussed in Section 3.1.7) were recruited to participate in phase 2 of the pilot study. Six (6) of the ten (10) patients that were diagnosed with central vestibular dysfunction based on the above-mentioned criteria in phase 1 of the pilot study, were recruited to participate in phase 2 of the pilot study. After the purpose and procedures of phase 2 of the pilot study were explained to them in detail, the six (N=6) patients were randomly allocated to either an experimental group (N=3) or a control group (N=3) using a formula on a Microsoft Excel program to randomly allocate patients to either intervention group (Van Wyk *et al* 2014:857). The patients from the experimental group and the control group were blinded to the group they were assigned to (Blanton *et al* 2006:1520). The results of the battery of objective measures completed during phase 1 of the pilot study served as the baseline measurements for phase 2 of the pilot study

because the patients that participated in phase 2 were recruited from the same study sample than phase 1. Patients in the experimental group received VRT integrated with task-specific activities as an intervention approach compared to the control group that received only task-specific activities as an intervention approach (Table 3.2) for a two (2) week intervention period. After the two (2) week intervention period, the battery of objective measures was repeated. Twenty (20) weeks after rehabilitation was terminated, the independent assessor contacted all six (6) patients who participated in the experimental and control groups of phase 2 of the pilot study telephonically, to complete the telephonic-administered IPAQ. The IPAQ was completed to determine the long-term effect of the interventions on the two (2) groups of patients. After the completion of the battery of objective measures, the data obtained during phase 2 of the pilot study were analysed. No changes were made to the methodological procedures which included the study design, research setting, study population, sample size, eligibility criteria, data collection procedure, interventions or battery of objective measures following completion of phases 1 and 2 of the pilot study. These six (6) patients were then included into the sample size of the main study.

3.1.10. Data management and analysis

Data analysis of phase 1 entailed the calculation of the prevalence of the clinical features associated with central vestibular dysfunction on body structure and function, as well as the activity and participation limitations of post-stroke patients in the sub-acute phase as a measure of frequency (Ressing, Blettner and Klug 2010:187). The calculation of prevalence was based on the formula presented in Figure 3.3. (Ressing *et al* 2010:187).

$$\text{Prevalence} = \frac{\text{Number of diseased patients in the study population}}{\text{Number of persons in the study population}} \times 100$$

Figure 3.3.: The formula used in the calculation of prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in phase 1 of the study (Ressing *et al* 2010:187).

Data analysis of phase 2 entailed the use of a mixed error-component model approach which is a statistical model containing both fixed and random effects. The use of the

mixed error-component model approach is appropriate in settings where repeated measurements are made on the same statistical units, or where measurements are made on clusters of related statistical units. The mixed error-component model approach fits linear mixed models. Mixed models are characterized as containing both fixed effects and random effects. The fixed effects are analogous to standard regression coefficients and are estimated directly. The random effects are not directly estimated but are summarised according to their estimated variances and co-variances. Random effects may take the form of either random intercepts or random coefficients and the grouping structure of the data may consist of multiple levels of nested groups. The overall error distribution of the linear mixed model is assumed to be Gaussian, heteroscedasticity and correlations within lowest-level groups may also be modelled.

The median and inter-quartile ranges were used to describe the effect of the intervention on the clinical features and activity limitations associated with central vestibular dysfunction in patients in the experimental and control groups. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the; (a) gain of smooth pursuit eye movement of the left and right eyes into the left and right visual fields using VNG; (b) latency, velocity and accuracy of saccadic eye movement of the left and right eyes into the left and right visual fields; (c) static visual acuity of the left eye, right eye and both eyes; (d) left and right VOR-gain; (e) dynamic visual acuity; (f) left and right cVEMP P1, cVEMP N1 and cVEMP amplitude; (g) speed and accuracy of residual oculomotor visual performance; (h) visual-perceptual function; (i) cognitive function; (j) level of anxiety and/ or depression; (k) functional balance; (l) ability to modify gait in response to changing task demands; and (m) functional ability of patients within the experimental and control groups. The Wilcoxon rank-sum test was used to detect whether there was a significant difference in differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups, the pre and post values, as well as the differences were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression

adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups.

3.1.11. Ethics and legal considerations

The autonomy (Owonikoko 2013:242) of all the patients who participated in phases 1 and 2 were upheld throughout the study. The first exclusion criterion of phase 1 entailed the exclusion of patients that scored less than (7) on the MMSE (Hafsteinsdóttir *et al* 2005:788). A MMSE-score of less than seven (7) indicates the presence of severe cognitive impairment. Exclusion of patients with severe cognitive impairment protected the autonomy of a vulnerable population by preventing the imposition of unwanted decisions such as participation in the study (Owonikoko 2013:242). Patients who had completed phase 1 of the study were recruited to participate in phase 2 of the study. Since the same exclusion criteria of phase 1 were applicable in phase 2 (Section 3.1.4.1), the autonomy of patients who participated in phase 2 were upheld as patients with severe cognitive impairment were already excluded in phase 1 of the study.

Autonomy of patients were further upheld through the process of obtaining informed consent prior to participation in the study (Addendum D). In phase 1 of the study, patients who met the eligibility criteria (Section 3.1.4.1) in the seven research settings (Section 3.1.2) were recruited for participation in the study. After the patients were recruited in a particular setting, the purpose and procedures of the study were carefully explained to them in a way that they understood (Addendum D). The eligible patients were informed that participation in the trial was voluntary and they were free from undue coercion. An information sheet and informed consent form with a clear explanation of what the study entailed, were given to all prospective patients prior to commencement of the study (Addendum D). The patients were provided with all information necessary to make a well-informed decision. The patient was informed that participation in the trial was voluntary and that they could withdraw from the study at any time without any prejudice or discrimination. Patients who voluntarily agreed to participate in the study were asked to give written informed consent where after they were included into the study (Owonikoko 2013:242) (Addendum D). Patients were

informed that withdrawal from the study would not affect their treatment at the rehabilitation center that they were admitted (Section 3.1.2).

Anonymity (Saunders, Kitzinger and Kitzinger 2015:616) of all the patients who participated in phases 1 and 2 were upheld throughout the study. Anonymity of patients were upheld through the allocation of a code/number to ensure that all patients who participated in the study were only identified by that code/number throughout the study. This number was entered into the data sheets to ensure complete confidentiality (Addendum E) (Vanclay, Baines and Taylor 2013:243). Data was stored on an electronic data management system of the University of Pretoria, Alfresco. Data will be stored electronically on the same site for a period of 15 years (http://icarus.up.ac.za). Obtained information is used for research purposes only and will not be disclosed to any other party than the principal investigator and the research supervisors.

Beneficence and non-malfeasance (Owonikoko 2013:242) were upheld throughout the study. The battery of objective measures used within the study (phases 1 and 2) were selected based upon the outcome of a literature study that critically reviewed and appraised the various assessment methods and objective measures used to quantify the clinical features and activity limitations associated with central vestibular dysfunction in patients post-stroke (Section 2.4). The validity or reliability of the assessment methods and objective measures used within the study had been demonstrated by previously published literature with no harm or adverse effects reported (Section 3.1.7.1). The results of this study may therefore be compared to similar studies where the same data capturing methods or outcomes measures have been implemented on both national and international level (Section 3.1.7.1).

The battery of objective measures used in the study consisted of assessment methods and objective measures that ranged from highly sophisticated apparatus to conventional paper-and-pencil tests (Section 3.1.7.1). Although highly sophisticated apparatus such as VNG, EyeSeeCam vHIT, cVEMP and oVEMP were used in the study, these tests were non-invasive and well tolerated by patients of all ages.

Beneficence and non-malfeasance (Owonikoko 2013:242) were further upheld in phase 2 of the study. Although the experimental group received VRT integrated with task-specific activities and patients in the control group did not receive the VRT, the intervention received by the experimental group was an “add-on” intervention that can ethically be accounted for as VRT integrated with task-specific activities is not part of the present standard rehabilitation protocol that patients receive at the rehabilitation centres (Section 3.1.6). Patients in the control group were therefore not deprived of treatment that they would have received in these rehabilitation centers. The VRT that patients in the experimental group received was also non-invasive and not harmful at all (Table 3.2).

Lastly, justice was upheld in phases 1 and 2 of the study. Distributive justice was upheld since the study was conducted at seven (7) public and private rehabilitation centres for post-stroke patients in Pretoria and Johannesburg, Gauteng, South Africa (Section 3.1.2). Patients were referred to these rehabilitation centres by multiple private and public acute health care facilities (Section 3.1.2). Male and female patients of all races, aged 19 years - 84 years, who suffered either an ischaemic or haemorrhagic stroke, were eligible to participate in the study (Section 3.1.4). Patients were not excluded from the study based on their Human Immunodeficiency Virus (HIV) status. Distributive justice was therefore upheld throughout the study by ensuring that the sample group in phase 1 and phase 2 was a representative sample group of the study population (Section 3.1.3) of post-stroke patients in the sub-acute phase (Section 1.1.4) in rehabilitation centres in the Gauteng province.

3.1.12. Summary

In Chapter 3, a detailed description of the research methodology that was implemented to achieve the aims and objectives of this study, is discussed. The discussion includes the study design, research setting, study population, sample size, eligibility criteria, data-collection procedure, interventions, battery of objective measures, quality control, pilot study, data management and analysis, ethics and legal considerations of phases 1 and 2.

The quantitative data that was collected throughout the research procedure described in this chapter was analysed by an independent statistician and the results are presented in Chapters 4 and 5. In Chapter 4, the results of the cross-sectional survey that was conducted during phase 1 are discussed to determine the prevalence of diagnostic features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke. In Chapter 5, the results of the single-blind cluster randomised controlled trial that was conducted during phase 2 are discussed to determine the effect of VRT integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group. The long-term effect of the two (2) interventions on patients' participation in physical activity twenty (20) weeks after rehabilitation was terminated, is also presented and interpreted in Chapter 5.

CHAPTER 4

RESULTS OF PHASE 1

CROSS-SECTIONAL SURVEY

4.1. INTRODUCTION

In Chapter 4, the results of the cross-sectional survey that was conducted as phase 1 of the study, are presented and interpreted in Section 4.2 and Section 4.3. The results of phase 2 of the study (single-blind cluster randomised controlled trial) are presented and interpreted in Chapter 5.

The cross-sectional survey was conducted to achieve the first aim of the study, namely to determine the prevalence of diagnostic features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke.

The results of phase 1 are presented and interpreted within the ICF conceptual framework (Table 2.32) (Lazaro *et al* 2013:187) on which this study is based.

4.2. DEMOGRAPHICAL DATA OF THE PATIENTS IN THE CROSS-SECTIONAL SURVEY

One hundred and fifteen (N=115) patients were assessed for eligibility to participate in the study (Section 3.1.4.1). One hundred and two (N=102) patients met the minimum inclusion criteria to participate in the study (Figure 3.1). Fifty five percent (54.9%) of patients in the cross-sectional survey were recruited from a private rehabilitation centre, compared to 45.1% that were recruited from a public rehabilitation centre (Section 3.1.2).

The one exclusion criteria that required assessment of potential participants prior to be included in the study, was the presence of severe cognitive impairment identified by a MMSE score. Patients had to have a MMSE score of at least seven (7) (Hafsteinsdóttir *et al* 2005:788) (Section 3.1.4.1), to be included in the study. The results of patients' cognitive function on the MMSE are therefore presented in Table 4.1.

Table 4.1.: Cognitive function of patients who participated in the cross-sectional survey (N=102).

The results of patients MMSE scores are presented in the categories prescribed by the application criteria of the MMSE (Folstein *et al* 2001:1), namely 'no cognitive impairment', 'mild', 'moderate' and 'severe cognitive impairment'.

COGNITIVE IMPAIRMENT (N=102)					
Cognitive function		**Objective measure**	**Number of patients (N)**	**Prevalence of cognitive function within normal range (%)**	**Prevalence of cognitive impairment (%)**
No cognitive impairment		Mini-Mental State Examination score: ≥ 27	18	17.65%	0%
Cognitive impairment	**Mild**	Mini-Mental State Examination score: 21-26	43	0%	42.16%
	Moderate	Mini-Mental State Examination score: 11-20	39	0%	38.24%
	Severe	Mini-Mental State Examination score: 7-10	2	0%	1.96%

Eighty two percent (82.4%) of patients in the cross-sectional survey presented with cognitive impairment that ranged from mild to severe cognitive impairment, which could be ascribed to the stroke. Eighteen percent (17.7%) of patients presented with no cognitive impairment.

The biographical variables that were recorded and analysed in this study were patients' age, gender, race, level of education and occupation. The biographical variables of patients are presented in Table 4.2.

Table 4.2.: Biographical variables of patients who participated in the current survey.

BIOGRAPHICAL VARIABLES		
AGE DISTRIBUTION (N=102)		
Age group	**Number of patients (N)**	**Percentage (%)**
20yr-49yr	29	28.43
50yr-69yr	49	48.04
70yr-79yr	21	20.59
80yr-98yr	3	2.94
GENDER (N=102)		
Gender	**Number of patients (N)**	**Percentage (%)**
Male	49	48.04
Female	53	51.96
ETHNICITY(N=102)		
Race	**Number of patients (N)**	**Percentage (%)**
Caucasian	41	40.20
African	58	56.86
Coloured	2	1.96
Indian	1	0.98
LEVEL OF EDUCATION (N=102)		
Level of education	**Number of patients (N)**	**Percentage (%)**
No formal schooling	6	5.88
Primary school	10	9.80
High school: Grade 8-11	36	35.29
High school: Grade 12	22	21.57
Tertiary	28	27.45

Table 4.2.: Biographical variables of patients who participated in the current survey (continued).

OCCUPATION PRIOR TO THE STROKE (N=101)*		
Occupation prior to the stroke	**Number of patients (N)**	**Percentage (%)**
Medium duty[1]	15	14.85
Light duty[2]	17	16.83
Sedentary[3]	35	34.65
Retired	27	26.73
Unemployed	7	6.93
* One (1) patient declined to provide information regarding his occupation prior to the stroke.		
[1] = (a) Exerting 9-22.5kg of force occasionally and/or 4.5-11.2kg of force frequently and/or up to 4.5kg of force constantly. Physical demand requirements are greater than that requires for 'Light duty' (Field and Field 1992:1).		
[2] = (a) Involves walking or standing to a significant degree; (b) involves sitting most of the time but involves pushing and/or pulling of arm or leg controls; (c) exerting 9kg of force occasionally and/or 4.5kg of force frequently (Field and Field 1992:1).		
[3] = (a) Involves sitting most of the time but may involve walking or standing for brief periods of time; (b) exerting 4.5kg of force occasionally to lift, carry, push or pull or otherwise move objects including the human body (Field and Field 1992:1).		

Almost a third of the patients were young stroke-survivors within the 20yr-49yr age group. The majority of the patients' ages ranged between 20 years to 79 years.

The study sample group represented a fairly equal number of male and female patients (49 males versus 53 females).

Although the majority of the patients were within the African ethnic group followed by the Caucasian ethnic group, it is not a valid representation of the race distribution of the South African population.

The majority of the sample group had high school (56.9%) to tertiary education (27.5%).

A third of the patients performed sedentary employment.

The demographic variables that were recorded and analysed in the current study were patients' side affected post-stroke, dominant side prior to the stroke, type of stroke, area of stroke and HIV-status. The demographic variables of patients are presented in Table 4.3.

Table 4.3.: Demographic variables of patients who participated in the current survey.

DEMOGRAPHIC VARIABLES		
SIDE AFFECTED OF THE BODY POST-STROKE (N=102)		
Side affected of the body	**Number of patients (N)**	**Percentage (%)**
Left hemiplegia due to right brain impairment	66	64.71
Right hemiplegia due to left brain impairment	36	35.29
DOMINANT SIDE PRIOR TO THE STROKE (N=102)		
Dominant side	**Number of patients (N)**	**Percentage (%)**
Left	10	9.80
Right	92	90.20
TYPE OF STROKE (N=102)		
Type of stroke	**Number of patients (N)**	**Percentage (%)**
Infarct	65	63.72
Haemorrhagic	17	16.67
Unknown (no information)	20	19.60

Table 4.3.: Demographic variables of patients who participated in the current survey (continued).

AREA OF STROKE (N=102)		
Area of stroke	**Number of patients (N)**	**Percentage (%)**
Hemispheric	29	28.43
Subcortical	21	20.59
Brainstem	3	2.94
Cerebellar	3	2.94
Mixed	14	13.73
Unknown (no information)	32	31.37

Almost two-thirds of the patients presented with left hemiplegia due to right brain impairment caused by the stroke.

Ninety percent of the sample group were right hand dominant side prior to the stroke which falls within the expected distribution of hand dominance of the general population.

Despite the fact that twenty percent of patients' information on the type of stroke were unavailable in their medical records, nearly two-thirds of patients suffered an infarction.

Although thirty-one percent of patients' information on the area of stroke were unavailable in their medical records, the majority of the sample group suffered either a hemispheric (28.4%) or subcortical (20.6%) stroke.

The HIV-status of only twenty-seven percent of patients were known as within three (3) of the seven (7) rehabilitation centres a confidentiality policy exists that does not allow disclosure of patients' HIV-status in their medical records.

In the following sections the clinical features associated with central vestibular dysfunction are discussed.

4.3. CLINICAL FEATURES ASSOCATED WITH CENTRAL VESTIBULAR DYSFUNCTION ON THE LEVEL OF BODY STRUCTURE AND FUNCTION

The first clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phase 1, was oculomotor control.

4.3.1. Oculomotor control

The three features of oculomotor control assessed in the current study were smooth pursuit and saccadic eye movements using VNG and static visual acuity using the LogMAR-chart (Section 1.1.3.1). Smooth pursuit eye movement is measured by its gain which is defined as the ratio of the velocity of smooth pursuit eye movement velocity to the velocity of the target (Sharpe 2008:241). Normative values for smooth pursuit eye movements (gain) and saccadic eye movements (latency, velocity and accuracy) of the left and right eyes into the left and right visual fields, are presented in Table 3.3. (Section 3.1.7.1). Normative values for static visual acuity of the left eye (right eye occluded), right eye (left eye occluded) and both eyes were presented in Table 3.4. (Section 3.1.7.1). The results of impairment of smooth pursuit eye movement, saccadic eye movement and static visual acuity in patients who participated in the cross-sectional survey, are presented in Table 4.4.

Table 4.4.: Results of impairment of smooth pursuit eye movement, saccadic eye movement and static visual acuity in patients who participated in the cross-sectional survey.

The results of patients' mean (%) gain of smooth pursuit eye movements are presented in the categories based upon the normative values for smooth pursuit eye movements prescribed by Interacoustics® American Institute of Balance; Seminole, Florida (https://www.dizzy.com/aib-technology-partners/), namely the 'gain of smooth pursuit eye movements of the left and right eyes into the left and right visual fields'.

The results of patients' mean latency (ms), velocity (°/s) and accuracy (%) of saccadic eye movements are presented in the categories based upon the normative values for saccadic eye movements prescribed by Interacoustics® American Institute of Balance; Seminole, Florida (https://www.dizzy.com/aib-technology-partners/), namely the 'latency, velocity and accuracy of saccadic eye movements of the left and right eyes into the left and right visual fields'.

The results of patients' static visual acuity scores are presented in the categories prescribed by the application criteria of the LogMAR chart (Rowe *et al* 2011:406), namely static visual acuity of the 'left eye (right eye occluded)', 'right eye (left eye occluded)' and 'both eyes open'.

SMOOTH PURSUIT EYE MOVEMENT IMPAIRMENT: GAIN (N=102)			
Impaired gain of smooth pursuit eye movements of the left and right eyes into the left and right visual fields		**Number of patients (N)**	**Prevalence of smooth pursuit eye movement gain impairment (%)**
Left Visual field	**Gain of the Right Eye**	101	99.02%
	Gain of the Left Eye	99	97.06%
Right Visual field	**Gain of the Right Eye**	100	98.04%
	Gain of the Left Eye	99	97.06%

Table 4.4.: Results of smooth pursuit and saccadic eye movements and static visual acuity as clinical features associated with central vestibular dysfunction in patients who participated in the cross-sectional survey (continued).

SACCADIC EYE MOVEMENT IMPAIRMENT: LATENCY, VELOCITY AND ACCURACY (N=102)				
Impaired latency, velocity and accuracy of saccadic eye movements of the left and right eyes into the left and right visual fields			**Number of patients (N)**	**Prevalence of saccadic eye movement gain impairment (%)**
Left Visual field	**Right Eye**	Latency	72	70.59%
		Velocity	28	27.45%
		Accuracy	72	70.59%
	Left Eye	Latency	61	59.80%
		Velocity	28	27.45%
		Accuracy	62	60.78%
Right Visual field	**Right Eye**	Latency	58	56.86%
		Velocity	8	7.84%
		Accuracy	55	53.92%
	Left Eye	Latency	61	59.80%
		Velocity	16	15.69%
		Accuracy	60	58.82%
STATIC VISUAL ACUITY IMPAIRMENT(N=102)				
Impaired static visual acuity of the left eye (right eye occluded), right eye (left eye occluded) and both eyes open		**Objective measure**	**Number of patients (N)**	**Prevalence of static visual acuity impairment (%)**
Visual acuity of Left Eye (right eye occluded)		LogMAR score: > 0.5	26	25.49%
Visual acuity of Right Eye (left eye occluded)		LogMAR score: > 0.5	19	18.63%
Visual acuity of Both Eyes (both eyes open)		LogMAR score: > 0.5	12	11.76%

Smooth pursuit eye movement impairment is the clinical feature with the highest prevalence observed in patients (Table 4.4). A high prevalence of impairment of smooth pursuit eye movement of both eyes into the left (97.1%-99.0%) and right (97.1%-98.0%) visual fields were observed.

Impaired latency and accuracy of saccadic eye movement were observed in both visual fields of patients. The prevalence of impaired **latency** was higher in the left visual field (59.8%-70.6%) compared to the right visual field (56.9%-59.8%) respectively. Similar to the values of impaired latency, patients demonstrated impaired **accuracy** in saccadic eye movements of both eyes into the left (60.8%-70.6%) and right (53.9%-58.8%) visual fields respectively.

The prevalence of impaired **velocity of saccadic eye** movement of both eyes into the left (27.5%) and right (7.8%-15.7%) visual fields observed in patients, were lower than the prevalence of impaired **saccadic eye movement latency and accuracy**.

Patients demonstrated decreased **static visual acuity** of the left eye with right eye occluded (25.5%), the right eye with left eye occluded (18.6%) and both eyes open (11.8%).

Smooth pursuit eye movement impairment was the feature of oculomotor control with the highest prevalence, followed by impaired latency and accuracy of saccadic eye movement. An asymmetry of both saccadic eye movement and static visual acuity impairment were observed between the left and right visual fields respectively. A higher prevalence of impaired saccadic eye movement latency (70.6%), velocity (27.5%) and accuracy (70.6%) of the right eye into the left visual field and impaired static visual acuity of the left eye (right eye occluded) (25.5%) within the left visual field, were observed. As it is well established that visual stimulation in the left or right visual field project unilaterally to the contralateral hemisphere (Figure 2.3), the increased prevalence of impaired saccadic eye movement (latency, velocity and accuracy) and static visual acuity impairment observed in the left visual field, may be partly attributed to the number of patients with right hemisphere versus left hemisphere impairment included in the study sample (64.7% vs. 35.3%) (Table 4.3).

The second clinical feature associated with central vestibular dysfunction on the level of body structure and function assessed in phase 1 was reflexive control of gaze.

4.3.2. Reflexive control of gaze

The two features of reflexive control of gaze assessed in the current study were VOR-gain using the vHIT and DVA using the LogMAR-chart (Section 1.1.3.1). Normative values for the vHIT and DVA were presented in Table 3.5. and Table 3.6. (Section 3.1.7.1) respectively. The results of VOR-gain dysfunction and dynamic visual acuity impairment in patients who participated in the cross-sectional survey, are presented in Table 4.5.

Table 4.5.: Results of VOR-gain dysfunction and dynamic visual acuity impairment in patients who participated in the cross-sectional survey.

The results of patients' VOR-gain scores are presented in the categories prescribed by the application criteria of the vHIT (MacDougall and Curthoys 2012:1; Choi *et al* 2018:90), namely 'left vestibular hypofunction', 'left vestibular hyperfunction', 'right vestibular hypofunction' and 'right vestibular hyperfunction'.

The results of patients' dynamic visual acuity scores are presented in the categories prescribed by the application criteria of the LogMAR chart (Tusa 2007:118), namely 'LogMAR score of >0.5 during ≥ 2Hz horisontal head rotation' and 'Dynamic visual acuity (visual acuity during 2Hz horisontal head motion) minus static visual acuity (visual acuity with no head motion): Decrease of ≥0.2 LogMAR'.

VESTIBULO-OCULAR REFLEX-GAIN DYSFUNCTION (N=102)				
Vestibulo-ocular reflex gain dysfunction		**Objective measure**	**Number of patients (N)**	**Prevalence of vestibulo-ocular reflex-gain dysfunction (%)**
Left VOR Gain	Vestibular *hypo*function	vHIT:< 0.68	27	26.47%
	Vestibular *hyper*function	vHIT:> 1.2	15	14.71%
Right VOR Gain	Vestibular *hypo*function	vHIT:< 0.68	13	12.75%
	Vestibular *hyper*function	vHIT:> 1.2	48	47.06%
DYNAMIC VISUAL ACUITY IMPAIRMENT (N=102)				
Dynamic visual acuity impairment		**Objective measure**	**Number of patients (N)**	**Prevalence of dynamic visual acuity impairment (%)**
Dynamic visual acuity of Both Eyes		LogMAR score during ≥ 2Hz horisontal head rotation: > 0.5 LogMAR	60	58.82%
		Dynamic visual acuity minus static visual acuity: Decrease of ≥0.2 LogMAR	67	65.69%

An asymmetry between left VOR-gain dysfunction (41.2%) and right VOR-gain dysfunction (59.8%) were observed in patients (Table 4.5). The increased prevalence of right vestibular *hyper*function (47.1%) may be attributed to the possible presence of diffuse cerebellar lesions (Choi *et al* 2018:90) observed through increased (hyperactive) VOR. The increased prevalence of vestibular hyperfunction due to

possibility of the presence of diffuse cerebellar lesions, are supported by findings of Becker-Bense *et al* (2014:1355) which indicated that the reflexive stabilization of the eye and head movements measured by the vHIT are mediated by the infrathalamic brainstem and cerebellar centers.

Forty to sixty percent (41.2%-59.8%) of patients were unable to keep their gaze stable in space during head motion as a result of the presence of VOR-gain dysfunction (Schubert, Migliaccio, Clendaniel, Allak and Carey 2008:500). Impaired gaze stability results in a retinal slip which leads to a reduction in dynamic visual acuity compared to static visual acuity when the head is kept still (Schubert *et al* 2008:500). Based on the outcome of a visual acuity score of higher than 0.5 LogMAR during 2Hz horisontal head rotation, 58.8% of patients in the cross-sectional survey assessed, demonstrated impaired dynamic visual acuity. Nearly two-thirds (65.7%) of the study sample demonstrated impaired dynamic visual acuity when a reduction of two (2) or more LogMAR were observed when the dynamic visual acuity score (visual acuity during 2Hz horisontal head motion) was subtracted from the static visual acuity score (visual acuity with no head motion). The results of impairment of saccule and inferior vestibular nerve function in patients, are presented in Section 4.3.3.

4.3.3. Saccule and inferior vestibular nerve function

Air conduction cervical vestibular evoked myogenic potentials (cVEMPs) were used to assess saccule and inferior vestibular nerve function and its central projections. Within the central vestibular system, cVEMPs are mediated by the vestibular nuclei and uncrossed medial vestibulospinal tract descending in the lower brainstem and spinal cord (Oh *et al* 2016:210). A stroke may cause a central vestibular tone imbalance at different levels within the central vestibular system (Becker-Bense *et al* 2014:1355; Becker-Bense *et al* 2016:1). The central vestibular tone imbalance may result in unilateral disruption of the inhibitory corticobulbar projections to the vestibular nuclei. The inhibition of the vestibular nuclei may further result in imbalance in the descending vestibular drive to the cervical motor neuron pools (Miller *et al* 2014:2070). Due to the bilateral structure and commissural connections between the ‘structures’ / areas of the central vestibular system (Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions within the central vestibular system that include the brainstem

and cerebellar circuits, vestibular thalamic pathways, vestibulospinal tracts and the vestibular cortical network (Cronin *et al* 2017:538), may result in saccule and inferior vestibular nerve function impairment. Normative values for air conduction cVEMP were presented in Table 3.7. (Section 3.1.7.1). The results of impairment of saccule and inferior vestibular nerve function in patients who participated in the cross-sectional survey, is presented in Table 4.6.

Table 4.6.: Results of impairment of saccule and inferior vestibular nerve function in patients who participated in the cross-sectional survey.

The results of patients' saccule and inferior vestibular nerve function scores are presented in the categories prescribed by the application criteria of the cervical vestibular-evoked myogenic potential (Kim *et al* 2011:1; Colebatch *et al* 2016:133) namely 'left cVEMP P1: > 19 ms', 'left cVEMP N1: > 28 ms', 'left absent cVEMP', 'right cVEMP P1: > 19 ms', 'right cVEMP N1: > 28 ms' and 'right absent cVEMP'.

IMPAIRMENT OF SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION (N=102)			
Impairment of saccular and inferior vestibular nerve function	**Objective measure**	**Number of patients (N)**	**Prevalence of saccule and inferior vestibular nerve function impairment (%)**
Left cervical vestibular-evoked myogenic potential	cVEMP P1: > 19 ms	3	2.94%
	cVEMP N1: > 28 ms	2	1.96%
	Absent cVEMP	62	60.78%
Right cervical vestibular-evoked myogenic potential	cVEMP P1: > 19 ms	2	1.96%
	cVEMP N1: > 28 ms	3	2.94%
	Absent cVEMP	58	56.86%
cVEMP = Cervical vestibular-evoked myogenic potential			
P1 = First positive peak on wave form			
N1 = First negative deflection on wave form			

An asymmetry of saccule and inferior vestibular nerve function impairment assessed by left and right air conduction cVEMP, were observed in patients (Table 4.6). The patients demonstrated left saccule and inferior vestibular nerve function impairment

(65.7%) compared to right saccule and inferior vestibular nerve function impairment (61.8%). Sixty one percent (60.8%) of the study sample presented with an absent left cVEMP compared to 56.9% that presented with an absent right cVEMP (Table 4.6). The results of impairment of utricle and superior vestibular nerve function in patients, are presented in Section 4.3.4.

4.3.4. Utricle and superior vestibular nerve function

Vestibular input from the labyrinth and vestibular nerve ascends ipsilaterally and contralaterally, mainly via the MLF, to the midbrain tegmentum, which contains the interstitial nucleus of Cajal. Thereafter, pathways travel via dorsolateral thalamic nuclei to multisensory vestibular cortex areas that include the PIVC and the MST of the visual cortex (Figure 1.2.). Within the central vestibular system, oVEMPs reflect the function of the vestibular nuclei and the VOR pathways mostly contained in the MLF. The lesions involving the MLF, the crossed ventral tegmental tract, *oculomotor nuclei* and the interstitial nucleus of Cajal, may result in impaired oVEMPs (Oh *et al* 2016:210). Air conduction oVEMPs were used to assess utricle and superior vestibular nerve function and its central projections (Table 4.7). Normative values for air conduction oVEMP are presented in Table 3.7. (Section 3.1.7.1). The results of impairment of utricle and superior vestibular nerve function in patients who participated in the cross-sectional survey, is presented in Table 4.7.

Table 4.7.: Results of impairment of utricle and superior vestibular nerve function in patients who participated in the cross-sectional survey.

The results of patients' utricle and superior vestibular nerve function scores are presented in the categories prescribed by the application criteria of the ocular vestibular-evoked myogenic potential (Kim *et al* 2011:1; Colebatch *et al* 2016:133) namely 'left oVEMP N1: > 11.1 ms', 'left oVEMP P1: > 17.6 ms', 'left absent oVEMP', 'right oVEMP N1: > 11.1 ms', 'right oVEMP P1: > 17.6 ms' and 'right absent oVEMP'.

Impairment of utricle and superior vestibular nerve function	Objective measure	Number of patients (N)	Prevalence of utricle and superior vestibular nerve function impairment (%)
Left ocular vestibular-evoked myogenic potential	oVEMP N1: > 11.1 ms	4	3.92%
	oVEMP P1: > 17.6 ms	1	0.98%
	Absent oVEMP	94	92.16%
Right ocular vestibular-evoked myogenic potential	oVEMP N1: > 11.1 ms	4	3.92%
	oVEMP P1: > 17.6 ms	2	1.96%
	Absent oVEMP	93	91.18%
oVEMP = Ocular vestibular-evoked myogenic potential			
N1 = First negative deflection on wave form			
P1 = First positive peak on wave form			

The patients' demonstrated symmetrical utricle and superior vestibular nerve function impairment (97.1%) on both sides assessed by left and right air conduction oVEMP. Ninety-two percent (92.2%) of the study sample presented with an absent left oVEMP compared to 91.2% that presented with an absent right oVEMP.

The results of impairment of higher vestibular dysfunction in patients who participated in the cross-sectional survey, are presented in Table 4.8.

4.3.5. Higher vestibular function

The two features of higher vestibular function assessed in the current study were residual oculomotor visual performance using the King-Devick Test© (Sub-test1-3) and visual-perceptual dysfunction using the Star Cancellation Test (Section 1.1.3.1). Normative values for the King-Devick Test© and Star Cancellation Test were presented in Table 3.8. and Table 3.9. (Section 3.1.7.1) respectively.

The results of impairment of residual oculomotor visual performance impairment and visual-perceptual dysfunction in patients who participated in the cross-sectional survey, are presented in Table 4.8.

Table 4.8.: Results of impairment of residual oculomotor visual performance and visual-perceptual dysfunction in patients who participated in the cross-sectional survey.

The results of patients' residual oculomotor visual performance scores are presented in the categories prescribed by the application criteria of the King-Devick Test© (Zoltan 1996:27) namely 'time taken to complete King Devick Sub-test 1: > 14.86s', 'errors made during completion of King Devick Sub-test 1: > 0.07', 'time taken to complete King Devick Sub-test 2: > 16.87s', 'errors made during completion of King Devick Sub-test 2: > 0.07', 'time taken to complete King Devick Sub-test 3: > 18.73s' and ''errors made during completion of King Devick Sub-test 3: > 0.33'.

The results of patients' visual-perceptual dysfunction are presented in the categories prescribed by the application criteria of the Star Cancellation Test (Van Kessel *et al* 2010:603), namely 'number of errors made during completion of the Star Cancellation Test: ≤ 51'.

RESIDUAL OCULOMOTOR VISUAL PERFORMANCE IMPAIRMENT (N=102)				
Impairment of residual oculomotor visual performance		**Objective measure**	**Number of patients (N)**	**Prevalence of residual oculomotor visual performance impairment (%)**
King Devick Sub-test 1	Time taken to complete the test	King Devick Sub-test 1:> 14.86s	92	90.20%
	Errors made during completion of the test	King Devick Sub-test 1:> 0.07	82	80.39%
King Devick Sub-test 2	Time taken to complete the test	King Devick Sub-test 2:> 16.87s	92	90.20%
	Errors made during completion of the test	King Devick Sub-test 2:> 0.07	78	76.47%
King Devick Sub-test 3	Time taken to complete the test	King Devick Sub-test 3:> 18.73s	90	88.24%
	Errors made during completion of the test	King Devick Sub-test 3:> 0.33	87	85.29%

Table 4.8.: Results of impairment of residual oculomotor visual performance and visual-perceptual dysfunction in patients who participated in the cross-sectional survey (continued).

VISUAL-PERCEPTUAL DYSFUNCTION (N=102)			
Visual-perceptual dysfunction	**Objective measure**	**Number of patients (N)**	**Prevalence of visual-perceptual dysfunction (%)**
Number of errors made during completion of the test	Star Cancellation Test: ≤ 51	99	97.06%

A high prevalence of impaired **velocity** (88.2%-90.2%) and **accuracy** (76.5%-85.3%) of residual oculomotor visual performance based upon the time taken and errors made during completion of the King Devick Test©, were observed.

The prevalence of **visual-perceptual dysfunction** (97.1%) observed in patients in the current study, were higher than the prevalence of impaired residual oculomotor visual performance (Table 4.8) observed.

The results of impairment of anxiety and depression in patients who participated in the cross-sectional survey, are presented in Table 4.9.

4.3.6. Level of anxiety and/ or depression post-stroke

The Hospital Anxiety and Depression Scale (Anxiety and Depression Sub-scales) was used to assess anxiety and depression in patients who participated in the cross-sectional survey. Normative values for the Hospital Anxiety and Depression Scale were presented in Table 3.11. (Section 3.1.7.1). The results of the level of anxiety and depression in patients who participated in the cross-sectional survey, are presented in Table 4.9.

Table 4.9.: Results of the level of anxiety and depression in patients who participated in the cross-sectional survey.

The results of patients' anxiety and depression scores are presented in the categories prescribed by the application criteria of the Hospital Anxiety and Depression Scale (Stern 2014:393), namely 'mild anxiety', 'moderate to severe anxiety', 'mild depression' and 'moderate to severe depression'.

LEVEL OF ANXIETY AND DEPRESSION (N=102)				
Level of anxiety		**Objective measure**	**Number of patients (N)**	**Prevalence of impairment of anxiety (%)**
Anxiety	Mild	Anxiety Sub-scale: 8-10	21	20.59%
	Moderate to severe	Anxiety Sub-scale: 11-21	47	46.08%
Depression	Mild	Depression Sub-scale: 8-10	20	19.61%
	Moderate to severe	Depression Sub-scale: 11-21	38	37.25%

The prevalence of anxiety (66.7%) was higher compared to depression (56.9%) in patients (Table 4.9). An almost equal prevalence of mild anxiety (20.6%) and depression (19.6%) were observed in the study sample.

In the following sections, the activity limitations associated with central vestibular dysfunction, are discussed.

4.4. ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION ON THE LEVEL OF ACTIVITY AND PARTICIPATION

In the current study, the activity limitations associated with central vestibular dysfunction, were assessed using the BBS, DGI and BI (Section 3.1.7.2). The BBS was used to assess the functional balance in patients who participated in the cross-sectional survey. The DGI was used to assess patients' ability to modify gait in response to changing task demands and consequent fall risk. Normative values for the BBS and DGI were presented in Table 3.12. and Table 3.13. (Section 3.1.7.2) respectively. The BI was used to assess patients' functional ability and categorise their

dependence on assistance to perform ADLs such as feeding, bathing, ambulation and stair climbing. Normative values for the BI was presented in Table 3.14. (Section 3.1.7.2). The results of impairment of functional balance, ability to modify gait in response to changing task demands and functional ability in patients who participated in the cross-sectional survey, are presented in Table 4.10.

Table 4.10.: Results of impaired functional balance, ability to modify gait in response to changing task demands and functional ability in patients who participated in the cross-sectional survey.

The results of patients' functional balance scores are presented in the categories prescribed by the application criteria of the Berg Balance Scale (Berg *et al* 1992:7-11), namely 'low fall risk', 'medium fall risk' and 'high fall risk'.

The results of patients' ability to modify gait in response to changing task demands and consequent fall risk scores, are presented in the category prescribed by the application criteria of the Dynamic Gait Index (Whitney *et al* 2000:99), namely 'high fall risk'.

The results of patients' functional ability scores are presented in the categories prescribed by the application criteria of the Barthel Index (Mahoney and Barthel 1965:61), namely 'minimal dependence', 'moderate dependence', 'severe dependence' and 'total dependence' in activities of daily living.

IMPAIRED FUNCTIONAL BALANCE (N=102)				
Impairment of functional balance		**Objective measure**	**Number of patients (N)**	**Prevalence of functional balance impairment (%)**
Fall risk	**Low**	Berg Balance Scale score: 41–56	13	12.75%
	Medium	Berg Balance Scale score: 21–40	19	18.63%
	High	Berg Balance Scale score: 0 – 20	70	68.63%

Table 4.10.: Results of impaired functional balance, ability to modify gait in response to changing task demands and functional ability in patients who participated in the cross-sectional survey (continued).

IMPAIRED ABILITY TO MODIFY GAIT IN RESPONSE TO CHANGING TASK DEMANDS (N=102)				
Impaired ability to modify gait in response to changing task demands		**Objective measure**	**Number of patients (N)**	**Prevalence of impaired ability to modify gait (%)**
Fall risk	**High**	Dynamic Gait Index score: 0-18	99	97.06%
IMPAIRED FUNCTIONAL ABILITY (N=102)				
Impaired functional ability		**Objective measure**	**Number of patients (N)**	**Prevalence of impaired functional ability (%)**
Dependence in activities of daily living	**Minimal**	Barthel Index score: 91–99	6	5.88%
	Moderate	Barthel Index score: 61–90	17	16.67%
	Severe	Barthel Index score: 21–60	47	46.08%
	Total	Barthel Index score: 0-20	30	29.41%

A high prevalence of impaired functional balance (87.3%) that resulted in a medium (18.6%) to high (68.6%) fall risk, was observed in the study sample.

The majority of the study sample presented with impaired ability to modify gait in response to changing task demands (97.1%), which resulted in a high fall risk.

A high prevalence of impaired functional ability (98.0%) that resulted in minimal to total dependence in ADLs, were observed in the sample group. Only 2.0% of the patients assessed in the current study were independent in ADLs. The summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey, are presented in Table 4.11.

Table 4.11.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function					**Activity and participation level**	
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**			**Activity limitations associated with central vestibular dysfunction**	**Prevalence (%)**
OCULOMOTOR FUNCTION	**Smooth pursuit eye movements**	97.1%-99.0%		**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	87.3%
	Saccadic eye movements	Latency	56.9%-70.6%		**Ability to modify gait in response to changing task demands**	97.1%
		Velocity	7.8%-27.5%			
		Accuracy	53.9%-70.6%			
	Static visual acuity	Left eye	25.5%			
		Right eye	18.6%			
		Both eyes	11.8%			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	Left Gain	41.2%	**FUNCTIONAL ABILITY**	**Functional ability**	98.0%
		Right Gain	59.8%			
	Dynamic visual acuity	58.8%-65.7%				

Table 4.11.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**			
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	61.8%-65.7% %			
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION	**oVEMP**	97.1%			
HIGHER VESTIBULAR FUNCTION	**Residual oculomotor visual performance**	Velocity	88.2%-90.2%		
		Accuracy	76.5%-85.3%		
	Visual-perceptual function	97.1%			
	Cognition	82.4%			

Table 4.11.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey (continued).

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**			
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	Anxiety	66.7%		
		Depression	56.9%		

Smooth pursuit eye movement impairment is the clinical feature associated with central vestibular dysfunction with the highest prevalence (97.1%-99.0%) observed in patients in the current study. An equal prevalence of impairment of utricle and superior vestibular nerve function (97.1%) and visual-perceptual dysfunction (97.1%), were observed in the study sample. Impaired velocity of residual oculomotor visual performance is the clinical feature with the third highest prevalence (88.2%-90.2%) observed in patients.

In the current study, impaired functional ability is the activity limitation with the highest prevalence (98.0%) observed in patients. Impaired ability to modify gait in response to changing task demands (97.1%) is the activity limitation with the second highest prevalence followed by impaired functional balance with the third highest prevalence (87.3%) observed in patients in the current study.

4.5. SUMMARY OF CHAPTER 4

The cross-sectional survey was conducted to achieve the first aim of the study, namely to determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke. Results of the cross-sectional survey demonstrated a high prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients. A high prevalence of clinical features associated with central vestibular dysfunction included impairment of smooth pursuit eye movement, utricle and superior vestibular nerve function and higher vestibular function, were observed.

A high prevalence of activity limitations associated with central vestibular dysfunction included impaired functional ability, ability to modify gait in response to changing task demands and functional balance, were observed in the current study.

In Chapter 5, the results of the single-blind cluster randomised controlled trial that was conducted during phase 2 of the study, are presented and interpreted.

CHAPTER 5

RESULTS OF PHASE 2

SINGLE-BLIND CLUSTER RANDOMISED CONTROLLED TRIAL

5.1. INTRODUCTION

The results of the single-blind cluster randomised controlled trial which was conducted as phase 2 of the study, are presented and interpreted in Section 5.2. to Section 5.5. of Chapter 5.

The single-blind cluster randomised controlled trial was conducted to determine the effect of VRT integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group. The duration of the intervention period was two (2) weeks. The long-term effect of the two (2) interventions on patients' participation in physical activity twenty (20) weeks after rehabilitation was terminated and is also presented and interpreted (Section 5.5.3).

The data analysis was done in Stata 14.2.

The results of phase 2 are presented and interpreted within the ICF conceptual framework (Table 2.32) (Lazaro *et al* 2013:187), on which this study was based.

5.2. DEMOGRAPHICAL DATA OF THE PATIENTS IN THE SINGLE-BLIND CLUSTER RANDOMISED CONTROLLED TRIAL

The biographical variables that were recorded and analysed in this study were patients' age, gender, race, level of education and occupation. The biographical variables of patients in the experimental group and control group are presented in Table 5.1.

Table 5.1.: Biographical variables of patients in the experimental group and control group.

BIOGRAPHICAL VARIABLES		
AGE DISTRIBUTION (N=60)		
Age group	**Experimental group (N=30)**	**Control group (N=30)**
20yr-49yr	9 (30%)	5 (17%)
50yr-69yr	18 (60%)	14 (47%)
70yr-79yr	3 (10%)	10 (33%)
80yr-98yr	0	1 (3%)
GENDER (N=60)		
Gender	**Experimental group (N=30)**	**Control group (N=30)**
Male	18 (60%)	11 (37%)
Female	12 (40%)	19 (63%)
ETHNICITY (N=60)		
Race	**Experimental group (N=30)**	**Control group (N=30)**
Caucasian	5 (17%)	13 (43%)
African	22 (73%)	17 (57%)
Coloured	2 (7%)	0
Indian	1 (3%)	0
LEVEL OF EDUCATION (N=60)		
Level of education	**Experimental group (N=30)**	**Control group (N=30)**
No formal schooling	3 (10%)	0
Primary school	2 (7%)	5 (17%)
High school: Grade 8-11	11 (37%)	11 (37%)
High school: Grade 12	8 (27%)	6 (20%)
Tertiary	6 (20%)	8 (27%)

Table 5.1.: (Continued) Biographical variables of patients in the experimental group and control group.

OCCUPATION PRIOR TO THE STROKE (N=59)*		
Occupation prior to the stroke	**Experimental group (N=29)***	**Control group (N=30)**
Medium duty[1]	5 (17%)	5 (17%)
Light duty[2]	6 (20%)	4 (13%)
Sedentary[3]	9 (30%)	9 (30%)
Retired	8 (27%)	10 (33%)
Unemployed	1 (3%)	2 (7%)
* One (1) patient declined to provide information regarding his occupation prior to the stroke		
[1] = (a) Exerting 9-22.5kg of force occasionally and/or 4.5-11.2kg of force frequently and/or up to 4.5kg of force constantly. Physical demand requirements are greater than that required for 'Light duty' (Field and Field 1992:1).		
[2] = (a) Involves walking or standing to a significant degree; (b) involves sitting most of the time but involves pushing and/or pulling of arm or leg controls; (c) exerting 9kg of force occasionally and/or 4.5kg of force frequently (Field and Field 1992:1).		
[3] = (a) Involves sitting most of the time but may involve walking or standing for brief periods of time; (b) exerting 4.5kg of force occasionally to lift, carry, push or pull or otherwise move objects including the human body (Field and Field 1992:1).		

The majority of patients were in the 50-69 years age group. The distribution of patients in the 50-69 years age group was 60% in the experimental group, versus 47% in the control group. Twenty three percent (23.3%) of patients were in the 20-49 years age group followed by twenty two percent (21.7%) in the 70-79 years age group. Despite the fact that patients were randomly allocated to either intervention groups, the control group consisted of fewer patients in the 20-49 years age group and more patients in the 70-79 years age group, compared to the experimental group. The mean age of the patients in the experimental group was 54.5 years and 62.9 years in the control group.

The gender ratio of the experimental group was 1.5 (18 males versus 12 females), compared to the control group's gender ratio of 0.6 (11 males versus 19 females).

Despite the fact that patients were randomly allocated to either intervention groups, the experimental group consisted of more male patients and fewer female patients, compared to the control group.

The distribution of patients within the African ethnic group was 73% in the experimental group, versus 57% in the control group. The distribution of patients within the Caucasian ethnic group was 17% in the experimental group, versus 43% in the control group. Despite the fact that patients were randomly allocated to either intervention groups, the control group consisted of fewer patients within the African ethnicity race group and more patients in the Caucasian ethnicity race group, compared to the experimental group. In the experimental group, the distribution of patients within the Coloured and Indian ethnic groups were 7% and 3% respectively. Despite the fact that patients were randomly allocated to either intervention groups, no patients within the Coloured and Indian ethnic groups were included in the control group.

An equal number of patients (36.7%) in the experimental group and control group completed high school (Grade 8-11). A nearly equal number of patients in the experimental (26.7%) and control groups (20.0%) completed Grade 12. Twenty percent (20.0%) of patients in the experimental group, compared to 26.7% of patients in the control group, had a tertiary education.

An equal number of patients in the experimental group and control group performed either a sedentary (30.0%) or ‘medium duty’ (16.7%) occupation.

The biographic variables that were recorded and analysed in this study were patients’ side-affected by the stroke, dominant side prior to the stroke, type of stroke, area of stroke and HIV-status. The biographic variables of patients in the experimental group and control group, are presented in Table 5.2.

Table 5.2.: Biographic variables of patients in the experimental group and control group.

BIOGRAPHIC VARIABLES		
SIDE-AFFECTED POST-STROKE (N=60)		
Side-affected	**Experimental group (N=30)**	**Control group (N=30)**
Right brain impairment	22 (73%)	18 (60%)
Left brain impairment	8 (27%)	12 (40%)
DOMINANT SIDE PRIOR TO THE STROKE (N=60)		
Dominant side	**Experimental group (N=30)**	**Control group (N=30)**
Left	3 (10%)	2 (7%)
Right	27 (90%)	28 (93%)
TYPE OF STROKE (N=60)		
Type of stroke	**Experimental group (N=30)**	**Control group (N=30)**
Infarct	17 (57%)	19 (63%)
Haemorrhagic	9 (30%)	5 (17%)
Unknown (no information)	4 (13%)	6 (20%)
AREA OF STROKE (N=60)		
Area of stroke	**Experimental group (N=30)**	**Control group (N=30)**
Hemispheric	8 (27%)	7 (23%)
Subcortical	5 (17%)	8 (27%)
Brainstem	0	1 (3%)
Cerebellar	0	2 (7%)
Mixed	7 (23%)	5 (17%)
Unknown (no information)	10 (33%)	7 (23%)

The ratio of right versus left brain impairment of patients in the experimental group was 2.8 (22 versus 8 respectively), compared to the control group that presented with a right versus left brain impairment ratio of 1.5 (18 versus 12). Despite the fact that patients were randomly allocated to either intervention groups, the experimental group consisted of more patients with right brain impairment and fewer patients with left brain impairment, compared to the control group. A fairly equal number of patients in the experimental group (90.0%) and control group (93.3%) were right dominant prior to the stroke, which falls within the expected distribution of hand dominance of the general population.

Despite the fact that seventeen percent (16.5%) of patients' information on the type of stroke were unavailable in their medical records, sixty percent (60%) of patients suffered an infarction. Although twenty eight percent (28%) of patients' information on the area of stroke were unavailable in their medical records, twenty five percent (25%) of patients suffered a hemispheric stroke.

The HIV-status of only thirty two percent (31.7%) of patients were known because in three (3) of the seven (7) rehabilitation centres, a confidentiality policy exists that does not allow disclosure of patients' HIV-status in their medical records.

5.3. ABSENT DATA OF THE CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION OF THE PATIENTS IN THE SINGLE-BLIND CLUSTER RANDOMISED CONTROLLED TRIAL

The data that is presented further in this chapter are incomplete due to absent data. Reasons for the absent data of the clinical feature of oculomotor control were the inability to obtain reliable measurements in these patients due to failure to maintain a steady level of alertness during the measurement of smooth pursuit eye movement (Table 5.4) and/or saccadic eye movement (Table 5.5a, Table 5.5b and Table 5.5c), using VNG or that patients presented with a static visual acuity score > 1.3 LogMAR of the left or right eye respectively.

Reasons for the inability to obtain a measurement of static visual acuity (Table 5.6) in these patients, were a static visual acuity score of higher than 1.3 LogMAR of the left or right eye respectively. Reasons for the inability to obtain a measurement of dynamic visual acuity (Table 5.8) in these patients, were a dynamic visual acuity score > 1.3 LogMAR during ≥ 2Hz horisontal head rotation or a static visual acuity score > 1.3 LogMAR. As dynamic visual acuity is indicated by a decrease of ≥0.2 LogMAR when the dynamic visual acuity LogMAR score is subtracted from the static visual acuity LogMAR score, the inability to obtain a static visual score at baseline results in the inability to obtain a dynamic visual acuity score.

Sixteen patients (N=16) from the experimental group presented with an absent left and right cVEMP respectively at baseline. From the control group, nineteen (N=19) patients presented with an absent left cVEMP, compared to eighteen (N=18) patients that presented with an absent right cVEMP at baseline. Twenty-five patients (N=25) from the experimental group, compared to twenty-nine patients (N=29) from the control group, presented with an absent left and right oVEMP as indicated in Table 5.3.

Data were obtained from all patients in the experimental group (N=30) and control group (N=30) for the clinical features associated with central vestibular dysfunction, which include VOR-gain (Table 5.7), residual oculomotor visual performance (Table 5.11), visual-perceptual function (Table 5.12), cognitive function (Table 5.13), level of anxiety and depression (Table 5.14). Measurements could also be obtained from all patients in the experimental group (N=30) and control group (N=30) for the activity limitations associated with central vestibular dysfunction, which include functional balance (Table 5.15), ability to modify gait in response to changing task demands (Table 5.16) and functional ability (Table 5.17).

The absent data of the clinical features and activity limitations associated with central vestibular dysfunction of the patients in the single-blind cluster randomised controlled trial, is presented in Table 5.3.

Table 5.3.: Absent data of the clinical features and activity limitations associated with central vestibular dysfunction of the patients in the single-blind cluster cross-sectional clinical trial.

Objective measure			Experimental group		Control group		Total absent on Differences (matched test)	
			Pre	Post	Pre	Post	Experimental group	Control group
Smooth pursuit eye movement	Left Visual field	Gain of Right eye	N=1	N=1	N=2	N=0	N=1	N=2
		Gain of Left eye	N=2	N=2	N=2	N=0	N=2	N=2
	Right Visual field	Gain of Right eye	N=2	N=2	N=2	N=1	N=3	N=2
		Gain of Left eye	N=3	N=2	N=2	N=1	N=3	N=2
Saccadic eye movement	Left Visual field	Latency of Left eye	N=4	N=2	N=0	N=0	N=4	N=0
		Latency of Right eye	N=3	N=1	N=0	N=0	N=3	N=0
	Right Visual field	Latency of Left eye	N=2	N=2	N=0	N=0	N=2	N=0
		Latency of Right eye	N=1	N=1	N=1	N=0	N=1	N=1
	Left Visual field	Velocity of Left eye	N=2	N=4	N=0	N=0	N=4	N=0
		Velocity of Right eye	N=3	N=1	N=0	N=0	N=3	N=0
	Right Visual field	Velocity of Left eye	N=2	N=2	N=0	N=0	N=2	N=0
		Velocity of Right eye	N=1	N=1	N=1	N=0	N=1	N=1

Table 5.3.: (Continued) Absent data of the clinical features and activity limitations associated with central vestibular dysfunction of the patients in the single-blind cluster cross-sectional clinical trial.

Objective measure			Experimental group		Control group		Total absent on Differences (matched test)	
			Pre	Post	Pre	Post	Experimental group	Control group
Saccadic eye movement	Left Visual field	Accuracy of Left eye	N=4	N=2	N=0	N=0	N=4	N=0
		Accuracy of Right eye	N=3	N=1	N=0	N=0	N=3	N=0
	Right Visual field	Accuracy of Left eye	N=2	N=2	N=0	N=0	N=2	N=0
		Accuracy of Right eye	N=1	N=1	N=1	N=0	N=1	N=1
Static visual acuity	Left eye		N=4	N=3	N=0	N=1	N=4	N=1
	Right eye		N=2	N=2	N=1	N=3	N=3	N=3
	Both eyes		N=1	N=1	N=0	N=0	N=2	N=0
Vestibulo-ocular reflex	Gain: Left		N=0	N=0	N=0	N=0	N=0	N=0
	Gain: Right		N=0	N=0	N=0	N=0	N=0	N=0
Dynamic visual acuity	> 0.5 LogMAR score during ≥ 2Hz horisontal head rotation		N=4	N=1	N=4	N=4	N=5	N=4
	Line difference: DVA minus SVA: Decrease of ≥0.2 LogMAR		N=4	N=1	N=4	N=4	N=5	N=4

DVA = Dynamic visual acuity

SVA = Static visual acuity

Table 5.3.: (Continued) Absent data of the clinical features and activity limitations associated with central vestibular dysfunction of the patients in the single-blind cluster cross-sectional clinical trial.

Objective measure			Experimental group		Control group		Total absent on Differences (matched test)	
			Pre	Post	Pre	Post	Experimental group	Control group
Saccular and inferior vestibular nerve function	Left	cVEMP P1	N=16	N=14	N=19	N=16	N=20	N=16
		cVEMP N1	N=16	N=14	N=19	N=16	N=20	N=16
		cVEMP Amplitude	N=16	N=14	N=19	N=16	N=20	N=16
	Right	cVEMP P1	N=16	N=16	N=18	N=16	N=20	N=17
		cVEMP N1	N=16	N=16	N=18	N=16	N=20	N=17
		cVEMP Amplitude	N=16	N=16	N=18	N=16	N=20	N=17
Utricle and superior vestibular nerve function	Left	oVEMP P1	N=25	N=23	N=29	N=28	N=29	N=25
		oVEMP N1	N=25	N=23	N=29	N=28	N=29	N=25
		oVEMP Amplitude	N=25	N=23	N=29	N=28	N=29	N=25
	Right	oVEMP P1	N=25	N=24	N=29	N=28	N=29	N=26
		oVEMP N1	N=25	N=24	N=29	N=28	N=29	N=26
		oVEMP Amplitude	N=25	N=24	N=29	N=28	N=29	N=26

cVEMP = Cervical Vestibular Evoked Myogenic Potential

oVEMP = Ocular Vestibular Evoked Myogenic Potential

P1 = First positive peak on wave form

N1 = First negative deflection on wave form

The effect of the intervention on the clinical features associated with central vestibular dysfunction, is presented and interpreted in the following sections.

5.4. THE EFFECT OF THE INTERVENTION ON THE CLINICAL FEATURES ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION ON THE LEVEL OF BODY STRUCTURE AND FUNCTION

The effect of the intervention on the clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group assessed, was oculomotor control.

5.4.1. Oculomotor control

The effect of the intervention on smooth pursuit eye movement, saccadic eye movement and static visual acuity of patients in the experimental group and control group, were assessed after two weeks of respective intervention. The effect of the intervention on the smooth pursuit eye movement gain of patients in the experimental group and control group, is presented in Section 5.4.1.1.

5.4.1.1. Smooth pursuit eye movement

The median and inter-quartile ranges were used to describe the effect of the intervention on the smooth pursuit eye movement of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the gain of smooth pursuit eye movement of patients *within* the experimental group and control group (Table 5.4). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) *between* the experimental group and control group post-intervention. To allow adjustment for possible confounding by differences in age, gender and race, in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and

post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' smooth pursuit eye movement gain between the experimental group and control group pre and post intervention, is presented in Table 5.4.

Table 5.4.: Comparison of patients' smooth pursuit eye movement gain between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SMOOTH PURSUIT EYE MOVEMENT GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=57)	**Objective measure**		**Pre / Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental: control group (Wilcoxon matched-pair signed-rank test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison *between*-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=29)	Left Visual field	Gain of Right Eye	Pre	75.0	63.0--79.0	0.004**	0.20	2.70 （0.65—11.18）	0.17
			Post	80.5	74.0--83.0				
Control group (N=28)			Pre	68.8	58.3--77.9	0.20			
			Post	70.8	57.9--79.7				
Experimental group(N=28)	Left Visual field	Gain of Left Eye	Pre	74.7	60.3--83.8	0.04*	0.57	0.51 （0.14—1.90）	0.32
			Post	80.1	66.9--82.4				
Control group (N=28)			Pre	68.3	57.3--77.2	0.03*			
			Post	72.3	61.7--82.8				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

**=Significant at the 1% level

Table 5.4.: (Continued) Comparison of patients' smooth pursuit eye movement gain between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SMOOTH PURSUIT EYE MOVEMENT GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=55)	**Objective measure**		**Pre / Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair signed-rank test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=27)	Right Visual field	Gain of Right Eye	Pre	71.0	61.0--81.7	0.35	0.54	2.24 （0.58—8.70）	0.24
			Post	76.5	62.3--81.0				
Control group (N=28)			Pre	63.8	55.3--72.8	0.05*			
			Post	66.0	60.5--73.7				
Experimental group (N=27)	Right Visual field	Gain of Left Eye	Pre	70.3	57.5--84.0	0.81	0.16	0.41 （0.12—1.42）	0.16
			Post	72.6	60.5--78.7				
Control group (N=28)			Pre	63.5	54.3--72.7	0.08			
			Post	65.7	60.0--75.3				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

** =Significant at the 1% level

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the gain of smooth pursuit eye movement of patients *within* the experimental group and control group (Table 5.4). Results of the Wilcoxon matched-pair signed-rank test indicated that within the **left visual field**, the experimental group demonstrated statistically significant improvement in the gain of **right** and **left eye** smooth pursuit eye movement (P=0.004 and P=0.04 respectively) post-intervention. The control group demonstrated statistically significant improvement in the gain of **left eye** smooth pursuit into the **left visual field** (P=0.03) post-intervention.

Results of the Wilcoxon matched-pair signed- rank test indicated that within the **right visual field**, neither the experimental nor control group showed statistically significant difference in the gain of smooth pursuit eye movement of the left eye (P=0.81 and P=0.08 respectively) pre-intervention, compared to post-intervention. The control group demonstrated statistically significant improvement in the gain of **right eye** smooth pursuit eye movement into the right visual field (P=0.05) post-intervention. The experimental group demonstrated no statistically significant difference in the gain of right eye smooth pursuit eye movement into the right visual field (P=0.35).

The Wilcoxon rank-sum test was used to compare the difference in the gain of smooth pursuit eye movement *between* the experimental group and control group. Although some significant differences between baseline and post-intervention measures of the gain of smooth pursuit eye movements were observed *within* the experimental group, the results of Table 5.4. showed that there was no statistically significant difference in smooth pursuit eye movement gain of both eyes in the left and right visual fields *between* the groups' pre and post-intervention measurements.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in the gain of smooth pursuit eye movement following VRT. The odds ratio (OR) with its P-value were calculated. For the outcome of the gain of smooth pursuit eye movement of patients in the experimental group, no statistically significant improvement of smooth pursuit eye movement of the right eye (P=0.17 and P=0.24 respectively) and the left eye (P=0.32 and P=0.16 respectively) in the left and right visual fields were observed post-

intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the gain of smooth pursuit eye movement *between* the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the gain of smooth pursuit eye movement between the experimental group and control group. As the P-values were all greater than 0.05, no statistically significant difference was observed *between* the groups post-intervention (Addendum N).

The implication of the results (Table 5.4), is that when the data are adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of the gain of smooth pursuit eye movement of the left and right eye in both left and right visual fields, *compared* to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the saccadic eye movement of patients in the experimental group and control group, are discussed in Section 5.4.1.2.

5.4.1.2. Saccadic eye movement

The effect of the intervention on the three features of saccadic eye movement (latency, velocity and accuracy) of patients in the experimental group and control group, were assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the latency, velocity and accuracy of saccadic eye movement of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the latency (Table 5.5a), velocity (Table 5.5b) and accuracy (Table 5.5c) of saccadic eye movement of patients *within* the experimental group and control group. The Wilcoxon rank-sum test was used to

detect whether there was a significant difference in the differences (pre-post) *between* the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' latency, velocity and accuracy of saccadic eye movement between the experimental group and control group pre and post intervention, are presented in Table 5.5a., Table 5.5b. and Table 5.5c., respectively.

Table 5.5a.: Comparison of patients' saccadic eye movement latency between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT LATENCY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=56)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)2**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=26)	Left Visual field	Latency of Left Eye	Pre	262.7	238.3--298.7	0.01*	0.16	1.24 (0.34—4.57)	0.75
			Post	242.7	225.8--290.8				
Control group (N=30)			Pre	265.5	232.7--302.0	0.78			
			Post	266.8	231.0--315.0				
Experimental group(N=28)	Left Visual field	Latency of Right Eye	Pre	246.0	226.0--286.7	0.70	0.80	2.84 (0.74—10.84)	0.13
			Post	253.6	206.5--278.9				
Control group (N=30)			Pre	259.2	225.5--287.3	0.21			
			Post	242.3	200.0--287.7				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

**=Significant at the 1% level

Table 5.5a.: Comparison of patients' saccadic eye movement latency between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT LATENCY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=57)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=27)	Right Visual field	Latency of Left Eye	Pre	263.0	240.0--302.5	0.13	0.50	0.92 (0.26—3.22)	0.90
			Post	247.3	232.8--300.5				
Control group (N=30)			Pre	270.9	227.7--310.7	0.52			
			Post	251.3	202.3--298.5				
Experimental group(N=29)	Right Visual field	Latency of Right Eye	Pre	250.7	226.5--279.7	0.08	0.47	0.89 (0.26—3.05)	0.85
			Post	251.0	203.0--267.0				
Control group (N=29)			Pre	266.5	205.0--285.0	0.13			
			Post	232.8	197.3--285.0				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

**=Significant at the 1% level

Table 5.5b.: Comparison of patients' saccadic eye movement velocity between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT VELOCITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=56)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=26)	Left Visual field	Velocity of Left Eye	Pre	371.5	318.3--416.3	0.08	0.01*	9.06 (1.98—41.57)	0.01*
			Post	392.3	338.8--456.3				
Control group (N=30)			Pre	380.3	261.3--435.3	0.53			
			Post	365.0	284.0--407.0				
Experimental group(N=28)	Left Visual field	Velocity of Right Eye	Pre	398.3	357.7--439.8	0.06	0.06	3.31 (0.85—12.83)	0.08
			Post	414.1	381.7--494.8				
Control group (N=30)			Pre	379.5	334.3--442.3	0.81			
			Post	387.8	343.3--454.0				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

**=Significant at the 1% level

Table 5.5b.: Comparison of patients' saccadic eye movement velocity between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT VELOCITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=57)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=27)	Right Visual field	Velocity of Left Eye	Pre	361.5	319.3--458.7	0.13	0.10	5.55 (1.29—23.80)	0.02*
			Post	423.0	361.7--446.5				
Control group (N=30)			Pre	356.3	281.3--419.7	1.00			
			Post	356.2	264.3--417.0				
Experimental group(N=29)	Right Visual field	Velocity of Right Eye	Pre	393.0	350.0--441.5	0.02*	0.004**	6.86 (1.52—31.09)	0.01*
			Post	407.0	365.3--469.0				
Control group (N=29)			Pre	402.3	331.5--440.0	0.90			
			Post	398.2	308.3--452.7				

[1] = P-value: Exceedance probability

[2] = Interquartile range: 25th – 75th percentile

[3] = Odds ratio (OR) 95% confidence interval (CI)

* = Significant at the 5% level

**=Significant at the 1% level

Table 5.5c.: Comparison of patients' saccadic eye movement accuracy between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT ACCURACY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=56)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=26)	Left Visual field	Accuracy of Left Eye	Pre	90.5	84.0--96.3	0.02*	0.15	4.58 (1.17—17.92)	0.03*
			Post	90.8	79.9--102.7				
Control group (N=30)			Pre	83.2	73.3--95.7	0.92			
			Post	83.3	75.0--93.0				
Experimental group(N=28)	Left Visual field	Accuracy of Right Eye	Pre	93.3	79.3--101.2	0.78	0.58	1.18 (0.33—4.24)	0.80
			Post	91.4	81.0--101.8				
Control group (N=30)			Pre	82.9	75.0--94.5	0.28			
			Post	87.3	79.3--94.7				
[1] = P-value: Exceedance probability									
[2] = Interquartile range: 25th – 75th percentile									
[3] = Odds ratio (OR) 95% confidence interval (CI)									
* = Significant at the 5% level									
**=Significant at the 1% level									

Table 5.5c.: Comparison of patients' saccadic eye movement accuracy between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCADIC EYE MOVEMENT LATENCY, VELOCITY AND ACCURACY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups (N=57)	**Objective measure**		**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
						P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=27)	Right Visual field	Accuracy of Left Eye	Pre	88.7	77.0--96.3	0.15	0.71	2.50 (0.66—9.48)	0.18
			Post	89.0	79.8--98.7				
Control group (N=30)			Pre	80.5	62.3--90.5	0.39			
			Post	82.0	68.5--95.0				
Experimental group(N=27)	Right Visual field	Accuracy of Right Eye	Pre	90.0	78.0--95.3	0.08	0.73	1.93 (0.53—6.97)	0.32
			Post	88.3	82.0--102.0				
Control group (N=29)			Pre	82.5	76.3--98.0	0.22			
			Post	88.9	79.0--99.3				
[1] = P-value: Exceedance probability									
[2] = Interquartile range: 25th – 75th percentile									
[3] = Odds ratio (OR) 95% confidence interval (CI)									
* = Significant at the 5% level									
**=Significant at the 1% level									

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the latency (Table 5.5a), velocity (Table 5.5b) and accuracy (Table 5.5c) of saccadic eye movement of patients *within* the experimental group and control group. Results of the Wilcoxon matched-pair signed-rank test indicated that within the **left visual field**, the experimental group demonstrated statistically significant **lower latency** (Table 5.5a) and **greater accuracy** of **left eye** saccadic movement into the left visual field (Table 5.5c) (P=0.01 and P=0.02 respectively). No statistically significant difference in latency, velocity and accuracy of right eye saccadic movement into the left visual field were demonstrated by the experimental group. The control group showed no statistically significant difference in the latency, velocity and accuracy of saccadic eye movement of both eyes into the left visual field pre-intervention, compared to post-intervention.

Results of the Wilcoxon matched-pair signed-rank test indicated that within the **right visual field**, the experimental group demonstrated statistically significant increased **velocity** of **right eye** saccadic movement (P=0.02) (Table 5.5b). The experimental group demonstrated no statistically significant difference in the latency and accuracy of saccadic eye movement of both eyes into the right visual field. The control group showed no statistically significant difference in the latency, velocity and accuracy of saccadic eye movement of both eyes into the right visual field pre-intervention, compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the latency, velocity and accuracy of saccadic eye movement *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group demonstrated statistically significant increased **velocity** of **left eye** saccadic eye movement (P=0.01) in the left visual field and better **velocity** of **right eye** saccadic movement (P=0.004) in the right visual field when compared to the control group post-intervention (Table 5.5b).

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in saccadic eye movement following VRT. The odds ratio (OR) with its P-value were calculated. For the outcome

of saccadic eye movement, it was found that the experimental group demonstrated better; (a) velocity of left eye saccadic eye movement (P=0.01) in the left visual field; (b) velocity of the left (P=0.02) and right (P=0.01) eyes into the right visual field; (c) accuracy of left eye saccadic eye movement (P=0.03) in the left visual field, compared to the control group post-intervention.

The mean difference and the rank of the mean difference, which were used in linear regression, were calculated to compare the differences in the latency, velocity and accuracy of saccadic eye movement *between* the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the latency, velocity and accuracy of saccadic eye movement between the experimental group and control group (Addendum N).

The implication of the results (Tables 5.5a., 5.5b., and 5.5c.), is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group, improved the outcome of the *velocity* and *accuracy* of saccadic eye movement, when compared to the patients in the control group who received task-specific activities alone. Although statistically significant improvement in saccadic velocity and accuracy was observed, the intervention of VRT received by patients in the experimental group did not improve the outcome of the latency of saccadic eye movement, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the static visual acuity of patients in the experimental group and control group, are discussed in Section 5.4.1.3.

5.4.1.3. Static visual acuity

The effect of the intervention on the static visual acuity of patients in the experimental group and control group, were assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the static visual acuity of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between

baseline and post-intervention measures in the static visual acuity of patients *within* the experimental group and control group (Table 5.6). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) *between* the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' static visual acuity between the experimental group and control group pre and post intervention, is presented in Table 5.6.

Table 5.6.: Comparison of patients' static visual acuity between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' STATIC VISUAL ACUITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=26)	Left Eye	Pre	0.25	0.10--0.30	0.53	0.05*	1.61 (0.36—7.28)	0.53
		Post	0.10	0.00--0.40				
Control group (N=29)		Pre	0.30	0.10--0.60	0.06			
		Post	0.40	0.20--0.40				
Experimental group (N=27)	Right Eye	Pre	0.30	0.15--0.40	0.66	0.36	1.41 (0.38—5.28)	0.61
		Post	0.20	0.10--0.40				
Control group (N=27)		Pre	0.30	0.20--0.50	0.36			
		Post	0.30	0.20--0.50				
Experimental group (N=28)	Both Eyes	Pre	0.20	0.10--0.30	0.78	0.60	2.27 (0.43—12.04)	0.34
		Post	0.10	0.00--0.30				
Control group (N=30)		Pre	0.20	0.10--0.40	0.88			
		Post	0.20	0.10--0.30				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level					**=Significant at the 1% level			

The Wilcoxon matched-pair signed- rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the static visual acuity of patients *within* the experimental group and control group (Table 5.6). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group*, neither the experimental nor the control group showed statistically significant difference in static visual acuity of the left eye with right eye occluded, right eye with left eye occluded or both eyes open, post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in static visual acuity *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group demonstrated statistically significant better static visual acuity (P=0.05), when compared to the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in static visual acuity following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of static visual acuity, it was found that there was no statistically significant improvement in static visual acuity of the left eye with right eye occluded, right eye with left eye occluded or both eyes open post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in static visual acuity between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in static visual acuity between the experimental group and control group (Addendum N).

The implication of the results (Table 5.6) is that when the data are adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of static visual acuity, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the second clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group assessed, was reflexive control of gaze (Section 5.4.2).

5.4.2. Reflexive control of gaze

The effect of the intervention on VOR-gain and dynamic visual acuity of patients in the experimental group and control group, were assessed. The effect of the intervention on the VOR-gain of patients in the experimental group and control group are discussed firstly in Section 5.4.2.1.

5.4.2.1. Vestibulo-ocular reflex-gain

The effect of the intervention on the VOR-gain of patients in the experimental group and control group, were assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the VOR-gain of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the VOR-gain of patients within the experimental group and control group (Table 5.7). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' VOR-gain between the experimental group and control group pre and post intervention, is presented in Table 5.7.

Table 5.7.: Comparison of patients' vestibulo-ocular reflex-gain between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' VESTIBULO-OCULAR REFLEX-GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	VOR-gain: Left	Pre	1.0	0.8--1.2	0.18	0.37	0.62 (0.17—2.28)	0.47
		Post	1.1	0.9--1.3				
Control group (N=30)		Pre	0.7	0.5--0.9	0.02*			
		Post	0.9	0.7--1.1				
Experimental group(N=30)	VOR-gain: Right	Pre	1.3	1.1--1.6	0.44	0.67	0.78 (0.23—2.71)	0.70
		Post	1.5	1.0--1.7				
Control group (N=30)		Pre	1.0	0.8--1.3	0.15			
		Post	1.1	0.9--1.5				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								
VOR = Vestibulo-ocular reflex								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the VOR-gain of patients *within* the experimental group and control group (Table 5.7). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the control group demonstrated a statistically significant difference in *left VOR-gain* (P=0.02) post-intervention. The control group showed no statistically significant difference in right VOR-gain (P=0.15). The experimental group demonstrated no statistically significant difference in left or right VOR-gain (P=0.18 and P=0.44 respectively) post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in VOR-gain *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that although a significant difference between baseline and post-intervention measures in the left VOR-gain were observed within the control group, the results of Table 5.6. showed that there was no statistically significant difference in left or right VOR-gain between the groups' pre and post-intervention measurements.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in VOR-gain following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of VOR-gain, it was found that there was no statistically significant improvement in left or right VOR-gain post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the VOR-gain between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in the VOR-gain between the experimental group and control group. As the P-values were all greater than 0.05, no statistically significant difference was observed between the groups post-intervention (Addendum N).

The implication of the results (Table 5.7), is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention

of VRT received by patients in the experimental group did not improve the outcome of the VOR-gain, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the dynamic visual acuity of patients in the experimental group and control group, is discussed in Section 5.4.2.2.

5.4.2.2. Dynamic visual acuity

The effect of the intervention on the dynamic visual acuity of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the dynamic visual acuity of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the dynamic visual acuity of patients within the experimental group and control group (Table 5.8). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' dynamic visual acuity between the experimental group and control group pre and post intervention, is presented in Table 5.8.

Table 5.8.: Comparison of patients' dynamic visual acuity between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' DYNAMIC VISUAL ACUITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=57)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=26)	> 0.5 LogMAR score during ≥ 2Hz horisontal head rotation	Pre	0.60	0.50--0.80	0.00*	0.09	0.52 (0.14—1.95)	0.33
		Post	0.50	0.20--0.60				
Control group (N=26)		Pre	0.60	0.40--0.80	0.11			
		Post	0.55	0.40--0.70				
Experimental group(N=27)	Line difference: DVA minus SVA: Decrease of ≥0.2 LogMAR	Pre	3.50	2.00--5.00	0.11	0.40	0.63 (0.19—2.11)	0.45
		Post	3.00	2.00--4.00				
Control group (N=26)		Pre	4.00	2.00--6.00	0.49			
		Post	3.50	2.00--5.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								
DVA = Dynamic visual acuity								
SVA = Static visual acuity								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the dynamic visual acuity of patients *within* the experimental group and control group (Table 5.8). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the experimental group demonstrated a statistically significant difference in **dynamic visual acuity** (P=0.00) (visual acuity score of higher than 0.5 LogMAR during 2Hz horisontal head rotation). The experimental group showed no statistically significant difference in dynamic visual acuity based on the outcome of a decrease of $\geqslant$0.2 LogMAR when the dynamic visual acuity score (visual acuity during 2Hz horisontal head motion) was subtracted from the static visual acuity score (visual acuity with no head motion) (P=0.11).

The control group showed no statistically significant difference in dynamic visual acuity based on the outcome of a visual acuity score of higher than 0.5 LogMAR during 2Hz horisontal head rotation (P=0.11), or when the line difference resulted in a reduction of two (2) or more LogMAR when the dynamic visual acuity score (visual acuity during 2Hz horisontal head motion) was subtracted from the static visual acuity score (visual acuity with no head motion) (P=0.49).

The Wilcoxon rank-sum test was used to compare the difference in dynamic visual acuity *between* the experimental group and control group. Although some significant differences between baseline and post-intervention measures of dynamic visual acuity were observed *within* the experimental group, the results of Table 5.8. showed that there was no statistically significant difference in dynamic visual acuity *between* the groups' pre and post-intervention measurements.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in dynamic visual acuity following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of dynamic visual acuity, it was found that there was no statistically significant improvement in dynamic visual acuity post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the dynamic visual acuity between the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the dynamic visual acuity between the experimental group and control group. As the P-values were all greater than 0.05, no statistically significant difference was observed between the groups post-intervention (Addendum N).

The implication of the results (Table 5.8) is that when the data are adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of the dynamic visual acuity, compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the third clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group assessed, was saccule and inferior vestibular nerve function (Section 5.4.3).

5.4.3. Saccule and inferior vestibular nerve function

The effect of the intervention on the saccule and inferior vestibular nerve function of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on saccule and inferior vestibular nerve function of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the saccule and inferior vestibular nerve function of patients within the experimental group and control group (Table 5.9). The Wilcoxon rank-sum test was used to detect

whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' saccule and inferior vestibular nerve function between the experimental group and control group pre and post intervention, is presented in Table 5.9.

Table 5.9.: Comparison of patients' saccular and inferior vestibular nerve function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=24)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=14)	cVEMP LEFT P1	Pre	15.85	14.70--17.30	0.53	0.05*	1.86 (0.42—8.18)	0.41
		Post	15.85	15.15--17.50				
Control group (N=10)		Pre	16.00	15.00--18.70	0.06			
		Post	15.00	14.70--17.00				
Experimental group (N=14)	cVEMP LEFT N1	Pre	25.00	23.70--27.00	0.66	0.36	0.82 (0.18—3.74)	0.80
		Post	25.00	23.85--26.15				
Control group (N=10)		Pre	25.30	23.30--27.30	0.36			
		Post	25.50	24.00--26.30				
Experimental group (N=14)	cVEMP LEFT Amplitude	Pre	62.50	44.30--72.40	0.78	0.60	1.02 (0.18—5.68)	0.97
		Post	62.45	41.95--93.75				
Control group (N=10)		Pre	65.90	43.90--73.40	0.88			
		Post	64.95	40.40--87.80				

[1] = P-value: Exceedance probability	P1 = First positive peak on wave form
[2] = Interquartile range: 25th – 75th percentile	N1 = First negative deflection on wave form
[3] = Odds ratio (OR) 95% confidence interval (CI)	cVEMP = Cervical Vestibular Evoked Myogenic Potential
* = Significant at the 5% level	** = Significant at the 1% level

Table 5.9.: (Continued) Comparison of patients' saccular and inferior vestibular nerve function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=24)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=13)	cVEMP RIGHT P1	Pre	16.5	15.7--17.0	0.20	0.71	0.77 (0.15—4.01)	0.76
		Post	15.7	15.0--17.0				
Control group (N=10)		Pre	15.5	14.5--17.1	0.72			
		Post	16.0	14.3--17.6				
Experimental group (N=13)	cVEMP RIGHT N1	Pre	25.4	23.3--26.7	0.48	0.76	0.54 (0.08—3.59)	0.53
		Post	25.6	23.3--26.3				
Control group (N=10)		Pre	23.5	22.0--26.4	0.26			
		Post	25.0	22.0--26.7				
Experimental group (N=13)	cVEMP RIGHT Amplitude	Pre	55.4	36.7--73.4	0.86	0.95	0.97 (0.19—4.99)	0.97
		Post	60.8	39.1--78.7				
Control group (N=10)		Pre	52.4	39.5--90.8	0.72			
		Post	51.5	32.9--113.5				

[1] = P-value: Exceedance probability	P1 = First positive peak on wave form
[2] = Interquartile range: 25th – 75th percentile	N1 = First negative deflection on wave form
[3] = Odds ratio (OR) 95% confidence interval (CI)	cVEMP = Cervical Vestibular Evoked Myogenic Potential
* = Significant at the 5% level	** = Significant at the 1% level

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the saccular and inferior vestibular nerve function of patients *within* the experimental group and control group (Table 5.9). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* neither the experimental group, nor control group, demonstrated statistically significant difference at the 5% significance level in left and right cVEMP P1, cVEMP N1 and cVEMP amplitude, in both groups post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in saccular and inferior vestibular nerve function between the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group demonstrated statistically significant better left cVEMP P1 (P=0.05), when compared to the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in saccular and inferior vestibular nerve function following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of saccular and inferior vestibular nerve function, it was found that there was no statistically significant improvement in saccular and inferior vestibular nerve function post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the saccular and inferior vestibular nerve function between the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the saccular and inferior vestibular nerve function between the experimental group and control group. As the P-values were all greater than 0.05, no statistically significant difference was observed between the groups post-intervention (Addendum N).

The implication of the results (Table 5.8) is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention

of VRT received by patients in the experimental group did not improve the outcome of the saccular and inferior vestibular nerve function, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the fourth clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group assessed, was utricle and superior vestibular nerve function (Section 5.4.4).

5.4.4. Utricle and superior vestibular nerve function

The effect of the intervention on the utricle and superior vestibular nerve function of patients in the experimental group and control group, was assessed. Twenty-five patients (N=25) from the experimental group, compared to twenty-nine patients (N=29) from the control group, presented with an *absent* left and right oVEMP as indicated in Table 5.3.

Due to the high number of patients that presented with an absent oVEMP, the Wilcoxon matched-pair signed-rank test could not be applied to determine whether there was a significant difference between baseline and post-intervention measures in the utricle and superior vestibular nerve function of patients *within* the experimental group and control group (Table 5.10). The Wilcoxon rank-sum test could also not be applied to determine whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. The median and inter-quartile ranges were therefore used to describe the effect of the intervention on utricle and superior vestibular nerve function of patients in the experimental group (N=5) and control group (N=1). The comparison of patients' utricle and superior vestibular nerve function between the experimental group and control group pre and post intervention, is presented in Table 5.10.

Table 5.10.: Comparison of patients' utricle and superior vestibular nerve function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION				
Intervention groups (N=6)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[1]**
Experimental group (N=5)	oVEMP LEFT P1	Pre	10.7	10.7--10.7
		Post	10.3	9.3--10.6
Control group (N=1)		Pre	11.7	11.7--11.7
		Post	10.0	9.7--10.3
Experimental group (N=5)	oVEMP LEFT N1	Pre	15.0	14.0--15.3
		Post	15.0	14.0--15.3
Control group (N=1)		Pre	16.7	16.7--16.7
		Post	14.0	12.7--15.3
Experimental group (N=5)	oVEMP LEFT Amplitude	Pre	5.7	4.8--8.1
		Post	4.6	1.8--11.1
Control group (N=1)		Pre	3.5	3.5--3.5
		Post	9.1	2.2--16.0
[1] = Interquartile range: 25th – 75th percentile				
oVEMP = Ocular Vestibular Evoked Myogenic Potential				
P1 = First positive peak on wave form				
N1 = First negative deflection on wave form				

Table 5.10.: (Continued) Comparison of patients' utricle and superior vestibular nerve function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION				
Intervention groups (N=5)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[1]**
Experimental group (N=5)	oVEMP RIGHT P1	Pre	10.3	10.0--10.3
		Post	10.3	10.0--10.3
Control group (N=1)		Pre	10.3	10.3--10.3
		Post	9.2	9.0--9.3
Experimental group (N=4)	oVEMP RIGHT N1	Pre	15.3	14.7--16.7
		Post	14.9	14.0--16.0
Control group (N=1)		Pre	15.7	15.7--15.7
		Post	13.6	11.7--15.6
Experimental group (N=4)	oVEMP RIGHT Amplitude	Pre	5.4	3.8--6.8
		Post	6.2	3.5--9.1
Control group (N=1)		Pre	5.6	5.6--5.6
		Post	3.4	2.3--4.4
[1] = Interquartile range: 25th – 75th percentile				
oVEMP = Ocular Vestibular Evoked Myogenic Potential				
P1 = First positive peak on wave form				
N1 = First negative deflection on wave form				

The utricle and superior vestibular nerve function assessed by left and right oVEMP N1, oVEMP P1 and oVEMP amplitude of patients *within* the experimental group and control group, remained relatively unchanged pre-intervention, compared to post-intervention.

The effect of the intervention on the fifth clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group assessed, was higher vestibular function.

5.4.5. Higher vestibular function

The effects of the intervention on residual oculomotor visual performance, visual-perceptual function and cognitive function of patients in the experimental group and control group, were assessed. The effect of the intervention on the residual oculomotor visual performance of patients in the experimental group and control group, is discussed in Section 5.4.5.1.

5.4.5.1. Residual oculomotor visual performance

The effect of the intervention on the speed and accuracy of residual oculomotor visual performance of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the speed and accuracy of residual oculomotor visual performance of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the speed and accuracy of residual oculomotor visual performance of patients within the experimental group and control group (Table 5.11). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for

possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' speed and accuracy of residual oculomotor visual performance between the experimental group and control group pre and post intervention, is presented in Table 5.11.

Table 5.11.: Comparison of patients' speed and accuracy of residual oculomotor visual performance between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' RESIDUAL OCULOMOTOR VISUAL PERFORMANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	King Devick Sub-test 1: Time	Pre	63.50	43.00--112.00	0.004**	0.02*	0.46 (0.13—1.62)	0.23
		Post	45.50	32.50--80.00				
Control group (N=30)		Pre	53.00	32.00--93.00	0.76			
		Post	70.00	27.50--114.00				
Experimental group (N=30)	King Devick Sub-test 1: Errors	Pre	11.50	2.00--22.00	0.01*	0.09	0.84 (0.19—3.67)	0.82
		Post	1.00	0.00--12.50				
Control group (N=30)		Pre	4.00	1.00--14.00	0.40			
		Post	6.50	0.00--13.00				
Experimental group (N=30)	King Devick Sub-test 2: Time	Pre	68.50	38.00--96.00	0.00*	0.00*	0.63 (0.18—2.23)	0.47
		Post	46.50	32.00--69.50				
Control group (N=30)		Pre	45.00	35.00--71.00	0.60			
		Post	53.50	28.50--109.50				
[1] = P-value: Exceedance probability					[3] = Odds ratio (OR) 95% confidence interval (CI)			
[2] = Interquartile range: 25th – 75th percentile					* = Significant at the 5% level		** = Significant at the 1% level	

Table 5.11.: (Continued) Comparison of patients' speed and accuracy of residual oculomotor visual performance between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' RESIDUAL OCULOMOTOR VISUAL PERFORMANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	King Devick Sub-test 2: Errors	Pre	5.50	1.00--21.00	0.03*	0.33	0.60 (0.15—2.35)	0.46
		Post	2.00	0.00--18.50				
Control group (N=30)		Pre	4.00	1.00--26.00	0.41			
		Post	5.50	0.50--14.00				
Experimental group (N=30)	King Devick Sub-test 3: Time	Pre	54.50	48.00--109.00	0.00*	0.00*	0.87 (0.26—2.91)	0.82
		Post	52.00	33.50--72.50				
Control group (N=30)		Pre	53.00	32.00--66.00	0.27			
		Post	55.50	34.50--118.50				
Experimental group (N=30)	King Devick Sub-test 3: Errors	Pre	10.00	5.00--26.00	0.01*	0.46	0.34 (0.09—1.30)	0.12
		Post	8.00	0.00--22.50				
Control group (N=30)		Pre	12.00	2.00--34.00	0.23			
		Post	9.00	0.50--24.00				
[1] = P-value: Exceedance probability					[3] = Odds ratio (OR) 95% confidence interval (CI)			
[2] = Interquartile range: 25th – 75th percentile					* = Significant at the 5% level		** = Significant at the 1% level	

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the speed and accuracy of residual oculomotor visual performance of patients *within* the experimental group and control group (Table 5.11). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group* the experimental group demonstrated a statistically significant difference in the time taken (speed) (P=0.004, P=0.00 and P=0.00 respectively) to complete the King Devick Test© (Sub-test 1-3) post-intervention. The experimental group also demonstrated a statistically significant difference in the number of errors made (accuracy) (P=0.01, P=0.03 and P=0.01 respectively) during completion of the King Devick Test© (Sub-test 1-3) post-intervention.

The control group showed no statistically significant difference in the time taken (speed) (P=0.76, P=0.60 and P=0.27 respectively) and number of errors made (accuracy) (P=0.40, P=0.41 and P=0.23 respectively) during completion of the King Devick Test© (Sub-test 1-3) pre-intervention, compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the speed and accuracy of residual oculomotor visual performance *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group demonstrated statistically significant decreased time (speed) (P=0.02, P=0.00 and P=0.00 respectively) to complete the King Devick Test© (Sub-test 1-3), compared to the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in residual oculomotor visual performance following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of residual oculomotor visual performance, it was found that there was no statistically significant improvement in the speed and accuracy of residual oculomotor visual performance post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the residual oculomotor

visual performance between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in the residual oculomotor visual performance between the experimental group and control group (Addendum N).

The implication of the results (Table 5.11) is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of residual oculomotor visual performance (speed and accuracy), when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the visual-perceptual function of patients in the experimental group and control group, is discussed in Section 5.3.5.2.

5.3.5.2. Visual-perceptual function

The effect of the intervention on the visual-perceptual function of patients in the experimental and control groups, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the visual-perceptual function of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the visual-perceptual function of patients within the experimental group and control group (Table 5.12). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The

comparison of patients' visual-perceptual function between the experimental group and control group pre and post intervention, is presented in Table 5.12.

Table 5.12.: Comparison of patients' visual-perceptual function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' VISUAL-PERCEPTUAL FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Star Cancellation Test : Time	Pre	103.00	90.00--103.00	0.93	0.26	2.25 (0.63—8.12)	0.21
		Post	106.50	80.00--149.00				
Control group (N=30)		Pre	102.50	78.00--155.00	0.14			
		Post	100.50	68.00--156.00				
Experimental group(N=30)	Star Cancellation Test : Errors	Pre	6.00	4.00--16.00	0.00*	0.15	0.36 (0.08—1.56)	0.17
		Post	3.00	1.00--10.00				
Control group (N=30)		Pre	4.50	1.00--36.00	0.14			
		Post	4.00	1.00--15.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								

The Wilcoxon matched-pair signed- rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the visual-perceptual function of patients *within* the experimental group and control group (Table 5.12). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the experimental group demonstrated a statistically significant difference in visual-perceptual function (P=0.00) in the number of errors made during completion of the Star Cancellation Test. The experimental group showed no statistically significant difference in the time taken (P=0.93) to complete the Star Cancellation Test post-intervention.

The control group showed no statistically significant difference in visual-perceptual function in the time taken (P=0.14) and the number of errors made (P=0.14) during completion of the Star Cancellation Test pre-intervention, when compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in visual-perceptual function between the experimental group and control group. Although some significant differences between baseline and post-intervention measures of visual-perceptual function were observed within the experimental group, the results of Table 5.11. showed that there was no statistically significant difference in visual-perceptual function between the groups' pre and post-intervention measurements.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in visual-perceptual function following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of visual-perceptual function, it was found that there was no statistically significant improvement in visual-perceptual function post-intervention (VRT).

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the visual-perceptual function between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were

used to assess the difference in the visual-perceptual function between the experimental group and control group (Addendum N).

The implication of the results (Table 5.12) is that when the data is adjusted for the confounding factors of age, gender and race, results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of visual-perceptual function, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the cognitive function of patients in the experimental group and control group, is discussed in Section 5.4.5.3.

5.4.5.3. Cognitive function

The effect of the intervention on the cognitive function of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the cognitive function of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the cognitive function of patients *within* the experimental group and control group (Table 5.13). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, when compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' cognitive function between the experimental group and control group pre and post intervention, is presented in Table 5.13.

Table 5.13.: Comparison of patients' cognitive function between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' COGNITIVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Mini-Mental State Examination	Pre	22.00	16.00--24.00	0.00	0.01	1.48 (0.39—5.61)	0.56
		Post	25.00	21.00--28.00				
Control group (N=30)		Pre	22.00	16.00--24.00	0.25			
		Post	21.00	19.00--26.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the cognitive function of patients *within* the experimental group and control group (Table 5.13). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the experimental group demonstrated a statistically significant difference in cognitive function (P=0.00) post-intervention. The control group showed no statistically significant difference in cognitive function (P=0.25) pre-intervention, when compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in cognitive function between the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group demonstrated statistically significant better cognitive function (P=0.01), when compared to the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in cognitive function following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of cognitive function, it was found that the experimental group demonstrated no statistically significant improvement in cognitive function following VRT.

The mean difference and the rank of the mean difference, which were used in linear regression, were calculated to compare the differences in the cognitive function between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in the cognitive function between the experimental group and control group (Addendum N).

The implication of the results (Table 5.13), is that when the data is adjusted for the confounding factors of age, gender and race, results indicate that the intervention of VRT received by patients in the experimental group did not improve the outcome of cognitive function, when compared to the patients in the control group who received task-specific activities alone.

The effects of the intervention on the sixth clinical feature associated with central vestibular dysfunction on the level of body structure and function of patients in the experimental group and control group that was assessed, was anxiety and depression post-stroke.

5.4.6. Level of anxiety and/ or depression post-stroke

The effect of the intervention on the level of anxiety and/ or depression in patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the level of anxiety and/ or depression in patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the level of anxiety and/ or depression of patients within the experimental group and control group (Table 5.14). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, when compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' level of anxiety and/ or depression between the experimental group and control group pre and post intervention, is presented in Table 5.14.

Table 5.14.: Comparison of patients' level of anxiety and/ or depression between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' LEVEL OF ANXIETY AND/ OR DEPRESSION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Hospital Anxiety and Depression Scale: Anxiety sub-scale	Pre	8.00	6.00--13.00	0.001**	0.01*	0.50 (0.13—1.95)	0.32
		Post	4.00	2.00--9.00				
Control group (N=30)		Pre	11.00	8.00--13.00	0.97			
		Post	10.00	6.00--13.00				
Experimental group(N=30)	Hospital Anxiety and Depression Scale: Depression sub-scale	Pre	8.00	4.00--13.00	0.003**	0.001**	0.12 (0.03—0.49)	0.003**
		Post	4.00	2.00--7.00				
Control group (N=30)		Pre	9.00	6.00--12.00	0.52			
		Post	9.00	5.00--13.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level					**=Significant at the 1% level			

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the level of anxiety and depression of patients *within* the experimental group and control group (Table 5.14). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the experimental group demonstrated a statistically significant improvement in anxiety (P=0.001) and depression (P=0.003) post-intervention. The control group showed no statistically significant difference in anxiety and depression (P=0.97 and P=0.52 respectively) pre-intervention, when compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the level of anxiety and depression *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group's anxiety (P=0.01) and depression (P=0.001) improved significantly more than in the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in anxiety and depression following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of level of anxiety and depression post-stroke, it was found that the experimental group demonstrated a statistically significant reduced level of depression (P=0.003), when compared to the control group post-intervention.

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the level of anxiety and depression between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in the level of anxiety and depression between the experimental group and control group (Addendum N).

The implication of the results (Table 5.14) is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group improved the outcome of the level of depression, compared to the patients in the control group who received task-

specific activities alone. Although statistically significant improvement in level of depression post-stroke was observed, the intervention of VRT received by patients in the experimental group did not improve the outcome of the level of anxiety, compared to the patients in the control group who received task-specific activities alone.

The results of the effect of the intervention on the activity limitations associated with central vestibular dysfunction on the levels of activity and participation of patients in the experimental group and control group, is presented and interpreted in Section 5.5.

5.5. EFFECT OF THE INTERVENTION ON THE ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION ON THE LEVELS OF ACTIVITY AND PARTICIPATION

The effects of the intervention on the activity limitation associated with central vestibular dysfunction on the levels of activity and participation of patients in the experimental group and control group assessed, was their sensorimotor balance, mobility and gait.

5.5.1. Sensorimotor balance, mobility and gait

The effect of the intervention on the functional balance and the ability to modify gait in response to changing task demands of patients in the experimental group and control group, was assessed. The effect of the intervention on the functional balance of patients in the experimental group and control group, is discussed firstly in Section 5.5.1.1.

5.5.1.1. Functional balance

The effect of the intervention on patients' functional balance in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to

describe the effect of the intervention on the functional balance of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the functional balance of patients within the experimental group and control group (Table 5.15). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' functional balance between the experimental group and control group pre and post intervention, is presented in Table 5.15.

Table 5.15.: Comparison of patients' functional balance between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' FUNCTIONAL BALANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Berg Balance Scale	Pre	6.50	3.00--18.00	0.000**	0.000**	1 (-)	-
		Post	37.50	29.00--47.00				
Control group (N=30)		Pre	4.00	3.00--7.00	0.001**			
		Post	9.50	3.00--25.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the functional balance of patients *within* the experimental group and control group (Table 5.15). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* both the experimental group and control group demonstrated a statistically significant improvement in their functional balance (P=0.000 and P=0.001 respectively) post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the functional balance *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group's functional balance (P=0.000) improved significantly more than the control group post-intervention.

The mean difference and the rank of the mean difference, which were used in linear regression, were calculated to compare the differences in the functional balance between the experimental group and control group. Linear regression, as well as mixed models before adjusting and after adjusting for age, gender and race, were used to assess the difference in the functional balance between the experimental group and control group (Addendum N).

The implication of the results (Table 5.15) is that based on the Wilcoxon rank-sum test on differences, without adjusting for confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group improved the outcome of functional balance, when compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the ability to modify gait in response to changing task demands of patients in the experimental group and control group, is discussed in Section 5.5.1.2.

5.5.1.2. Ability to modify gait in response to changing task demands

The effect of the intervention on the ability to modify gait in response to changing task demands of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the ability to modify gait in response to changing task demands of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the ability to modify gait in response to changing task demands of patients within the experimental group and control group (Table 5.16). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' ability to modify gait in response to changing task demands between the experimental group and control group pre and post intervention, is presented in Table 5.16.

Table 5.16.: Comparison of patients' ability to modify gait in response to changing task demands between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' ABILITY TO MODIFY GAIT IN RESPONSE TO CHANGING TASK DEMANDS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Dynamic Gait Index	Pre	9.00	9.00--11.00	0.04*	0.46	1(-)	-
		Post	14.50	11.00--18.00				
Control group (N=30)		Pre	9.00	6.00--10.00	0.47			
		Post	10.50	7.00--15.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the ability to modify gait in response to changing task demands of patients *within* the experimental group and control group (Table 5.16). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* the experimental group demonstrated a statistically significant greater ability to modify gait in response to changing task demands (P=0.04) post-intervention. The control group showed no statistically significant difference in the ability to modify gait in response to changing task demands (P=0.47) pre-intervention, compared to post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the ability to modify gait in response to changing task demands *between* the experimental group and control group. Although some significant differences between baseline and post-intervention measures of the ability to modify gait in response to changing task demands were observed within the experimental group, the results of Table 5.15. showed that there was no statistically significant difference in the ability to modify gait in response to changing task demands between the groups' pre and post-intervention measurements.

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the ability to modify gait in response to changing task demands between the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the ability to modify gait in response to changing task demands between the experimental group and control group (Addendum N).

The implication of the results (Table 5.16) is that based on the Wilcoxon rank-sum test on differences, without adjusting for confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group improved the outcome of the ability to modify gait in response to changing task demands, compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the functional ability of patients in the experimental group and control group, is discussed in Section 5.5.2.

5.5.2. Functional ability

The effect of the intervention on the functional ability of patients in the experimental group and control group, was assessed. The median and inter-quartile ranges were used to describe the effect of the intervention on the functional ability of patients in the experimental group and control group. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the functional ability of patients within the experimental group and control group (Table 5.17). The Wilcoxon rank-sum test was used to detect whether there was a significant difference in the differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups (Table 5.1), the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, when compared to baseline and logistic regression adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups. The comparison of patients' functional ability between the experimental group and control group pre and post intervention, is presented in Table 5.17.

Table 5.17.: Comparison of patients' functional ability between the experimental group and control group pre and post intervention.

COMPARISON OF PATIENTS' FUNCTIONAL ABILITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups (N=60)	**Objective measure**	**Pre/ Post**	**Median**	**Interquartile range (P25--P75)[2]**	**Comparison within group - experimental : control group (Wilcoxon matched-pair rank-sum test)**	**Comparison between-group - experimental : control group (Wilcoxon rank-sum test on differences)**	**Comparison between-group - experimental : control group (logistic regression inspects the improvement between control and experimental group, adjusted)**	
					P-value[1]	P-value[1]	OR (95%CI)[3]	P-value[1]
Experimental group (N=30)	Barthel Index	Pre	40.00	15.00--55.00	0.000**	0.000**	10.73 (1.11—103.77)	0.04*
		Post	82.50	70.00--90.00				
Control group (N=30)		Pre	37.50	10.00--50.00	0.004**			
		Post	37.50	20.00--65.00				
[1] = P-value: Exceedance probability								
[2] = Interquartile range: 25th – 75th percentile								
[3] = Odds ratio (OR) 95% confidence interval (CI)								
* = Significant at the 5% level								
**=Significant at the 1% level								

The Wilcoxon matched-pair signed-rank test was applied to determine whether there was a significant difference between baseline and post-intervention measures in the functional balance of patients *within* the experimental group and control group (Table 5.17). Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group,* both the experimental group and control group demonstrated a statistically significant improvement in their functional ability (P=0.000 and P=0.004 respectively) post-intervention.

The Wilcoxon rank-sum test was used to compare the difference in the functional ability *between* the experimental group and control group. Results of the Wilcoxon rank-sum test indicated that the experimental group's functional ability (P=0.000) improved significantly more than the control group post-intervention.

Logistic regression adjusted for age, gender and race, was used to determine whether the experimental group demonstrated improvement in functional ability following VRT. The odds ratio (OR) with its P-value, was calculated. For the outcome of functional ability, it was found that the experimental group demonstrated better functional ability (P=0.04), compared to the control group post-intervention.

The mean difference and the rank of mean difference, which were used in linear regression, were calculated to compare the differences in the functional ability *between* the experimental group and control group. Linear regression, as well as mixed models, before adjusting and after adjusting for age, gender and race, were used to assess the difference in the functional ability between the experimental group and control group (Addendum N).

The implication of the results (Table 5.17) is that when the data is adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT received by patients in the experimental group improved the outcome of the functional ability, compared to the patients in the control group who received task-specific activities alone.

The effect of the intervention on the participation in physical activity of patients in the experimental group and control group, is presented and interpreted in Section 5.5.3.

5.5.3. Participation in physical activity post-stroke

Twenty (20) weeks after rehabilitation had been terminated, the independent assessor contacted all patients in the experimental group (N=30) and the control group (N=30) who participated in phase 2 of the study to complete the telephonic-administered IPAQ. Twenty (20) patients in the experimental group and fourteen (14) patients in the control group, completed the telephonic-administered IPAQ at the twenty (20)-week follow-up.

The results of patients' participation in physical activity post-stroke, are presented in the categories prescribed by the application criteria of the IPAQ (Craig *et al* 2003:1381) namely 'number of days per week participated in vigorous activities', 'number of hours per week participated in vigorous activities', 'number of minutes per day participated in vigorous activities', 'number of days per week participated in moderate activities', 'number of hours per week participated in moderate activities', 'number of minutes per day participated in moderate activities', 'number of days per week participated in walking', 'number of hours per week participated in walking', 'number of minutes per day participated in walking', 'number of hours per day spent sitting' and 'number of minutes per day spent sitting'. The participation of patients in vigorous, moderate, walking and sitting during the seven (7) days prior to the telephonic follow-up, is presented in Table 5.18.

Table 5.18a.: Participation of patients in vigorous activities, moderate activities, and walking during the seven (7) days prior to the telephonic follow-up.

TELEPHONIC-ADMINISTERED INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)							
Experimental group (N=20)				**Control group (N=14)**			
Participation in physical activity			**Number of patients**	**Participation in physical activity**			**Number of patients**
Vigorous activities	Days per week	0	20	Vigorous activities	Days per week	0	14
	Hours per day	0	20		Hours per day	0	14
	Min per day	0	20		Min per day	0	14
Moderate activities	Days per week	0	16	Moderate activities	Days per week	0	12
		1	1			1	0
		4	0			4	1
		5	3			5	0
		6	0			6	1
	Hours per day	0	18		Hours per day	0	13
		1	2			1	1
	Min per day	0	18		Min per day	0	13
		20	1			20	1
		40	1			40	0
Walking Days per week	Days per week	0	2	Walking Days per week	Days per week	0	2
		3	1			3	0
		7	17			7	12
	Hours per day	0	10		Hours per day	0	4
		1	3			1	8
		2	1			2	0
		3	3			3	1
		4	3			4	0
		5	0			5	1
	Min per day	0	8		Min per day	0	9
		20	2			20	0
		30	10			30	4
		40	0			40	1

Table 5.18b.: Participation of patients in sitting during the seven (7) days prior to the telephonic follow-up.

TELEPHONIC-ADMINISTERED INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)							
Experimental group (N=20)				**Control group (N=14)**			
Participation in physical activity			**Number of patients**	**Participation in physical activity**			**Number of patients**
Sitting	Hours per day	0	3	Sitting	Hours per day	0	1
		1	1			1	1
		3	3			3	2
		4	3			4	5
		5	3			5	2
		6	2			6	0
		7	2			7	3
		8	2			8	0
		11	1			11	0
	Min per day	0	17		Min per day	0	10
		30	3			30	3
		45	0			45	1

None of the patients in either intervention groups participated in vigorous activities such as heavy lifting, digging, aerobics or fast cycling, during the seven (7) days prior to the telephonic follow-up.

More patients in the experimental group (13.3%), compared to the control group (0.07%), participated in moderate activities that required moderate physical effort, such as carrying light loads.

More than half of patients in the experimental group (56.7%), compared to 40.0% of patients in the control group, indicated that they walked daily.

Forty-three percent (43.3%) of the patients in the experimental group, compared to a third (33.3%) of the patients in the control group, demonstrated increased sedentary sitting behaviour by spending four (4) or more hours per day sitting.

5.6. SUMMARY OF CHAPTER 5

The single-blind cluster randomised controlled trial was conducted to determine the effect of VRT integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group, on their clinical features and activity limitations associated with central vestibular dysfunction in the sub-acute phase post-stroke. Results of the single-blind cluster randomised controlled trial demonstrated that *within-group comparison*, patients in the experimental group demonstrated statistically significant improved oculomotor function which included improved gain of smooth pursuit eye movements and saccadic eye movements (latency, velocity and accuracy). Patients in the experimental group also demonstrated statistically significant improved reflexive control of gaze, specifically dynamic visual acuity and improved higher vestibular function, which included improved residual oculomotor visual performance, visual-perceptual function and cognitive function. Statistically significant improved levels of anxiety and depression were also demonstrated by patients within the experimental group.

Statistically significant improvement in activity limitations associated with central vestibular dysfunction which included functional balance, ability to modify gait in response to changing task demands and functional ability, were observed in patients in the experimental group post-intervention.

Results of the single-blind cluster randomised controlled trial demonstrated that *within-group comparison*, patients in the control group demonstrated statistically significant improvement of oculomotor control and reflexive control of gaze, which included improved gain of smooth pursuit eye movements and VOR-gain respectively. Patients in the control group also demonstrated statistically significant improvement in activity limitations associated with central vestibular dysfunction, which included improved functional balance and functional ability post-intervention.

Results of the single-blind cluster randomised controlled trial demonstrated that *between-group comparison,* based on the Wilcoxon rank-sum test on differences without adjusting for confounding factors of age, gender and race, patients in the

experimental group improved significantly more than the control group in oculomotor function, specifically saccadic movement (velocity) and static visual acuity. The experimental group also demonstrated significant improvement in saccule and inferior vestibular nerve function (left first positive peak on wave form) post-intervention. Statistically significant improvement in the higher vestibular function, which included residual oculomotor visual performance (velocity) and cognitive function, were demonstrated by the experimental group. Statistically significant improved levels of anxiety and depression, were also demonstrated by patients in the experimental group, when compared to the control group. The experimental group also improved significantly more than the control group in functional balance and functional ability post-intervention.

Results of the single-blind cluster randomised controlled trial demonstrated that *between-group comparison,* based on logistic regression adjusted for age, gender and race, patients in the experimental group improved significantly more than the control group in oculomotor function, specifically saccadic movement (velocity and accuracy), level of depression and functional ability.

The results of the study are discussed in the context of the relevant literature in Chapter 6. The conclusion, limitations of the current study and suggestions for further studies are discussed in Chapter 7.

CHAPTER 6

DISCUSSION

6.1. INTRODUCTION

In Chapter 6, the results of the cross-sectional survey (phase 1) and single-blind cluster randomised controlled trial (phase 2) are discussed in relation to the literature and presented within the same ICF conceptual framework (Lazaro *et al* 2013:187) within which the literature review and results of phases 1 and 2 were presented & interpreted. The results in this chapter are discussed in logical sequence based on the aims and objectives of the study.

6.2. THE STUDY POPULATION

6.2.1. Background

The patients in this study (phase 1 and phase 2) were in the sub-acute phase post-stroke (Section 1.1.4) and were admitted at a public or private rehabilitation centre in Pretoria or Johannesburg, Gauteng, South Africa (Section 3.1.3) at the time of inclusion in the study. In order to ensure that the results obtained during this study were a valid representation of a particular sub-group of the South African population who sustained a stroke, patients were recruited based on specific inclusion and exclusion criteria (Section 3.1.4). In phase 1, male and female patients in the age group 19 years – 84 years, who suffered either an ischaemic or haemorrhagic stroke and whom were in the sub-acute phase (Section 1.1.4) post-stroke, were recruited (Section 3.1.4.1). Patients were excluded if they presented with severe cognitive impairment (MMSE<7), were unable to follow instructions and were unable to provide informed consent (Section 3.1.4.1). Patients were also excluded if they had a history of an organic disorder, major psychiatric impairment, co-morbid disease or disability that would have prevented or limited the functional assessment and their participation in the study. Lastly, patients with a positive Dix-Hallpike test or whom participated in other pharmacological or rehabilitation intervention studies, were excluded from the study (Section 3.1.4.1).

6.2.2. Demographic data interpretation of phase 1

Nearly half (48.0%) of the patients in the cross-sectional survey were patients within the 50 years - 69 years age group, followed by patients in the 20 years - 49 years age group (28.4%). The distribution of age of patients in the cross-sectional survey are supported by findings by De Villiers, Badri, Ferreira and Bryer (2011:345) who indicated that the median age (IQR) of stroke survivors in South Africa is 60 years (51 years –69 years). These findings by De Villiers *et al* (2011:345) are supported by Mudzi, Stewart and Musenge (2012:765) who indicated that the mean age of post-stroke patients is 53.2±11.4 years. The gender ratio of patients in the cross-sectional survey was 0.9 (49 males versus 53 females). The ratio of male versus female patients in the cross-sectional survey is supported by findings of The SASPI Project Team (2004:627) that also indicated a 0.9 ratio of male versus female stroke survivors in South Africa. The age and gender of the patients who participated in the cross-sectional survey were thus a valid representation of the South African population who sustain a stroke.

More than half of the patients were within the African ethnic group (56.9%) followed by the Caucasian ethnic group (40.2%). Although the race of patients who participated in the current study coincided with the ratio of the ethnic groups who sustain a stroke in SA described by De Villiers *et al* (2011:345) and Connor, Modi and Warlow (2009:355), a higher number of patients within the Caucasian ethnic group were included in the sample group compared to previous published studies (De Villiers *et al* 2011:345; Connor *et al* 2009:355). Despite the fact that patients were recruited from seven (7) public and private rehabilitation centres, the Coloured (2.0%) and Indian (1.0%) ethnic groups included in the study sample were not according to the national representation of the racial groups in SA. A possible explanation for the variance in the ethnic groups of the sample group compared to De Villiers *et al* (2011:345) and Connor *et al* (2009:355) may be that these studies were done on patients in geographical areas in which Indian and Coloured people do not reside.

The number of patients in the current cross-sectional survey who didn't receive any formal schooling, were marginally less (5.9%) compared to the cross-sectional survey reported (7.4%) by Kusambiza-Kiingi, Maleka and Ntsiea (2017:1). In the current cross-sectional survey, a higher number of patients completed primary school (9.8%), Grade 12 (21.6%) and had tertiary education (27.5%) compared to the educational level described by Kusambiza-Kiingi *et al* (2017:1). The cross-sectional survey by Kusambiza-Kiingi *et al* (2017:1) found that a lower number of patients completed primary school (7.4%), Grade 12 (13.9%) and had tertiary education (5.6%) compared to the current study. In comparison to the cross-sectional survey by Kusambiza-Kiingi *et al* (2017:1), a higher number of patients in the current study were employed (66.3%) compared to a lower number of patients that were unemployed (6.9%) at the time of the stroke. The cross-sectional survey by Kusambiza-Kiingi *et al* (2017:1) found a higher unemployment rate (55.0%) compared to only 17.0% of patients that were employed in the current study. A similar number of patients in the current cross-sectional survey were retired (26.7%) compared to the cross-sectional survey reported (28.0%) by Kusambiza-Kiingi *et al* (2017:1). A possible explanation for the difference in the educational level and employment rate of the current study's sample group compared to Kusambiza-Kiingi *et al* (2017:1), may be that the studies were done on patients living in different geographical areas. Kusambiza-Kiingi *et al* (2017:1) recruited stroke patients at four *public* community health centres in areas around Johannesburg, Gauteng Province, South Africa. In comparison to the cross-sectional survey by Kusambiza-Kiingi *et al* (2017:1), patients in the current study were recruited at seven *public* and *private* rehabilitation centers in Pretoria and Johannesburg, Gauteng Province, South Africa.

With regard to the demographic variables of the sample group of the current study, the side affected post-stroke ratio of patients was 1.8 (64.7% left versus 35.3% right hemiplegia) compared to Kusambiza-Kiingi *et al* (2017:1) who indicated a side affected post-stroke ratio of 1.1 (53.0% left versus 47.0% right hemiplegia). A higher number of patients who sustained a right brain stroke (left hemiplegia) than a left brain lesion (right hemiplegia) (66 left versus 36 right hemiplegia) were included in the current study's sample group compared to the cross-sectional survey which reported 57 left versus 51 right hemiplegia, by Kusambiza-Kiingi *et al* (2017:1). Ninety percent (90.2%)

of the current sample group were right hand dominant prior to the stroke which falls within the expected distribution of hand dominance of the general population (Scharoun and Bryden 2014:1).

The number of patients in the current study who suffered an ischaemic (63.7%) or haemorrhagic (16.7%) stroke were marginally less compared to the findings of Daffue, Joubert and Otto (2016:1) who indicated that the prevalence of type of stroke suffered by stroke survivors in South Africa were 67.8% ischaemic and 32.2% haemorrhagic. Information on the type of stroke suffered by patients (N=20) who participated in the current cross-sectional survey could not be obtained. The reason for this lack of information on the type of stroke is that patients participating in the current study were referred to the rehabilitation centres in which the study was conducted, by multiple private and public acute healthcare facilities, including rural community clinics. Information on the type of stroke did not accompany the patient to the rehabilitation centre at all times. No valid conclusion can be drawn on the prevalence of ischaemic or haemorrhagic stroke suffered by patients in the sub-acute phase post-stroke due to the fact that 19.6% of the respondents' type of stroke suffered, were unknown.

Hemispheric (28.4%) and subcortical (20.6%) strokes were the most common areas in which the patients in the current survey had their strokes. No valid conclusion can be drawn on the prevalence of hemispheric or subcortical stroke suffered by patients in the sub-acute phase post-stroke because 31.4% of the respondents' area of their stroke were unknown. Unavailability of information related to the area of stroke may be attributed to the fact that although CT scans are part of the gold standard diagnostic procedure of an acute stroke, CT scans are done in less than 50.0% of patients presenting with stroke in sub-Saharan Africa (Adeloye 2014:1). Thus, the unavailability and/or high costs of cranial CT imaging may result in limited information on the location of the lesion post-stroke (Adeloye 2014:1). Another contributing factor to the unavailability of information is that patients were referred to the rehabilitation centres by multiple private and public acute healthcare facilities which included rural community clinics. Information on the area of stroke does not accompany the patient to the rehabilitation centre at all times.

The HIV-status of 28 out of the 102 patients in the phase 1 cross-sectional survey were known of which 13.7% were HIV-positive. No information could be obtained on the HIV-status of 74 patients. In three (3) of the seven (7) rehabilitation centres, a confidentiality policy exist that does not allow disclosure of patients' HIV-status in their medical records. Although 72.5% of the patients' information on their HIV-status were unavailable, the prevalence of HIV-positive stroke patients (13.7%) recruited to participate in the study was higher than the 6.2% reported by Tipping, de Villiers, Wainwright, Candy and Bryer (2007:1320).

In summary, the biographical variables related to age, gender, race (African ethnic group) and occupation of the study sample were a valid representation of the South African population who sustain a stroke, compared to the findings of previous published studies (The SASPI Project Team 2004:627; De Villiers *et al* 2011:345; Mudzi *et al* 2012:765; Kusambiza-Kiingi *et al* 2017:1). Although the race of patients who participated in the current study coincided with the ethnic groups described by De Villiers *et al* (2011:345) and Connor *et al* (2009:355), a higher number of patients within the Caucasian ethnic group were included in the sample group compared to previous published studies (De Villiers *et al* 2011:345; Connor *et al* 2009:355). A possible explanation for the variance in the ethnic groups of the sample group compared to De Villiers *et al* (2011:345) and Connor *et al* (2009:355) may be that the studies were done on patients living in different geographical areas and the fact that the surveys conducted by these authors were not limited to private and public rehabilitation centres.

A higher number of patients in the phase 1 cross-sectional survey completed primary school, Grade 12, had tertiary education and were employed compared to the findings of Kusambiza-Kiingi *et al* (2017:1) who found a lower educational level and employment rate in their study sample. A possible explanation for the difference in the educational level and employment rate of the current study's sample group compared to Kusambiza-Kiingi *et al* (2017:1), may be that the studies were done on patients living in different geographical areas. Kusambiza-Kiingi *et al* (2017:1) recruited stroke patients at four public community health centres in areas around Johannesburg,

Gauteng Province, South Africa compared to the current study that recruited patients at seven public and private rehabilitation centers in Pretoria and Johannesburg, Gauteng Province, South Africa. Despite the fact that patients were recruited from seven (7) public and private rehabilitation centres, a higher number of patients who sustained a right brain stroke (left hemiplegia) than a left brain lesion (right hemiplegia) (64.7% left versus 35.3% right hemiplegia) were included in the current study's sample group compared to the cross-sectional survey by Kusambiza-Kiingi *et al* (2017:1). Kusambiza-Kiingi *et al* (2017:1) reported a relatively equal distribution of left versus right hemiplegia (53.0% left versus 47.0% right hemiplegia) in their study sample. No valid conclusion can be drawn on the prevalence of the type (ischaemic versus haemorrhagic) and area (hemispheric versus subcortical) of stroke suffered by patients in the sub-acute phase post-stroke due to the fact that 19.6%-31.4% of the respondents' information related to the type and area of their stroke were unknown in the current study.

In the following sections, the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke determined during the cross-sectional survey are discussed.

6.3. PREVALENCE OF CLINICAL FEATURES ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

The phase 1 cross-sectional survey was conducted to achieve the first aim of the study namely to determine the prevalence of the clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke. Results of the cross-sectional survey demonstrated a high prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke (Table 4.11). Although a high prevalence of multiple clinical features and activity limitations were observed in patients in the current survey, each clinical feature and activity limitation is discussed holistically to interpret both the prevalence and the possible interrelation

between these clinical features and activity limitations measured in the current survey to demonstrate a pattern of impairment that may reveal more insight into central vestibular dysfunction in post-stroke patients in the sub-acute phase.

The prevalence of the clinical features associated with central vestibular dysfunction on the level of body structure and function are discussed in relation to the literature in Section 6.3.1.

6.3.1. LEVEL OF BODY STRUCTURE AND FUNCTION

The first clinical feature associated with central vestibular dysfunction on the level of body structure and function discussed in relation to the literature, is oculomotor control.

6.3.1.1. Oculomotor control

The three features of oculomotor control assessed in the current study were smooth pursuit eye movement, saccadic eye movement and static visual acuity. Smooth pursuit eye movement impairment is the first oculomotor impairment to be discussed.

(i) Impairment of smooth pursuit eye movement

In the current study, smooth pursuit eye movement impairment was the clinical feature associated with central vestibular dysfunction, with the highest prevalence (97.1%-99.0%) observed in patients. Results indicated that irrespective of the side and area of stroke, a high prevalence of smooth pursuit eye movement of both eyes into the left (97.1%-99.0%) and right (97.1%-98.0%) visual fields were observed. The generation of smooth pursuit eye movements into the left and right visual fields involve the visual cortex, medial temporal area, MST, FEF, dorsolateral pontine nuclei, cerebellum, vestibular and ocular motor nuclei (Strupp *et al* 2014:542). Based on the anatomy, functional role and structural neural connectivity of the *bilateral* structure and organisation of the central vestibular system (Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions within these brain regions result in smooth pursuit eye movement impairment in *both* visual fields due to central vestibular dysfunction post-stroke. The high prevalence of smooth pursuit eye movement impairment of both eyes into the left and right visual fields thus indicate that impaired

smooth pursuit eye movement is a strong indication of the presence of central vestibular dysfunction in patients in the sub-acute phase post-stroke.

The high prevalence of smooth pursuit eye movement impairment (97.1%-99.0%) identified in the current study is supported by Jang *et al* (2018:727) who investigated the structural neural connectivity of the vestibular nuclei using DTT. Jang *et al* (2018:727) demonstrated a hundred percent (100%) connectivity between the vestibular nuclei and the cerebellum, thalamus, oculomotor nucleus, trochlear nucleus, abducens nucleus and reticular formation (Section 1.1.2). These connected brain regions relate 100% to the functions of the vestibular nuclei and thus the control over eye movements (Brandt and Dieterich 2017:352; Jang *et al* 2018:727). In all brain regions investigated by Jang *et al* (2018:727), no significant difference ($P>0.05$) in connectivity of the vestibular nuclei was observed between the right and left hemispheres. The increased prevalence of smooth pursuit eye movement impairment observed within the current study sample are further supported by Kikuchi and Yamasoba (2007:59) who demonstrated a 100% prevalence of smooth pursuit eye movement impairment in patients with VSCIs (N=5) (Section 2.3.1.1).

Findings of Kikuchi and Yamasoba (2007:59) indicated that although a 100% prevalence of smooth pursuit eye movement impairment were observed in their study, none of the patients demonstrated any abnormality of saccadic eye movements or optokinetic nystagmus. Findings of their study (Kikuchi and Yamasoba (2007:59) demonstrated that impairment of saccadic eye movements and optokinetic nystagmus may not be evident unless a patient presents with an extensive cerebellar lesion. The symptoms and signs of VSCIs may mimic similar symptoms and signs to benign peripheral vestibular disorders, except that smooth pursuit eye movement was also impaired in patients with VSCIs. Findings of the study by Kikuchi and Yamasoba (2007:59) therefore support findings of Jang *et al* (2018:727) that central vestibular dysfunction in patients post-stroke may be identified by the presence of the clinical features of oculomotor function, specifically smooth pursuit eye movement impairment.

In the current study, only three (3) patients with cerebellar lesions were included in the study sample. Although only three percent (2.9%) of the study sample presented with cerebellar lesions, Olivito *et al* (2017:9) demonstrated that patients with unilateral

cerebellar lesions showed a specific pattern of diffusion changes within the white matter architecture of the middle cerebellar peduncle (MCP) and the superior cerebellar peduncle (SCP). It is important to highlight that despite the presence of a unilateral lesion, microstructural changes with no corresponding abnormalities visible on a MRI scan, were present *bilaterally* in the MCP and the SCP (Olivito *et al* 2017:9). The findings of Olivito *et al* (2017:9) demonstrated that *bilateral* changes in the microstructure of the cerebellar peduncles is associated with a unilateral cerebellar lesion. This finding suggested that impairment of smooth pursuit eye movement in both visual fields may also be attributed to diffuse *bilateral* microstructural changes in the cerebellum post-stroke.

Based on the preceding discussion the researcher concludes that a high prevalence of smooth pursuit eye movement impairment of *both* eyes into the left and right visual field in patients in the sub-acute phase post-stroke, indicates the presence of central vestibular dysfunction in these patients.

The second impairment of oculomotor function to be discussed is the impairment of saccadic eye movement.

(ii) Impairment of saccadic eye movement

In the current study, the standard parameters used to measure saccadic eye movement included latency, velocity and accuracy of saccadic eye movements of both eyes into the left and right visual fields. Results of the cross-sectional survey indicated that an almost similar prevalence of impaired latency and accuracy of saccadic eye movement across both visual fields. Patients demonstrated impaired latency of both eyes into the left (59.8%-70.6%) and right (56.9%-59.8%) visual fields. Similar to the prevalence of impaired latency of saccadic eye movements, patients demonstrated impaired accuracy of both eyes into the left (60.8%-70.6%) and right (53.9%-58.8%) visual fields. The prevalence of impaired velocity of saccadic eye movement observed in patients in the cross-sectional survey were lower than the prevalence of impaired latency and accuracy of saccadic eye movement. Patients demonstrated impaired velocity of both eyes into the left (27.5%) and right (7.8%-15.7%) visual fields.

The generation of saccadic eye movements into the left and right visual fields involves the parietal and frontal cortices, basal ganglia, thalamus, superior colliculus, cerebellum, brainstem reticular formation and oculomotor nuclei (Munoz 2002:89). The *left* and *right* oculomotor nuclei send signals directly to the medial rectus muscles for an inward eye movement and to the adjacent abducens nuclei via the descending pathway of the MLF to the PPRF for outward eye movement. The abducens nuclei also contain internuclear inhibitory neurons that project back up the MLF to the *contralateral* oculomotor nucleus, to inhibit the medial rectus muscles that is responsible for inward eye movement to allow for the maximum activation of the lateral rectus muscles for outward eye movement (Tyler *et al* 2015:173). Based on the anatomy, functional role and structural neural connectivity of the *bilateral* structure and organisation of the central vestibular system (Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions within these brain regions result in saccadic eye movement impairment (latency, velocity and accuracy) in *both* visual fields due to central vestibular dysfunction post-stroke.

Although previous studies have described the relationship between saccadic eye movement impairment and stroke (Dong *et al* 2013:337; Carrick *et al* 2016:3), the researcher did not find any publication that differentiated between the parameters of saccadic eye movement parameters that include latency, velocity and accuracy. Previous published literature (Catz *et al* 1997:175; Ciuffreda *et al* 2007:155; Ciuffreda *et al* 2008:18; Rowe *et al* 2009:188; Pollock *et al* 2011:2; Rowe *et al* 2011:406; Dong *et al* 2013:337; Rowe *et al* 2013:2; Siong *et al* 2014:438; Willard and Lueck 2014:75; Carrick *et al* 2016:3; Herron 2016:72; Rizzo *et al* 2017:12) grouped all saccadic eye movement parameters under a single clinical feature, namely ‘eye movement disorders’ or ‘impaired saccadic eye movements’ when they reported on the prevalence of impairment of oculomotor control specifically impaired saccadic eye movement post-stroke. Based upon the articles reviewed (Table 2.4), the reported prevalence of saccadic eye movements in patients post-stroke ranged between 3.1% (Rowe *et al* 2013:2) and 77.1% (Herron 2016:72). The difference in the reported prevalence of saccadic eye movements in patients post-stroke may be attributed to the respective assessment methods used in the studies by Rowe *et al* (2013:2) and Herron (2016:72). The method of assessment of saccadic eye movement used by Rowe *et al* (2013:2) was based upon observation only compared to Herron (2016:72)

who identified saccadic eye movement impairment using an occupational therapy vision screening tool developed by an interdisciplinary team that included occupational therapists and an optometrist. Although Herron (2016:72) stated that the occupational therapy vision screening tool was developed by an interdisciplinary team and piloted prior to the study, the psychometric properties of the vision screening tool were not determined prior to the study (Section 2.3.1.1). The third impairment of oculomotor control to be discussed is reduced static visual acuity.

(iii) Reduced static visual acuity

Results of the current survey indicated that similar to smooth pursuit and saccadic eye movement impairment, patients presented with decreased static visual acuity across both visual fields. Patients demonstrated decreased static visual acuity of the left eye with right eye occluded (25.5%), the right eye with left eye occluded (18.6%) and both eyes (11.8%). Visual information travels from the retina to the primary visual cortex (V1) via long-range white matter tracts where visual information is then processed (Figure 2.3) (Raz and Levin 2014:1). The V1 are *connected* by the occipital-callosal fiber tract via the corpus callosum and is the structure through which the flow of information *between* the two hemispheres takes place (Raz and Levin 2014:1). Based on the bilateral structure and organisation of the visual pathway and central vestibular system (Raz and Levin 2014:1; Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions within these brain areas result in reduced static visual acuity of *both eyes* which indicate central vestibular dysfunction post-stroke.

Although previous studies have described the relationship between static visual acuity impairment and stroke (Rowe *et al* 2011:406), the researcher did not find any publication that differentiated between the static visual acuity of both eyes, left eye (right eye occluded) and right eye (left eye occluded) (Table 2.5). Previous published literature (Lotery *et al* 2000:221; Edwards *et al* 2006:45; Rowe *et al* 2009:188; Rowe *et al* 2011:406; Naeem 2012:55; Shrestha *et al* 2012:46; Siong *et al* 2014:438; Hepworth *et al* 2015:146) reported the presence of impaired visual acuity as a single

clinical feature in 15.0%-70.0% of post-stroke patients with central vestibular dysfunction.

Based upon the articles reviewed (Table 2.5), the reported prevalence of impaired static visual acuity in patients post-stroke ranged between 15.0% (Siong *et al* 2014:438) and 70.0% (Edwards *et al* 2006:45) (Section 2.3.1.1). Similarly to impairment of saccadic eye movement discussed (par (ii)), the difference in the reported prevalence of reduced static visual acuity in patients post-stroke may be attributed to the respective assessment methods used in the studies by Edwards *et al* (2006:45) and Siong *et al* (2014:438). The method of assessment of reduced static visual acuity used by Siong *et al* (2014:438) was the LogMAR chart, compared to Edwards *et al* (2006:45) who used the MIS Pocket Vision Guide. The LogMar chart is regarded as the gold standard for the assessment of visual acuity (Noushad *et al* 2012:87) and was therefore used to quantify patients' static visual acuity in both phases of the current survey. Although Edwards *et al* (2006:45) indicated that the MIS Pocket Vision Guide presented with well-documented reliability and validity, results of their study (Edwards *et al* 2006:45) may have reflected the sensitivity of the measure that led to the possibility of increased false positives (type I error) that resulted in an inflated level of impairment and as such, increased prevalence of impaired static visual acuity observed in their study sample.

Findings of a study by Willis *et al* (2013:1049) indicated an association between reduced static visual acuity and vestibular dysfunction in individuals ≥40 years (N=4590). Of the 2.8% (2.3-3.3) (95% CI) of the study population that reported a history of stroke, 2.6% (2.0-3.1) (95% CI) presented with normal vision, 4.9% (2.6-7.3) (95% CI) with uncorrected refractive error and 8.5% (2.8-14.2) (95% CI) with visual impairment defined as static visual acuity worse than 20/40 after refraction (Willis *et al* 2013:1049). Willis *et al* (2013:1049) demonstrated that reduced static visual acuity and uncorrected refractive error were associated with vestibular dysfunction that resulted in impaired balance (measured with eyes closed on a foam surface). Willis *et al* (2013:1049) hypothesised that reduced visual information due to reduced visual acuity or uncorrected refractive error may weaken the VOR that results in decreased ability to maintain balance. Although the association between reduced static visual acuity and vestibular dysfunction has been established by Willis *et al* (2013:1049), the evaluation of visual acuity and the vestibular system were limited to the use of an

autorefractor containing built-in visual acuity charts and the Romberg test of standing balance on a firm or compliant (foam) surface. No objective vestibular assessment was included in the battery of tests used to determine the possible association between static visual acuity and central vestibular dysfunction post-stroke.

(iv) Summary of the prevalence of impairment of oculomotor control in post-stroke patients in the sub-acute phase

The increased prevalence of impairment of gain of smooth pursuit and saccadic eye movement and reduced static visual acuity observed in the current cross-sectional survey may be attributed to a visual-vestibular activation-deactivation pattern of the central vestibular system post-stroke (Dieterich and Brandt 2008:2538). A visual-vestibular activation-deactivation pattern may be observed due a vestibular tone imbalance in the central vestibular system post-stroke (Becker-Bense *et al* 2014:1355). Dieterich and Brandt (2008:2538) had demonstrated that a stroke may result in significantly reduced activation of the multisensory vestibular cortex in the ipsilateral hemisphere. Activation of the similar areas in the contralateral hemisphere may also be diminished due to the disruption of the interhemispheric transcallosal connections and bilateral ascending vestibular pathways from the vestibular nuclei to the vestibular cortex areas caused by the stroke. Following a stroke, the rCGM increases in the multisensory vestibular cortical and subcortical areas, but simultaneously also significantly *decreases* in the visual and somatosensory cortex areas (Dieterich and Brandt 2008:2538; Brandt *et al* 2014:47). Patients in the sub-acute phase post-stroke may therefore demonstrate a visual-vestibular activation-deactivation pattern which results in altered excitability of the V1. As V1 receives visual information from the contralateral visual hemi-field, stroke patients may thus exhibit impairment of oculomotor control in both visual fields (Becker-Bense *et al* 2014:1355).

It is important to highlight that although stroke patients may exhibit impaired smooth pursuit and saccadic eye movement and reduced static visual acuity in both visual fields, an asymmetry between the left and right visual fields were observed in patients in the current cross-sectional survey. Patients presented with an increased prevalence of impaired oculomotor control within the left visual field. Within the left visual field, the largest prevalence of impaired oculomotor control included impairment of gain of

smooth pursuit and saccadic eye movement (latency, velocity and accuracy) of the ***right eye into the left visual field*** and static visual acuity of the ***left eye (right eye occluded)***.

As it is well established that visual stimulation in the left or right visual field project unilaterally to the contralateral hemisphere (Figure 2.3), the increased prevalence of impaired oculomotor control observed in the left visual field may be partly attributed to the increased number of patients with right hemisphere versus left hemisphere damage included in the study sample (64.7% versus 35.3%) (Table 4.3).

Lastly, the increased prevalence of impaired oculomotor control in both visual fields may be attributed to diffuse bilateral microstructural changes in the cerebellum post-stroke (Olivito *et al* 2017:9). Olivito *et al* (2017:9) demonstrated that efferent fibres from the cerebellum *crosses* at the level of the midbrain and project to the motor and associative cortices via the thalamus (central vestibular system). Within the bilateral structure and organisation of the central vestibular system (Figure 1.2), the cerebellum receive, optimise and send the information back (feedback and feedforward systems) that it receives from cerebral cortex regions via *parallel* cortico-cerebellar loops to accomplish motor and cognitive functions successfully (Olivito *et al* 2017:9). Olivito *et al* (2017:9) hypothesised that cerebellar white matter changes that may occur secondary to the presence of cerebellar damage post-stroke may affect the cerebello-cortical interaction that result in *hypo*function of supratentorial brain regions. Patients with *hypofunction* of supratentorial brain regions due to impaired cerebello-cortical interaction may demonstrate various clinical features associated with central vestibular dysfunction, such as the impairment of oculomotor control, higher vestibular function and sensorimotor balance, mobility and gait. Impairment of higher vestibular dysfunction as a clinical feature associated with central vestibular dysfunction is discussed in relation to the literature in Section 6.3.1.4. Impairment of sensorimotor balance, mobility and gait as an activity limitation associated with central vestibular dysfunction is discussed in relation to the literature in Section 6.3.2.1.

The prevalence of impairment of reflexive control of gaze as a clinical feature associated with central vestibular dysfunction on the level of body structure and function in relation to the literature is discussed in Section 6.3.1.2.

6.3.1.2. Reflexive control of gaze

The two features of reflexive control of gaze assessed in the current study were VOR-gain and DVA (Section 1.1.3.1). Dysfunction of VOR-gain as the first aspect of reflexive control of gaze is discussed first.

(i) Vestibular-ocular reflex gain dysfunction

Patients in the current study presented with left VOR-gain dysfunction (41.2%) compared to right VOR-gain dysfunction (59.8%). The largest prevalence of VOR-gain dysfunction in patients were right vestibular *hyper*function (47.1%). The higher prevalence of right vestibular *hyper*function may be attributed to the possible presence of diffuse cerebellar lesions observed through increased (hyperactive) VOR diagnosed with horizontal vHIT (Choi *et al* 2018:90).

Similar to smooth pursuit eye movement impairment, the higher prevalence of right vestibular *hyper*function (47.1%) identified in the study are supported by Olivito *et al* (2017:9) who investigated the pattern of pathological changes of cerebellar white matter microstructure in patients with focal cerebellar lesions using dMRI-based tractography. Findings by Olivito *et al* (2017:9) demonstrated that post-stroke patients may present with microstructural white matter changes in the cerebellum which may not be visible on a conventional MRI scan. Patients may thus present with vestibular *hyper*function due to impaired cerebello-cortical interaction as result of bilateral changes in the microstructure of the cerebellar peduncles post-stroke.

The increased prevalence of vestibular hyperfunction due to the possibility of the presence of diffuse cerebellar lesions, are also supported by findings by Becker-Bense *et al* (2014:1355) which indicated that the reflexive stabilization of the eyes and head are mediated by the infrathalamic brainstem and cerebellar centers. Previous published research (Inagaki and Hirata 2017:827) had indicated that the cerebellar flocculus is responsible for the adaptive control of the VOR (Section 2.5.1.2). It is thus postulated that the increased gain of the VOR may be due to cerebellar disinhibition as result of Purkinje cell activity post-stroke (Balaban *et al* 2012:101; Inagaki and Hirata 2017:827). The asymmetry between left and right VOR-gain dysfunction may also be attributed to an imbalance of the resting discharge of the VN complexes on

both sides of the brainstem as result of an acute unilateral vestibular de-afferentation, as result of a stroke. This imbalance may also be enhanced by a decrease of spontaneous firing rate and sensitivity of the Type I VN neurons observed in the ipsilesional medial VN and an increased inhibitory drive from the contralesional side through the inhibitory commissural pathways (Lacour *et al* 2016:54).

Although previous studies have described the relationship between VOR-gain dysfunction and stroke (Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279), the researcher did not find any publication that differentiated between left and right vestibular *hypo*function and vestibular *hyper*function. Previous published literature (Park *et al* 2013:1576; Rowe *et al* 2013:2; Chen *et al* 2014:83; Kim *et al* 2014:121; Baek *et al* 2015:279) mentioned a single clinical feature, namely 'impaired gaze holding' or 'impaired VOR-gain' when they reported on the prevalence of VOR-gain dysfunction post-stroke. Based upon the articles reviewed (Table 2.6), the reported prevalence of VOR-gain dysfunction in patients post-stroke ranged between 5.0% (Rowe *et al* 2013:2) and 100.0% (Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279). The difference in the reported prevalence of VOR-gain dysfunction in patients post-stroke may be attributed to the respective assessment methods used in the studies by Park *et al* (2013:1576), Rowe *et al* (2013:2), Kim *et al* (2014:121) and Baek *et al* (2015:279). The method of assessment of 'impaired gaze holding' used by Rowe *et al* (2013:2) was based upon observation only. In comparison to Rowe *et al* (2013:2), Park *et al* (2013:1576) and Kim *et al* (2014:121) implemented the HIT using the search coil system and Baek *et al* (2015:279) performed a bedside HIT to measure VOR-gain dysfunction in the respective study samples. The absence of objective measurement of the VOR-gain of patients post-stroke may result in limited accuracy in the measurement of the VOR-gain compared to the detailed assessment of the VOR using objective measures such as the vHIT (Section 2.4.1.2). Although all three (3) case studies (Park *et al* 2013:1576; Kim *et al* 2014:121; Baek *et al* 2015:279) indicated a hundred percent (100%) VOR-gain dysfunction in patients post-stroke, the study samples of these case studies were limited to only four (4) patients with cerebellar lesions. The results of the studies by Park *et al* (2013:1576), Kim *et al* (2014:121) and Baek *et al* (2015:279) thus limit the generalisability of the findings to patients who suffered isolated cerebellar strokes only.

Impairment of dynamic visual acuity as the second aspect of reflexive control of gaze is discussed secondly.

(ii) Impairment of dynamic visual acuity

Results of the current cross-sectional survey indicated that the prevalence of impaired dynamic visual acuity in post-stroke patients in the sub-acute phase ranged between 58.8% and 65.7%. Approximately two-thirds (65.7%) of the study sample presented with impaired dynamic visual acuity defined as a decrease of ≥0.2 logMAR (dynamic visual acuity minus static visual acuity). Fifty-nine percent (58.8%) presented with impaired dynamic visual acuity defined as visual acuity worse than 0.5 LogMAR during ≥ 2Hz horizontal head rotation.

Chau, Menant, Hübner, Lord and Migliaccio (2015:1) investigated the prevalence of BPPV, peripheral and central vestibular *hypofunction* in individuals aged ≥50 years who had experienced dizziness within the past year (N=76). Results of the study by Chau *et al* (2015:1) indicated a prevalence of *vestibular hypofunction* (horizontal SCC) (46.7% ipsilateral; 0% contralateral) and BPPV (horizontal SCC) (13.0% ipsilateral; 23.1% contralateral) based upon the outcome of the assessment of dynamic visual acuity.

The reported prevalence of impaired dynamic visual acuity (58.8%-65.7%) in post-stroke patients in the sub-acute phase observed in the current study are supported by Niwa *et al* (2015:203). During an extensive literature review (Table 2.7), only one non-randomised case control study (Niwa *et al* 2015:203) was found that investigated the prevalence of impairment of dynamic visual acuity in patients post-stroke. Niwa *et al* (2015:203) indicated that 60.0% of patients presented with impaired dynamic visual acuity post-stroke (Section 2.3.1.1). Although the reported prevalence of dynamic visual acuity impairment in patients post-stroke is similar to the prevalence reported in the current study, the study by Niwa *et al* (2015:203) posed several limitations. The study sample of Niwa *et al* (2015:203) included 40 post-stroke patients and 321 control subjects. Although the 40 patients who sustained a stroke were in-patients between 39 years and 86 years old, the time between onset of stroke and assessment of dynamic visual acuity, ranged between 28 days to 7070 days. The study sample therefore included patients both in the ‘early reorganization’ and ‘later reorganization’

phase post-stroke (Section 1.1.4.1). The results of the study by Niwa *et al* (2015:203) thus limit the translation of their findings to the current study as the researchers did not differentiate the study sample between patients that were in the sub-acute or chronic phases post-stroke.

(iii) Summary of the prevalence of impairment of reflexive control of gaze in post-stroke patients in the sub-acute phase

The VOR is responsible for the detection of head rotation followed by the generation of compensatory eye movements that undergo inhibition and excitation to stabilise images on the fovea of the eye to allow for clear vision during head movements. Impairment of VOR-gain results in a retinal slip which leads to a reduction in dynamic visual acuity post-stroke (Schubert *et al* 2008:500). Patients with vestibular disorders who present with impaired dynamic visual acuity post-stroke may experience oscillopsia, decreased independence in ADLs, limited social interactions and increased isolation (Herdman *et al* 2003:819).

The *cerebellum,* specifically the cerebellar flocculus and fastigial nuclei, play an important role in the modulation of the VOR and regulation of vestibular and oculomotor function (Wallace and Lifshitz 2016:153). Post-stroke patients may present with diffuse microstructural ischemic changes in the *cerebellum* which may not be visible on a conventional MRI scan (Olivito *et al* 2017:9). Although these diffuse microstructural ischemic changes in the cerebellum may not be visible on a conventional MRI scan, patients may continue to demonstrate impaired reflexive control of gaze during the assessment of VOR-gain (≥ 2Hz vHIT) and dynamic visual acuity. Impaired reflexive control of gaze (VOR-gain dysfunction and reduced dynamic visual acuity) may be attributed to impaired cerebello-cortical interaction due to bilateral changes in the microstructure of the *cerebellar* peduncles post-stroke. Impaired reflexive control of gaze may also be attributed to an imbalance of the resting discharge of the VN complexes on both sides of the brainstem as the result of an acute unilateral vestibular de-afferentation post-stroke. This imbalance of the resting discharge of the VN complexes may also be enhanced by a decrease of spontaneous firing rate and sensitivity of the Type I VN neurons observed in the ipsilesional medial

VN and an increased inhibitory drive from the contralesional side through the inhibitory commissural pathways between the structures that make up the central vestibular system (Lacour *et al* 2016:54; Brandt and Dieterich 2017:352; Jang *et al* 2018:727).

The prevalence of impairment of the saccule, inferior vestibular nerve function and utricle, as well as superior vestibular nerve, function as clinical features associated with central vestibular dysfunction on the level of body structure and function in relation to the literature are discussed.

6.3.1.3. Impairment of saccule, inferior vestibular nerve function and utricle, superior vestibular nerve function

The otolith organs (saccule and utricle) provide sensory neural input related to linear head acceleration (Wallace and Lifshitz 2016:153). The *saccule* senses linear movements of the head in the vertical plane compared to the *utricle* that senses linear head movements in the horizontal plane (Wallace and Lifshitz 2016:153). Another role of the otolith organs is to convey information related to a number of reflexes that include the vestibulo-spinal reflex (VSR), vestibulocollic reflex (VCR) and the cervico-collic reflex (CCR) (Section 1.1.3.1). The VSR are intimately involved in postural control and balance through the LVST and MVST (Keshner 2007:65) (Section 2.3.2.1). The LVST originates from the *vestibular nuclei* and extends the entire length of the spinal cord to transport information related to spinal and leg musculature involved in balance strategies (ankle, hip and stepping). The VSR is thus responsible for the generation of antigravity postural motor activity and protective extension primarily in the lower extremities in response to changes of head position, specifically during locomotion (Wallace and Lifshitz 2016:153). The VCR is a righting reflex that acts on the neck muscles to decrease head oscillations and stabilise the head in space during rapid and dynamic body movements (Wallace and Lifshitz 2016:153). Findings of McCall *et al*'s study (2017:1) indicate that VCR is mediated through the *otolith organs* and MVST that originates from the *vestibular nuclei* and provide input to the neck muscles and segments that contain upper limb motor neurons (McCall *et al* 2017:1) (Section 2.3.2.1). The CCR acts on deep neck muscles to also facilitate head stabilisation during head and body movements. It is important to emphasise that

rotation of the body with the head stabilised elicits CCR, whereas head rotation with the body stabilised elicits the VOR (Section 6.2.1.2).

Impairment of the saccule, inferior vestibular nerve function and utricle, superior vestibular nerve function in post-stroke patients in the sub-acute phase may thus result in impairment of sensorimotor balance, mobility and gait post-stroke. Post-stroke patients with impaired sensorimotor balance, mobility and gait may thus present with deficits in functional balance and the ability to modify gait in response to changing task demands post-stroke due to the impairment of the otolith receptors or the pathway of the vestibular reflexes (Rosengren and Colebatch 2018:481). Impairment of sensorimotor balance, mobility and gait as an activity level limitation associated with central vestibular dysfunction is discussed in relation to the literature in Section 6.3.2.1.

(i) Impairment of saccule and inferior vestibular nerve function

In the current cross-sectional survey, the prevalence of impairment of saccule and inferior vestibular nerve function was measured using air conduction cVEMPs (Section 1.1.3.1). Sixty one percent (60.8%) of the study sample presented with an absent left cVEMP compared to 56.9% who presented with an absent right cVEMP. The increased prevalence of bilateral saccule and inferior vestibular nerve impairment observed in the current study may be attributed to a central vestibular tone imbalance in patients in the sub-acute phase post-stroke (Becker-Bense *et al* 2014:1355; Becker-Bense *et al* 2016:1). The central vestibular tone imbalance may result in unilateral disruption of the inhibitory corticobulbar projections to the vestibular nuclei in post-stroke patients (Miller *et al* 2014:2070). The inhibition of the vestibular nuclei may further lead to an imbalance in the descending vestibular drive to the cervical motor neuron pools. This imbalance in the descending vestibular drive to the cervical motor neuron pools may result in an absent or abnormal cVEMP (Miller *et al* 2014:2070). Due to the *bilateral* structure and commissural connections between the 'structures' / areas of the central vestibular system (Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions within the central vestibular system that include the brainstem and cerebellar circuits, vestibular thalamic pathways, vestibulospinal tracts and the vestibular cortical network (Cronin *et al* 2017:538), may result in saccule

and inferior vestibular nerve function impairment post-stroke. It is important to highlight that although findings of Schlindwein *et al* (2008:19) indicated that cVEMP stimulation lead to the activation of the multisensory cortical vestibular network within *both* hemispheres, the saccular vestibular projection observed were predominantly ipsilateral with a predominance of the right hemisphere in right side dominant individuals. A minimal asymmetry between left (65.7%) and right (61.8%) cVEMP were observed in patients in the current study. The asymmetry between left versus right saccule and inferior vestibular nerve function impairment observed in the current study may thus be partly attributed to the increased number of patients with right versus left hemisphere impairment (64.7% versus 35.3%) (Table 4.3) included in the current study sample.

The prevalence of saccule and inferior vestibular nerve impairment (61.8%-65.7%) observed in the current study are higher in comparison to findings by Kim *et al* (2016:2424) and Chen and Young (2003:990) (Section 2.3.1.3). Findings by Kim *et al* (2016:2424) indicated that 28.9% of post-stroke patients presented with saccule and inferior vestibular nerve function impairment. The study sample of Kim *et al* (2016:2424) was restricted to 45 (N=45) patients with lateral medullary infarction. In contrast, findings by Chen and Young (2003:990) demonstrated that 78.6% of post-stroke patients presented with saccule and inferior vestibular nerve function impairment. The study sample of Chen and Young (2003:990) were limited to only seven (7) patients with brainstem stroke. None of the study samples included patients that sustained either a hemispheric, subcortical or cerebellar stroke (Kim *et al* 2016:2424; Chen and Young 2003:990). The results of the studies by Chen and Young (2003:990) and Kim *et al* (2016:2424) thus limit the generalisability of the findings to only patients that suffered isolated brainstem strokes.

Findings of Scarpa, Gioacchini, Cassandro, Tulli, Ralli and Cassandro (2019:298) indicated that abnormal cVEMPs for patients with vestibular neuritis (Figure 1.1) ranged from 36.6% to 51.0%. Abnormal cVEMPs were observed in 40.0% to 69.0% of patients with Ménière's disease (Scarpa *et al* 2019:298). Scarpa *et al* (2019:298) also demonstrated that 23.5% to 52.4% of patients with BPPV demonstrated abnormal cVEMPs.

The second impairment to be discussed in relation to the literature is utricle and superior vestibular nerve function impairment.

(ii) Impairment of utricle and superior vestibular nerve function

The prevalence of impairment of utricle and superior vestibular nerve function was measured using air conduction oVEMPs (Section 1.1.3.1). Results of the current cross-sectional survey indicated a high prevalence of *bilateral* utricle and superior vestibular nerve function impairment, irrespective of the side and area of stroke (97.1%). Ninety-two percent (92.2%) of the study sample presented with an absent left oVEMP compared to 91.2% that presented with an absent right oVEMP. The increased prevalence of bilateral utricle and superior vestibular nerve function impairment observed in the current study are supported by previous published findings (Oh *et al* 2016:210; Wallace and Lifshitz 2016:153). Findings of Wallace and Lifshitz (2016:153) indicate that vestibular information is primarily processed in the brainstem via afferent fibers of the vestibulocochlear nerve (eighth cranial nerve [CN VIII]). Vestibular information enters the brainstem at the medulla and pons (vestibular nuclear complex) which consist of four major vestibular nuclei which include the superior, inferior, medial and lateral vestibular nuclei. From the vestibular nuclei, vestibular input is sent ipsilaterally and contralaterally via the MLF to the oculomotor nuclei and oculomotor cranial nerves III, IV and VI. Thereafter, the extraocular muscles undergo excitation and inhibition that result in conjugate eye movements that are equal to and opposite of head movements to facilitate gaze stabilisation during head movements to ensure clear vision during head motion (Wallace and Lifshitz 2016:153). Vestibular input also travels via the MLF to the midbrain tegmentum which contains the interstitial nucleus of Cajal. Pathways then travel via the dorsolateral thalamic nuclei to multisensory vestibular cortex areas that include the PIVC and the MST of the visual cortex (Figure 1.2). Air-conduction oVEMPs reflect the function of the vestibular nuclei and the VOR pathways mostly contained in the MLF. Due to the *bilateral* structure and commissural connections between the central vestibular system (Brandt and Dieterich 2017:352; Jang *et al* 2018:727), it is suggested that lesions involving the MLF, the *crossed* ventral tegmental tract, *oculomotor nuclei* and the interstitial nucleus of Cajal may result in *bilaterally* impaired oVEMPs (Oh *et al* 2016:210). The high prevalence of bilateral utricle and superior vestibular nerve function impairment in patients in the current cross-sectional survey thus indicate the

presence of central vestibular dysfunction in patients in the sub-acute phase post-stroke.

The prevalence of utricle and superior vestibular nerve function impairment (97.1%) observed in the current study are higher in comparison to findings by Kim *et al* (2016:2424) and Su and Young (2011:923) (Section 2.3.1.3). Findings by Kim *et al* (2016:2424) indicated that 26.7% of post-stroke patients presented with utricle and superior vestibular nerve function impairment. Similar to the measurement of saccule and inferior vestibular nerve function previously discussed, the study sample of Kim *et al* (2016:2424) was restricted to 45 (N=45) patients with lateral medullary infarction. In contrast, findings by Su and Young (2011:923) indicated that 87.5% of post-stroke patients presented with utricle and superior vestibular nerve function impairment. The study sample of Su and Young (2011:923) included 12 patients with cerebellar disorders confirmed by MRI. Of these twelve (12) patients, eight (8) patients presented with extended cerebellar lesions that involved the brainstem compared to four (4) patients that presented with localised cerebellar lesions that excluded the brainstem. Furthermore, within this sample group (N=12), five (5) patients presented with cerebellar stroke compared to seven (7) patients that presented with cerebellar tumour. None of the studies (Kim *et al* 2016:2424; Su and Young 2011:923) included patients that sustained either a hemispheric or a subcortical stroke.

Findings of Scarpa *et al* (2019:298) indicated that abnormal oVEMPs for patients with vestibular neuritis ranged from 60.0% to 80.0%. Abnormal oVEMPs were observed in 16.7% to 50.0% of patients with Ménière's disease (Scarpa *et al* 2019:298). Scarpa *et al* (2019:298) also demonstrated that 25.0% to 56.7% of patients with BPPV demonstrated abnormal oVEMPs.

The prevalence of impairment of higher vestibular function as a clinical feature associated with central vestibular dysfunction on the level of body structure and function in relation to the literature are discussed.

6.3.1.4. Higher vestibular function

The three features of higher vestibular function measured in the current study were impairment of residual oculomotor visual performance, visual-perceptual function and cognitive function. As the findings by Karnath and Dieterich (2006:293), Becker-Bense *et al* (2013:1103), Brandt *et al* (2014:47) and Brandt and Dieterich (2017:352) demonstrated the interrelation of residual oculomotor visual performance and visual-perceptual function, these two features of higher vestibular function are discussed in conjunction. The discussion on 'impairment of cognitive function' follows the discussion in paragraph (i).

(i) Impairment of residual oculomotor visual performance and visual-perceptual function

Results of the current cross-sectional survey demonstrated an increased prevalence of higher vestibular function impairment, which includes impaired velocity (88.2%-90.2%) and accuracy (76.5%-85.3%) of residual oculomotor visual performance in patients post-stroke, irrespective of the side and area of stroke. The prevalence of impairment of residual oculomotor visual performance (76.5%-90.2%) observed in this study is higher compared to the findings of Cate and Richards (2000:326) (Section 2.3.1.5) who indicated that 56.7% of post-stroke patients present with impaired residual oculomotor visual performance. Alternatively, findings by Olk *et al* (2002:306) and Kapoor *et al* (2004:1667) indicated that 100.0% of post-stroke patients present with impaired residual oculomotor visual performance. The difference in the reported prevalence of residual oculomotor visual performance impairment in post-stroke patients may be attributed to the clinical picture of patients that were included in the study samples and the respective assessment methods used in the three (3) studies (Cate and Richards 2000:326; Olk *et al* 2002:306; Kapoor *et al* 2004:1667). Cate and Richards (2000:326) assessed the residual oculomotor visual performance of thirty (30) post-stroke patients and twenty (20) patients without a history of stroke using a 'basic visual skills screening battery'. Olk *et al* (2002:306) used a computerised visual search task and an eye tracker that assessed reaction time, latencies and amplitudes of eye movements. Kapoor *et al* (2004:1667) used a goggle-mounted, infrared limbal reflection eye movement system to assess both basic and 'reading eye movement parameters' and completed a subjective reading-related questionnaire. Both case

studies, one by Olk *et al* (2002:306) and the other by Kapoor *et al* (2004:1667), included only one (1) patient each in their study samples.

The second impairment of higher vestibular function to be discussed in relation to the literature is visual-perceptual dysfunction.

A high prevalence of visual-perceptual dysfunction (97.1%) were observed within the current study sample. The increased prevalence of visual-perceptual dysfunction (97.1%) in patients in the current study are higher compared to findings by previous published literature (Ng *et al* 2005:2138; Gottesman *et al* 2008:1439). Based upon the articles reviewed (Table 2.11), the reported prevalence of visual-perceptual dysfunction in post-stroke patients ranged between 19.1% (Ng *et al* 2005:2138) and 69.6% (Gottesman *et al* 2008:1439). The difference in the reported prevalence of visual-perceptual dysfunction in post-stroke patients may be attributed to the patients included in the study samples and the respective assessment methods used in the two (2) studies (Ng *et al* 2005:2138; Gottesman *et al* 2008:1439). The study sample of the retrospective study by Ng *et al* (2005:2138) was limited to patients with PCA-stroke admitted to a rehabilitation hospital over an eight (8)-year period. The low prevalence reported by Ng *et al* (2005:2138) was based on information obtained from a stroke registry over the eight (8)-year period. The absence of objective measurement of visual-perceptual dysfunction may have resulted in limited accuracy in the identification and quantification of visual-perceptual dysfunction compared to detailed visual-perceptual function assessment using objective measures such as the Star Cancellation Test. Although the method of assessment of visual-perceptual dysfunction used by Gottesman *et al* (2008:1439) consisted of a battery of tests that included the 'Line Bisection Test', 'Copying', 'Line Cancellation Test', 'visual and tactile extinction' and 'oral reading'; the study sample was limited to patients with only a right hemispheric stroke (N=204). Lastly, neither authors, Ng *et al* (2005:2138) nor Gottesman *et al* (2008:1439) mentioned the role of the central vestibular system involved in impaired higher vestibular function, specifically visual-perceptual dysfunction post-stroke based (Section 2.3.1.5).

The increased prevalence of visual-perceptual dysfunction (97.1%) observed in the current study is supported by findings of previous published studies (Karnath and Dieterich 2006:293; Becker-Bense *et al* 2013:1103; Brandt *et al* 2014:47; Arshad *et al*

2015:484; Brandt and Dieterich 2017:352) that investigated the relationship between impaired higher vestibular function, specifically visual-perceptual dysfunction as a result of central vestibular dysfunction and stroke. Findings of the studies by Karnath and Dieterich (2006:293), Becker-Bense *et al* (2013:1103), Brandt *et al* (2014:47) and Brandt and Dieterich (2017:352) demonstrated that the increased prevalence of residual oculomotor visual performance impairment and visual-perceptual dysfunction were interrelated. A stroke may result in both a vestibular tone imbalance and damage to the multisensory orientation (MSO) centers. As a result of the vestibular tone imbalance and damage to the MSO-centers, patients in the sub-acute phase post-stroke may present with impaired higher vestibular function, which include impaired residual oculomotor visual performance and visual-perceptual dysfunction within the contralesional visual field due to the increased activation from the MSO center in the contralesional hemisphere and decreased inhibition from the ipsilateral visual cortex via interhemispheric transcallosal connections (Brandt *et al* 2014:47). Increased visual-spatial attention within the ipsilateral visual field may be observed due to the increased activation from the non-dominant MSO in the contralesional hemisphere and decreased inhibition from the ipsilateral visual cortex (Brandt *et al* 2014:47). Despite having preserved visual fields, patients may thus spontaneously direct their eye movements, head movements and spatial attention to the ipsilesional visual field that further results in decreased stimuli in the contralateral visual field that may further contribute to impaired higher vestibular function specifically to visual-perceptual dysfunction (Brandt *et al* 2014:47).

The increased prevalence of impairment of residual oculomotor visual performance (76.5%-90.2%) and visual-perceptual dysfunction (97.1%) observed in the current study are also supported by findings by Arshad *et al* (2015:484). Arshad *et al* (2015:484) demonstrated that increased interhemispheric competition post-stroke may modulate V1 excitability and inhibition via top-down control. Patients in the sub-acute phase post-stroke may therefore present with impaired velocity and accuracy of residual oculomotor visual performance and visual-perceptual dysfunction due to the altered excitability of the V1 post-stroke. Similar to findings related to the impairment of oculomotor control (Section 6.2.1.1) and otolith function (see Section 6.2.1.3), Arshad *et al* (2015:484) demonstrated that the extent of an individual's right hemisphere dominance is directly related to their higher vestibular function and

excitability of V1. Right hemisphere damage post-stroke may therefore result in a visuo-vestibular interaction (Roberts *et al* 2017:2329) that may further influence a stroke patient's higher vestibular function which include residual oculomotor visual performance (velocity and accuracy) and visual-perceptual function post-stroke. As previously mentioned, the inclusion of more right hemisphere impaired patients (64.7% versus 35.3% left hemisphere impaired patients) (Table 4.3) in the sample group, may be associated with the increased prevalence of higher vestibular function observed within the current study.

The third impairment of higher vestibular function to be discussed in relation to the literature is the impairment of cognitive function.

(ii) Impairment of cognitive function

Results of the current cross-sectional survey indicated that irrespective of the side and area of stroke, a prevalence of cognitive impairment (82.4%) was observed within the current study sample. In the current study, 42.2% of the 82.4% of post-stroke patients measured on the MMSE presented with mild cognitive impairment while 38.2% presented with moderate cognitive impairment. Only 2.0% of the 82.4% in the study sample presented with severe cognitive impairment in the sub-acute phase post-stroke. The prevalence of cognitive impairment (82.4%) in post-stroke patients observed in the current study are higher compared to the findings of Påhlman *et al* (2011:1952). Påhlman *et al* (2011:1952) indicated that 38.7% of post-stroke patients present with impaired cognitive function measured on the MMSE. The increased prevalence of cognitive impairment identified in the current study is supported by findings from previous published literature (Hitier *et al* 2014:59; Bigelow and Agrawal 2015:83; Smith 2017:84). Hitier *et al* (2014:59) suggest that four (4) different pathways are responsible for the transmission of vestibular information to cortical areas involved in higher vestibular functions, namely: (1) the vestibulo-thalamo-cortical pathway; (2) a pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex; (3) a pathway via the nucleus reticularis pontis oralis, the supramammillary nucleus to the medial septum to the hippocampus; and (4) a possible pathway via the cerebellum and the ventral lateral nucleus of the thalamus (to the parietal cortex). Bigelow and Agrawal (2015:83), Smith (2017:84) and Kamil *et al* (2018:765) support the findings of Hitier *et al* (2014:59) that

central vestibular dysfunction may result in atrophy of areas within the cortical vestibular network that may include the hippocampus that is responsible for higher vestibular function of spatial cognition, memory and visuospatial ability (Bigelow and Agrawal 2015:83). The role of the vestibular system and cognition are also supported by Jang *et al* (2018:727) that indicated a high structural neural connectivity between the vestibular nuclei and the thalamus (100%), cerebellum (100%), reticular formation (100%), hypothalamus (86.5%) and posterior parietal cortex (75.7%) using DTT. Therefore, the increased prevalence of impairment of cognitive function observed in the study sample may indicate the possible presence of central vestibular dysfunction in patients in the sub-acute phase post-stroke.

(iii) Summary of the prevalence of impairment of higher vestibular function in post-stroke patients in the sub-acute phase

Apart from the role of the peripheral vestibular system to provide sensory neural input related to angular and linear head motion via the VOR, the vestibular system also plays an important role in higher vestibular function that include residual oculomotor visual performance, visual-perceptual function and cognition (Hitier *et al* 2014:59). Results of the current cross-sectional survey indicated a high prevalence of visual-perceptual dysfunction (97.1%) in post-stroke patients in the sub-acute phase. A high prevalence of smooth pursuit eye movement impairment (97.1%-99.0%) (Section 6.2.1.1) and utricle and superior vestibular nerve function impairment (97.1%) (Section 6.2.1.3) were also observed in the current study. Brandt *et al* (2014:1) demonstrated that the underlying mechanisms of higher vestibular function involves multisensory convergence at the level of the *vestibular nuclei*. As the motor output of the vestibular system runs via the vestibular nuclei through ascending fibres to the *oculomotor nuclei* to mediate the VOR, the fibres also run from the brainstem and the thalamus to several multisensory cortical areas in the temporo-parietal regions and posterior insula which is responsible for higher vestibular function which include motion perception and spatial orientation (Brandt *et al* 2014:1). As the brain regions responsible for the various clinical features associated with central vestibular dysfunction that include oculomotor control (Section 6.2.1.1), reflexive control of gaze (Section 6.2.1.2), otolithic function (Section 6.2.1.3), and higher vestibular function (Section 6.2.1.4)

overlap, the high prevalence of impairment of higher vestibular function, smooth pursuit eye movement, utricle and superior vestibular nerve function may indicate the presence of central vestibular dysfunction in post-stroke patients.

The prevalence of anxiety and/or depression post-stroke as a clinical feature associated with central vestibular dysfunction on the level of body structure and function in relation to the literature are discussed.

6.3.1.5. Level of anxiety and depression post-stroke

Results of the current cross-sectional survey indicated that two-thirds (66.7%) of the study sample presented with mild to severe *anxiety* compared to 56.9% that presented with mild to severe *depression* post-stroke. The prevalence of increased anxiety (66.7%) and depression (56.9%) observed in the current study are higher compared to the findings of Edwards *et al* (2006:45) and Ali *et al* (2013:133). Findings by Edwards *et al* (2006:45) and Ali *et al* (2013:133) indicated that the prevalence of anxiety and depression in post-stroke patients ranged between 31.0% (Edwards *et al* 2006:45) and 53.0% (Ali *et al* 2013:133). The difference in the reported prevalence of anxiety and depression in post-stroke patients may be attributed to the respective assessment methods used in the two (2) studies (Edwards *et al* 2006:45; Ali *et al* 2013:133). The outcomes measure / instrument with which Edwards *et al* (2006:45) assessed the level of anxiety and depression, was the Geriatric Depression Scale–Short Form while Ali *et al* (2013:133) used the EQ-5D. The EQ-5D is a visual analogue scale that enable patients to assess their own level of mobility, self-care, 'usual' activities, anxiety/depression and pain/discomfort. The EQ-5D is thus a combined score that also quantifies patients' perceived quality of life and is thus not a true reflection of only their perceived level of anxiety and depression. The retrospective study by Ali *et al* (2013:133) used anonymised stroke trial data from the acute ischemic, intracerebral haemorrhage and rehabilitation sections of the Virtual International Stroke Trials Archive (VISTA) to determine whether visual impairments influence the functional outcome and quality of life of post-stroke patients.

The increased prevalence of anxiety (66.7%) and depression (56.9%) observed in the current study are supported by findings from previous published literature (Nagaratnam *et al* 2005:253; Rajagopalan, Jinu, Sailesh, Mishra, Reddy and Mukkadan 2017:11). Rajagopalan *et al* (2017:11) suggest that patients' emotional well-being are modulated by extensive networks between the vestibular and limbic systems. The vestibular system has projections to the limbic system, insula, cingulate gyrus, hippocampus, parabrachial nucleus network via the brainstem and cerebellum, diencephalic centers, amygdala, dorsal raphe and the locus coeruleus which are important structures involved in the regulation of a patient's emotional state (Rajagopalan *et al* 2017:11). The findings by Rajagopalan *et al* (2017:11) are supported by Nagaratnam *et al* (2005:253) which indicated that the increased prevalence of anxiety and depression may be explained by overlapping and interacting brainstem pathways of both the vestibular system and the centre that controls psychopathology. The neuroanatomical link between the vestibular system and the centre that controls psychopathology includes the parabrachial nucleus network in the brainstem (Nagaratnam *et al* 2005:253). The parabrachial nucleus network is under the control of the higher cortical centres that receive input from the vestibular nuclei via the thalamo-cortical projections and is also the site of convergence of vestibular, somatic and visceral information pathways. The parabrachial nucleus is also connected to the central amygdaloid nucleus, infralimbic cortex and hypothalamus which are the regions involved in avoidance conditioning, anxiety and conditioned fear. The parabrachial nucleus is further connected to the brainstem respiratory centre and other regions that control the parasympathetic and sympathetic connections that are involved in the control of expression of emotions and the behavioural manifestation of anxiety disorder (Nagaratnam *et al* 2005:253).

It is important to highlight that the vestibulo-thalamo-cortical pathway is not only involved in the concurrent symptoms of vestibular dysfunction and anxiety, but is also a pathway for the transmission of vestibular information to cortical areas involved in higher vestibular function such as visual-perceptual function and cognition (Section 6.2.1.4). Findings of the study by Becker-Bense *et al* (2013:1103) also highlighted the involvement of the vestibulo-thalamo-cortical pathways, specifically visual acuity, in patients with central vestibular dysfunction following a lateral medullary stroke. A

central vestibular lesion may affect the vestibular nucleus on one side of the central vestibular system that results in acute impairment by interrupting the ascending vestibulo-thalamo-cortical pathways to the thalamus and cortex on the ipsilateral side, as well as vestibular projections to the contralateral vestibular nucleus and the ipsilateral vestibular-cerebellar structures (vestibulo-cerebellar tract). An error signal to the cortex results in downregulation in parts of both cortical sensory systems resulting in the visual areas more downregulated than the multisensory vestibular areas. The primary visual and motion-sensitive visual cortical areas are downregulated in both cortical hemispheres to suppress blurred vision as result of oscillopsia caused by spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction as result of a lateral medullary stroke (Becker-Bense *et al* 2013:1103).

Interestingly, the number of patients that presented with increased anxiety (66.7%) and depression (56.9%) were almost similar to the number of patients who presented with impairment of dynamic visual acuity (58.8%-65.7%) (Section 6.2.1.2), saccule and inferior vestibular nerve function (61.8%-65.7%) (Section 6.2.1.3). As a result of the vestibular tone imbalance of the central vestibular system and possible interruption of the vestibulo-thalamo-cortical pathways and vestibulo-cerebellar tract post-stroke (Becker-Bense *et al* 2013:1103), patients may thus present with multiple clinical features associated with central vestibular dysfunction.

The prevalence of activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke determined during the current cross-sectional survey are discussed in Section 6.3.

6.4. PREVALENCE OF ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

The first activity limitation associated with central vestibular dysfunction on the level of activity and participation discussed in relation to the literature was impairment of sensorimotor balance, mobility and gait.

6.4.1. Impaired sensorimotor balance, mobility and gait

The two features of sensorimotor balance, mobility and gait measured in the current study were the impairment of functional balance and the ability to modify gait in response to changing task demands. The impairment of functional balance is discussed in relation to the literature in paragraph (i).

(i) Impairment of functional balance

Results of the current survey indicated that irrespective of the side and area of stroke; an increased prevalence of impairment of functional balance (87.3%) were observed within the study sample. More than two-thirds (68.6%) of the study sample presented with a high risk for falling (measured with the BBS) due to impaired functional balance in the sub-acute phase post-stroke. Nineteen percent (18.6%) of the study sample presented with a medium risk for falling compared to only 12.8% of patients that presented with a low fall risk post-stroke. Based upon previous published literature reviewed (Table 2.14), the reported prevalence of impaired functional balance in post-stroke patients ranged between 59.5% (De Haart *et al* 2004:886) and 100.0% (Wee and Hopman 2005:604).

The prevalence of functional balance impairment (87.3%) observed in the current study are higher compared to findings of De Haart *et al* (2004:886) (59.5%). Although the study sample of De Haart *et al* (2004:886) included only patients in the sub-acute phase post-stroke (time post-stroke ranged from 3.3 to 24.1 weeks), the method of assessment of impaired functional balance used by De Haart *et al* (2004:886) was based on a trunk control score determined by the sitting balance item of the Trunk Control Test. A patient's trunk control was categorised as "disturbed" if a patient was unable to maintain balance in sitting while seated over the edge of a bed with feet lifted off the ground for a period of 30 seconds. In contrast, findings of Wee and Hopman (2005:604) indicated that all patients in their study sample (N=313) presented with impaired functional balance (100.0%) measured on the BBS, post-stroke.

The increased prevalence of impaired functional balance (87.3%) in post-stroke patients observed in the current study were also supported by findings from previous published literature (Marsden *et al* 2005:677; Hain and Helminski 2007:11; Jang *et al* 2018:727). Jang *et al* (2018:727) demonstrated that both the medial and lateral VSTs

that are involved in the control of balance and gait *originate* from the medial and lateral vestibular nuclei. The medial VST originates from the vestibular nuclei at the level of the lower pons where after it descends through the posteromedial region of the medulla oblongata and terminates at the anterior funiculus of the cervical spinal cord. The role of the medial VST is to activate the cervical axial musculature to mediate on-going postural changes or head righting in response to the sensory input (angular head motion) from the SCCs. The lateral VST also originates from the vestibular nuclei where-after the tract descends through the antero-lateral region of the medulla oblongata and terminates at the lateral funiculus through the total length of the spinal cord (Jang *et al* 2018:727). The role of the lateral VST is to generate antigravity postural motor activity and protective extension primarily in the lower extremities in response to changes of the head position that occur as a result of gravity (Hain and Helminski 2007:11).

A stroke may damage the multisensory cortex and the cortical projections to the *vestibular nuclei* that may result in a vestibular tone imbalance. The vestibular nuclei are reciprocally connected via inhibitory commissural connections. A lesion may result in decreased activity on one side of the neuroaxis and may also disinhibit the opposite side of the brainstem centre and thereby increase its excitability (Marsden *et al* 2005:677). Therefore, lesions of the multisensory cortex and vestibular tone imbalance of the central vestibular system as result of a stroke may result in impaired functional balance and altered perception of verticality post-stroke. Patients in the sub-acute phase post-stroke may thus present with a medium to high fall risk that result in further activity and participation limitations identified by the presence of decreased ability to modify gait in response to changing task demands and impaired functional ability (Section 6.3.2). The second impairment of sensorimotor balance, mobility and gait to be discussed in relation to literature is the impaired ability to modify gait in response to changing task demands.

(ii) Impaired ability to modify gait in response to changing task demands

Results of the current cross-sectional survey indicated that irrespective of the side and area of stroke; an increased prevalence of impaired ability to modify gait in response to changing task demands (97.1%) were observed within the study sample. Although

previous studies have described the relationship between the ability to modify gait in response to changing task demands and stroke (Lamontagne and Fung 2009:256; Pimenta *et al* 2017:69), the researcher did not find any publication that indicated the prevalence of impaired ability to modify gait in response to changing task demands of patients in the sub-acute phase post-stroke. Although no previous published literature were found, the increased prevalence of impaired ability to modify gait in response to changing task demands post-stroke in 97.1% of the post-stroke patients observed in the current study, are supported by findings from Gimmon *et al* (2017:3347). Gimmon *et al* (2017:3347) demonstrated that patients may present with impaired gait coordination, even in the absence of an identifiable peripheral vestibular system lesion. Gimmon *et al* (2017:3347) suggest that central vestibular processing is a control parameter regulating gait and may have a greater influence on gait coordination than peripheral vestibular processing. Gait coordination are achieved by neuronal interconnections between central pattern generators in the spinal cord governed by cortical areas (Gimmon *et al* 2017:3347) and therefore patients with central vestibular dysfunction may present with the impaired ability to modify gait in response to changing task demands in the sub-acute phase post-stroke.

It is also important to highlight that apart from the VSR that contributes to postural control and functional balance, the vestibular system is also responsible for the reflexive control of gaze by means of the VOR and smooth pursuit eye movements (Section 6.2.1.2). During locomotion, smooth pursuit eye movements and the VOR stabilise a patient's gaze to ensure adequate visual acuity during gait (Hain and Helminski 2007:2; Goldberg and Cullen, 2011:331; Pimenta *et al* 2017:69). Patients' gaze stability plays an important role in the ability to modify their gait in response to changing task demands. Adaptation of gait, such as turning during locomotion, is preceded by anticipatory components of postural control that include a horizontal gaze and head reorientation in the direction of the turn and then followed by the trunk (Lamontagne and Fung 2009:256). Thereafter the head and trunk are also tilted toward the inner side of the curve of the trunk in preparation of the turn (Lamontagne and Fung 2009:256). Pimenta *et al* (2017:69) support the findings of Lamontagne and Fung (2009:256) that gaze stability is essential to coordinate the movements of the head, trunk and pelvis during gait (Pimenta *et al* 2017:69). Stroke patients may present with impaired coordination of axial segments and pelvic rotations during head rotation,

which may contribute to changes in functional balance during gait (Pimenta *et al* 2017:69) and patients' impaired ability to modify gait in response to changing task demands.

It is important to highlight that the prevalence of decreased ability to modify gait in response to changing task demands were identical to the prevalence of the clinical feature associated with central vestibular dysfunction related to the impairment of higher vestibular function that includes visual-perceptual dysfunction (97.1%) (Section 6.2.1.4). A similar pattern was observed with the prevalence of the clinical features associated with central vestibular dysfunction related to oculomotor control, specifically impairment of smooth pursuit eye movement (Section 6.2.1.1), as well as utricle and superior vestibular nerve function (Section 6.2.1.3). Irrespective of the side and area of stroke, the majority of the study sample presented with an increased prevalence of clinical features associated with central vestibular dysfunction that included impairment of smooth pursuit eye movement (97.1%-99.0%), utricle and superior vestibular nerve function (97.1%) and visual-perceptual dysfunction (97.1%). It may thus be assumed that the increased prevalence of multiple clinical features associated with central vestibular dysfunction may be associated with the increased prevalence of activity limitations characteristic of central vestibular dysfunction that include the impaired ability to modify gait in response to changing task demands.

(iii) Summary of the prevalence of impairment of sensorimotor balance, mobility and gait in post-stroke patients in the sub-acute phase

The increased prevalence of impairment of functional balance (87.3%) and ability to modify gait in response to changing task demands (97.1%) demonstrated a similar pattern to the high prevalence of clinical features of central vestibular dysfunction observed within the study sample (Section 6.2.1.1. to Section 6.2.1.5.). The high prevalence of impaired functional balance and ability to modify gait in response to changing task demands may therefore also be attributed to the interrelation between impaired smooth pursuit eye movement, utricle and superior vestibular nerve function and visual-perceptual dysfunction of patients in the sub-acute phase post-stroke.

Findings of the current study is supported by Lacour *et al* (2018:1) who demonstrated that patients with vestibular dysfunction utilise their oculomotor control, specifically

extraocular signals from eye movements, which include smooth pursuit eye movement, saccadic eye movement and visual fixation to improve their postural control and functional balance. It is important to highlight that the cerebellar flocculus is responsible for both adaptive control of the VOR and also the generation of smooth pursuit eye movements to achieve gaze stability (Strupp *et al* 2014:542). Findings from a study by Schniepp, Möhwald and Wuehr (2017:87) also indicated that the cerebellum, specifically the flocculus, is responsible for the integration of afferent vestibular information and the intermediate cerebellar zones play an important role as the mediators of gait coordination. Schniepp *et al* (2017:87) suggest that future investigations of the flocculus, intermediate and lateral zones of the cerebellum may reveal pathology and related impairments unique to patients with central vestibular dysfunction (Gimmon *et al* 2017:3347). It may therefore be assumed that as a result of the specific brain regions (specifically the cerebellum) involved in oculomotor control, reflexive control of gaze, otolithic function and higher vestibular function overlaps, the increased prevalence of impaired functional balance and ability to modify gait in response to changing task demands may be attributed to the presence of central vestibular dysfunction in the sub-acute phase post-stroke.

The second activity limitation associated with central vestibular dysfunction on the level of activity and participation discussed in relation to the literature is the impairment of functional ability discussed in Section 6.3.2.

6.4.2. Functional ability

Results of the current survey indicated that 98.0% of the study sample presented with impaired functional ability in the sub-acute phase post-stroke. Forty-six percent (46.1%) of the study sample presented with severe dependence on assistance to perform ADLs. Six percent (5.9%) of the study sample required only minimal assistance to complete ADLs compared to two percent (2.0%) that were independent during ADLs. Interestingly the number of patients that were independent during ADLs in the current study (2.0%) were similar to the percentage of patients that presented

with ‘normal’ gain of smooth pursuit eye movements of the left and right eyes into the left and right visual fields (1.0%-2.9%), utricle and superior vestibular nerve function (2.9%), ‘normal’ visual-perceptual function (2.9%) and the ability to modify gait in response to changing task demands (2.9%).

Although previous studies have described the relationship between impaired functional ability and stroke (Lotery *et al* 2000:221; Oliveira *et al* 2011:2043; Bonan *et al* 2013:713; Nijboer *et al* 2013:2021; Kerkhoff *et al* 2014:557; Van Wyk *et al* 2014:856; Bonan *et al* 2015:521), the researcher did not find any publication that indicated the prevalence of impaired functional ability of patients in the sub-acute phase post-stroke. Although no previous published literature was found, the increased prevalence of impaired functional ability post-stroke observed in the current study is supported by Harun *et al* (2015:1). Harun *et al* (2015:1) demonstrated that patients (N=5017) with vestibular dysfunction presented with statistically significant (P<0.0001) impairment in ADLs. Harun *et al* (2015:1) also indicated that patients with vestibular dysfunction had statistically significant difficulty in performing nine (9) different ADLs that included; (i) managing money; (ii) getting in and out of bed; (iii) standing up from an armless chair; (iv) walking up to 10 steps; (v) standing for long periods of time; (vi) walking for a quarter mile (402 meters); (vii) completing house chores; (viii) stooping/crouching/kneeling; and (iv) going out to movies/events (Harun *et al* 2015:1). Although Harun *et al* (2015:1) demonstrated the relationship between the presence of vestibular dysfunction and functional ability, the study did not mention the role of the central vestibular system and the specific clinical features associated with central vestibular dysfunction based on impairment on the level of body structure and function, nor on activity level.

6.5. SUMMARY OF THE PREVALENCE OF THE CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

A high prevalence (97.1%-99.0%) of clinical features associated with central vestibular dysfunction that included the impairment of smooth pursuit eye movement, utricle & superior vestibular nerve function and higher vestibular function, were observed in

post-stroke patients in the sub-acute phase. A high prevalence (87.3%-98.0%) of activity limitations associated with central vestibular dysfunction that included the impairment of functional balance, ability to modify gait in response to changing task demands and functional ability, were observed in post-stroke patients in the sub-acute phase.

Due to the high prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in patients who are in the sub-acute phase post-stroke, it is recommended that all post-stroke patients in the sub-acute phase should undergo an assessment of the central vestibular system to determine the extent to which the clinical features and activity limitations associated with central vestibular dysfunction are present in the patient. Early detection and diagnosis of the presence of central vestibular dysfunction in post-stroke patients may ensure that specific and appropriate treatment strategies be implemented during the early rehabilitation of post-stroke patients to improve their functional outcome in the sub-acute phase post-stroke. In the absence of the diagnosis of central vestibular dysfunction, patients may develop maladaptive sensory strategies in the early months following a stroke in response to the absence of specific management to address vestibular dysfunction post-stroke. Maladaptive sensory strategies such as excessive visual reliance for balance control may result in further activity and participation limitations post-stroke.

6.6. THE EFFECT OF THE INTERVENTIONS ON THE CLINICAL FEATURES AND ACTIVITY LIMITATIONS ASSOCIATED WITH CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

6.6.1. The study population

6.6.1.1. Background

A single-blind cluster randomised controlled trial was conducted to determine the effect of VRT integrated with task-specific activities received by patients in the experimental group, compared to patients who received task-specific activities alone in the control group. Sixty (N=60) patients diagnosed with central vestibular

dysfunction during the cross-sectional survey based on the outcome of the assessment if one or more of the following criteria were fulfilled, which included impaired smooth pursuit and/or saccadic eye movements using VNG (Section 3.1.7) and/or increased (hyperactive) horizontal VOR-gains using vHIT (Section 3.1.7), were included in the single-blind cluster randomised controlled trial. The 60 (N=60) patients were randomly allocated to either an experimental group (N=30) or a control group (N=30) using a formula on a Microsoft Excel program (Van Wyk *et al* 2016:140). The duration of the intervention period was two (2) weeks (Section 3.1.5.2).

6.6.1.2. Demographic data interpretation of phase 2

More than half of the patients (53.3%) who participated in the single-blind cluster randomised controlled trial were patients within the 50 years -69 years age group (De Villiers *et al* 2011:345) followed by 20 years – 49 years age group (23.3%) (Mudzi *et al* 2012:765) and the 70 years - 79 years age group (21.7%). The distribution of patients in the 50 years - 69 years age group was 60.0% in the experimental group (N=18) versus 46.7% in the control group (N=14). Despite the fact that patients were randomly allocated to either intervention groups, the control group consisted of fewer patients in the 20 years – 49 years age group and more patients in the 70 years -79 years age group compared to the experimental group.

The gender ratio of the experimental group was 1.5 (18 males versus 12 females) compared to the control group's gender ratio of 0.6 (11 males versus 19 females). Despite the fact that patients were randomly allocated to either intervention group, the experimental group consisted of more male patients and fewer female patients compared to the control group.

More than half of the patients (65.0%) who participated in the single-blind cluster randomised controlled trial were patients within the African ethnicity race group followed by the Caucasian ethnicity race group (30.0%). The distribution of patients within the African ethnicity race group was 73.3% in the experimental group (N=22) versus 56.7% in the control group (N=17). The distribution of patients within the Caucasian ethnicity race group was 16.7% in the experimental group (N=5) versus 43.3% in the control group (N=13). Despite the fact that patients were randomly

allocated to either intervention groups, the control group consisted of fewer patients within the African ethnicity race group and more patients in the Caucasian ethnicity race group compared to the experimental group.

An equal number of patients (36.7%) in the experimental group and control group completed high school (Grade 8-11). Twenty seven percent (26.7%) of patients in the experimental group compared to 20.0% of patients in the control group completed Grade 12. A nearly equal number of patients in the experimental (20.0%) and control group (26.7%) had tertiary education. An equal number of patients in the experimental group and control group performed either a sedentary (30.0%) or 'medium duty' (16.7%) occupation.

The ratio of right versus left brain impairment of patients in the experimental group was 2.8 (22 versus 8) compared to the control group that presented with a right: left brain impairment ratio of 1.5 (18 versus 12). Despite the fact that patients were randomly allocated to either intervention groups, the experimental group consisted of more patients with right brain impairment and fewer patients with left brain impairment compared to the control group. A fairly equal number of patients in the experimental group (90.0%) and control group (93.3%) were right hand dominant prior to the stroke which falls within the expected distribution of hand dominance of the general population.

Despite the fact that 16.5% of patients' information on the type of stroke were unavailable in their medical records, 60% of patients in the single-blind cluster randomised controlled trial suffered an infarction. The ratio of patients with an ischaemic versus a haemorrhagic stroke in the experimental group was 1.9 (17 versus 9) compared to the control group that presented with an ischaemic versus haemorrhagic stroke ratio of 3.8 (19 versus 5). As patients were referred to the rehabilitation centres (Section 3.1.2) by multiple private and public acute healthcare facilities that included rural community clinics, information on the type of stroke did not always accompany the patient to the rehabilitation centre.

Although 28.3% of patients' information on the area of stroke were unavailable in their medical records, 25% of patients suffered a hemispheric stroke. The ratio of hemispheric versus a subcortical stroke of patients in the experimental group was 1.6 (8 versus 5) compared to the control group that presented with a hemispheric versus

a subcortical stroke ratio of 0.9 (7 versus 8). Unavailable information related to the area of stroke may be attributed to the fact that CT scans are conducted on less than 50.0% of patients presenting with stroke in Sub-Saharan Africa (Adeloye 2014:1). Thus, the unavailability and/or high costs of cranial CT imaging may result in limited information on the location of the lesion post-stroke (Adeloye 2014:1). Another contributing factor to the unavailability of information is that patients were referred to the rehabilitation centres (Section 3.1.2) by multiple private and public acute healthcare facilities that included rural community clinics. Information on the area of stroke does not accompany the patient to the rehabilitation centre at all times.

The HIV-status of only 31.7% of patients was known because three (3) of the seven (7) rehabilitation centres has a confidentiality policy that does not allow disclosure of patients' HIV-status in their medical records.

The median and inter-quartile ranges were used to describe the effect of the intervention on the clinical features and activity limitations associated with central vestibular dysfunction in patients in the experimental and control groups. The Wilcoxon matched-pair signed-rank test was used to determine whether there was a significant difference between baseline and post-intervention measures in the; (a) gain of smooth pursuit eye movement of the left and right eyes into the left and right visual fields using VNG; (b) latency, velocity and accuracy of saccadic eye movement of the left and right eyes into the left and right visual fields; (c) static visual acuity of the left eye, right eye and both eyes; (d) left and right VOR-gain; (e) dynamic visual acuity; (f) left and right cVEMP P1, cVEMP N1 and cVEMP amplitude; (g) speed and accuracy of residual oculomotor visual performance; (h) visual-perceptual function; (i) cognitive function; (j) level of anxiety and/ or depression; (k) functional balance; (l) ability to modify gait in response to changing task demands; and (m) functional ability of patients within the experimental and control groups. The Wilcoxon rank-sum test was used to detect whether there was a significant difference in differences (pre-post) between the experimental group and control group after the intervention. To allow adjustment for possible confounding by differences in age, gender and race in the two groups, the pre and post values, as well as the differences, were ranked to fit linear regression models on the differences and mixed-effect models on pre and post values. Patients were also classified as improved or not, compared to baseline and logistic regression

adjusting for age, gender and race, to compare improved outcomes between the experimental and control groups (Table 5.4. to Table 5.17.).

The mean difference and ranked mean difference of each outcome were used in a linear regression model to determine whether there was statistically significant difference between the two (2) intervention groups. Four (4) linear regressions that included; (a) linear regression of mean difference with and without adjusting for confounding variables of age, gender, race and units; and (b) linear regression of ranked mean difference with and without adjusting for confounding variables of age, gender, race and units were calculated. For each outcome, the original data was also ranked to determine whether normal distribution could be found to fit a mixed-effect model. A mixed-effect model for original data and ranked data was used to assess whether the interaction term of VRT over time differed between groups, which were adjusted for variables of age, gender, race and units. The data analysis of each outcome that included the linear regression of mean difference and ranked mean difference with and without adjusting for confounding variables of age, gender, race and units, as well as the mixed-effect model for original data and ranked data, are presented in Addendum N.

The effect of the interventions on the clinical features associated with central vestibular dysfunction on the level of body structure and function are discussed in relation to the literature in Section 6.7.

6.7. BODY STRUCTURE AND FUNCTION LEVEL

The effect of the interventions of the experimental and control groups on the oculomotor control of patients are discussed in Section 6.7.1.

6.7.1. The effect of intervention on patients' oculomotor control

Results of the single-blind cluster randomised controlled trial demonstrated that *within* the two intervention groups, the experimental group presented with statistically significant improved gain of smooth pursuit eye movement of *both eyes* into the *left*

visual field. The control group also demonstrated statistically significant improved gain of smooth pursuit of the *left eye movement* into the *left visual field* and *right eye* smooth pursuit into the *right visual field*.

When *between-group* difference in smooth pursuit eye movement was assessed, no statistically significant improvement in gain of smooth pursuit eye movement was observed between the two groups post-intervention when adjusted for the confounding factors of age, sex and race. The results indicate that the intervention of VRT integrated with task-specific activities received by patients in the experimental group did not improve the outcome of the gain of smooth pursuit eye movement of the left and right eyes in both left and right visual fields compared to the patients in the control group who received task-specific activities alone. Although no between-group changes were observed, it is important to emphasise that the largest statistically significant change in gain of smooth pursuit eye movement of the right eye into the left visual field (P=0.004) were demonstrated by the experimental group (Table 5.4). Impairment of smooth pursuit eye movement of the *right eye* into the *left visual field* was also the clinical feature with the highest prevalence (99.0%) observed in patients in the cross-sectional survey (Table 4.4).

Within the two intervention groups, the experimental group demonstrated statistically significant improved *latency* and *accuracy* of *left eye* saccadic movement into the *left visual field*. The experimental group also demonstrated statistically significant improved *velocity* of *right eye* saccadic movement into the *right visual field*. The control group showed no statistically significant difference in the latency, velocity and accuracy of saccadic eye movement of both eyes into both visual fields pre-intervention, compared to post-intervention.

When *between-group* difference in smooth pursuit eye movement was assessed, the results indicated when adjusted for the confounding factors of age, sex and race, the intervention of VRT integrated with task-specific activities improved the outcome of the *velocity* and *accuracy* of saccadic eye movement compared to the patients in the control group who received task-specific activities alone. Although statistically significant improvement in saccadic velocity and accuracy were observed, the intervention of VRT integrated with task-specific activities received by patients in the experimental group did not improve the outcome of the latency of saccadic eye

movement compared to the patients in the control group who received task-specific activities alone.

Neither the experimental nor the control group showed statistically significant *within-group* or *between-group* difference in static visual acuity of the left eye with right eye occluded, right eye with left eye occluded or both eyes open post-intervention.

The intervention of VRT integrated with task-specific activities received by patients in the experimental group included exercises to facilitate adaptation of the vestibular system and sensory substitution as well as to improve patients' balance and postural control (Alghadir *et al* 2013:1). The process of substitution facilitates the use of individual or a combination of sensory input such as visual and/or somatosensory (including proprioceptive) information to facilitate vestibular compensation through the process of sensory re-weighting as a result of impaired vestibular input attributable to central vestibular dysfunction (McDonnell and Hillier 2015:3). Substitution through saccadic eye movements were specifically implemented as a process of 'adaptation'. Patients in the experimental group received visual scanning exercises (VSEs) integrated with task-specific activities aimed to facilitate saccadic eye movement substitution (Van Wyk *et al* 2014:856). Visual scanning exercises (VSEs) integrated with task-specific activities consisted of the performance of horizontal, vertical and dynamic saccadic eye movements (visual scanning) while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856; Van Wyk *et al* 2016:140). Saccadic eye movement training activates the superior and inferior rectus muscles of the eye, medial and lateral rectus, inferior and superior oblique extraocular muscles that have reflexogenic connections to the cerebellum (Carrick *et al* 2016:3). The researcher hypothesises that due to the structural neural connectivity between the vestibular nuclei and the cerebellum, oculomotor nucleus, trochlear nucleus, abducens nucleus, thalamus and reticular formation (Jang *et al* 2018:727), inclusion of VSEs integrated with task-specific activities may facilitate vestibular compensation in the 'early re-organisation' phase post-stroke.

It is important to highlight that the cerebellum's inhibitory control on the vestibular nuclei may be modulated in the acute and sub-acute phase (Figure 1.5) of central vestibular dysfunction following a stroke. The presence of a central vestibular lesion may affect the vestibular nucleus on one side of the central vestibular system that

results in acute impairment by interrupting the ascending pathways to the thalamus and cortex on the ipsilateral side, as well as vestibular projections to the contralateral vestibular nucleus and the ipsilateral vestibulo-cerebellar structures. The primary visual and motion-sensitive visual cortical areas are downregulated in both cortical hemispheres to suppress blurred vision as a result of oscillopsia caused by regularly occurring spontaneous gaze-evoked nystagmus in the acute phase of central vestibular dysfunction following a stroke (Becker-Bense *et al* 2013:1103). A stroke may thus result in vestibular tone imbalance in the structures that make up the central vestibular system which result in an increased orientation bias to the ipsilateral visual field on the side of the lesion (Karnath and Dieterich 2006:293; Kerkhoff and Schenk 2012:1072; Brandt *et al* 2014:47). The increased orientation bias to the ipsilateral visual field due to decreased activation of the ipsilateral visual cortex and increased inhibition from the contralateral visual cortex, are also evident in the measurement of patients' oculomotor control (Section 6.3.1.1) and higher vestibular function (Section 6.3.1.5). The researcher hypothesises that inclusion of saccadic eye movement substitution through VSEs integrated with task-specific activities may improve patients' spontaneous exploratory movements of the left and right eye(s), as well as head movement into the left and right visual fields (180º) (Karnath *et al* 1998:2357).

The effect of the interventions on the reflexive control of gaze of patients in the experimental group and control group are discussed in Section 6.7.2.

6.7.2. The effect of intervention on patients' reflexive control of gaze

The neural structure of the VOR is bilateral and symmetric with commissural connections between the two sides of the brainstem, for normal functioning the VOR relies on balanced reciprocal stimulation of vestibular sensors from both sides of the vestibular system. A stroke may cause partial or complete loss of sensory (afferent) input to the central vestibular system which includes the brainstem circuit that may result in an asymmetry in the VOR pathway. Although measurement of the VOR was used in patients with peripheral vestibular dysfunction such as unilateral vestibular de-afferentation after surgery for vestibular schwannoma (MacDougall, McGarvie, Halmagyi, Curthoys and Weber 2013:2), bilateral vestibular loss (for example in idiopathic and previous systemic gentamicin resulting in vestibulotoxicity) (MacDougall

et al 2013:2), vestibular neuritis (MacDougall, Weber, McGarvie, Halmagyi and Curthoys 2009:1134) and in Ménière's Disease (Marques, Manrique-Huarte and Perez-Fernandez 2015:1915) (Figure 1.1), recent findings by Choi *et al* (2018:90) indicate that the measurement of the VOR may aid therapists to localise the lesions in the central vestibular system and facilitate the management of patients with impaired reflexive control of gaze post-stroke.

The VOR gain is quantified as the ratio of the size of the slow phase corrective eye movement response versus the size of the passive head movement stimulus. The ideal VOR gain is 1.0 that indicates the eye movement is exactly equal and opposite of the head movement with the result that the retinal image remains stable during head movement (MacDougall and Curthoys 2012:1). MacDougall *et al* (2009:1134) defined the presence of a VOR deficit and peripheral vestibular system lesion as a gain of less than 0.68. It is important to note that patients with lesions involving the central vestibular system that includes the vestibular nucleus, nucleus prepositus hypoglossi or flocculus may also present with vestibular hypofunction as result of significantly reduced unilateral or bilateral horizontal VOR gains (Choi *et al* 2018:90). Patients with diffuse cerebellar lesions may present with vestibular *hyper*function as result of an increased (hyperactive) horizontal VOR gain (and present with a gain of higher than 1.2) (Choi *et al* 2018:90).

Although the median and interquartile range of *left* VOR-gain of both the experimental group 1.0 (0.8-1.2) and control group 0.7 (0.5--0.9) demonstrated an absence of VOR-gain dysfunction within the two intervention groups, six (6) patients from the experimental group and 11 patients from control group presented with a *left unilateral hypofunction* pre-intervention. The median and interquartile range of *right* VOR-gain of the experimental group 1.3 (1.1-1.6) indicates that a number of patients in the experimental group presented with cerebellar inhibition of the VOR prior to commencement of the intervention. Three (3) patients from the experimental group compared to five (5) patients from the control group 1.0 (0.8-1.3) presented with *right unilateral hypofunction* pre-intervention. *Within* the two intervention groups, the control group demonstrated statistically significant improved *left* VOR-gain (P=0.02) post-intervention. Neither groups demonstrated a statistically significant difference in the right VOR-gain. After the intervention period, the median and interquartile range of the right VOR-gain of the experimental group was 1.5 (1.0-1.7) and in the control group,

1.1 (0.9--1.5). The implication of the results (Table 5.7) is that when the outcome of VOR-gain are adjusted for the confounding factors of age, gender and race, the results indicate that the intervention of VRT integrated with task-specific activities received by patients in the experimental group did not improve the VOR-gain compared to the patients in the control group who received task-specific activities alone.

It is postulated that the increased gain of the VOR observed in the experimental group is caused by the suppression of vestibular signals via LTD (long-term depression) and simultaneous enhancement of eye movement signals via LTP (long-term potentiation) at parallel fiber–Purkinje cell synapses (Inagaki and Hirata 2017:827). The cerebellar flocculus is responsible for the adaptive control of the VOR. Sensory-motor signals are projected from the vestibular nucleus, dorsolateral pontine nucleus, and neurons in the paramedian tract, respectively, via mossy fibers, evoking simple spikes (SSs) in Purkinje cell synapses and transferred to the cerebellar flocculus (Inagaki and Hirata 2017:827). Inhibition of the flocculonodular lobe Purkinje cell protein kinase C (PKC) prevents: (i) adaptive modification of vestibulo-ocular and optokinetic responses (Balaban *et al* 2012:101); and (ii) a compensatory increase in the intrinsic excitability of *medial vestibular nucleus* neurons during early vestibular compensation (Balaban *et al* 2012:101). Purkinje cells may induce cerebellar long-term depression (LTD) by processes that require simultaneous parallel and climbing fiber activity, as well as PKC activation. The PKC-mediated effects on both cerebellar motor learning and oculomotor aspects of vestibular compensation likely include mechanisms in addition to LTD (Balaban *et al* 2012:101). If the enhancement of eye movement signals via LTP (long-term potentiation) at the parallel fiber–Purkinje cell synapses may have resulted in an increased VOR-gain, it is important to also assess whether a change of the features of oculomotor control that include smooth pursuit and saccadic eye movements can be observed in either groups following the intervention period.

Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group comparison*, the experimental group demonstrated statistically significant improved: (a) gain of *smooth pursuit eye movement* of the left eye and right eye into the left visual field (b) *latency* and *accuracy* of *saccadic eye movement* of the left eye into the left visual field; and (c) *velocity* of *saccadic eye movement* of the right eye into the right visual field. In contrast, the control group demonstrated no statistically significant differences of the standard parameters of saccadic eye movements (latency, velocity

and accuracy) post-intervention. With adjustment for the confounding factors of age, gender and race, the results indicate that the intervention of VRT integrated with task-specific activities received by patients in the experimental group improved the outcome of the ***velocity*** and ***accuracy*** of saccadic eye movement compared to the patients in the control group who received task-specific activities alone. Results of the Wilcoxon matched-pair signed-rank test indicated that *within-group comparison*, the control group demonstrated statistically significant improved gain of smooth pursuit eye movements of the left eye into the left visual field and the right eye into the right visual field.

It is postulated that the significantly improved saccadic eye movements of patients in the experimental group may have attributed to the process of adaptation. Adaptation as a process of recovery is referred to in the literature as the processes of **sensory** and **behavioural substitution** (Lacour *et al* 2016:54). The process of sensory substitution refers to the process of possible sensory re-weighting by substituting lost or diminished vestibular function with other sensory input. Sensory re-weighting is a powerful mechanism of recovery and may play a key role in vestibular compensation as vestibular function is a multisensory modality and requires the integration of vestibular, visual, and somatosensory information to facilitate vestibular compensation in the 'early re-organisation' (sub-acute) phase post-stroke (Lacour *et al* 2016:54; Van Wyk *et al* 2016:140; Whitney *et al* 2016:13). The CNS presents with the capability to compensate for vestibular dysfunction and re-weight sensory inputs (Lacour *et al* 2016:54; Van Wyk *et al* 2016:140; Whitney *et al* 2016:13). Becker-Bense *et al* (2013:1103) suggests that a central vestibular lesion may affect one side of the vestibular nucleus and result in acute damage by interrupting the ascending pathways to the thalamus and cortex on the ipsilateral side as well as vestibular projections to the contralateral vestibular nucleus and the ipsilateral vestibulo-cerebellar structures. The cerebellum's inhibitory control on the vestibular nuclei which is mediated by vestibulo-cerebellar networks, can be modulated and occurs mainly in central vestibular disorders. The pattern of visual-vestibular interaction changes and activation processes mainly occur within the brainstem-cerebellar loops of the contralateral healthy side close to the damaged vestibular nucleus (Becker-Bense *et al* 2013:1103).

Behavioural substitution is based on the ability of the CNS to reorganize functionally by the processes of learning and to mimic lost or diminished vestibular functions. An example of behavioural substitution is the generation of saccadic eye movements during fast head movement, which is a saccadic substitution of the normal slow-phase eye movement to prevent oscillopsia during head rotation towards the side of the lesion (Lacour *et al* 2016:54). Increased ***velocity*** and ***accuracy*** of saccadic eye movements may keep the patient's gaze on a target, by generating a ballistic eye movement that reduces the smeared retinal image that may occur during head movements as result of inadequate VOR (MacDougall and Curthoys 2012:1). Saccadic eye movements are generated to substitute for the deficient VOR. It is important to note that no statistically significant differences in latency, velocity or accuracy of saccadic eye movements were noted in the control group following the two-week intervention period. It is thus postulated that patients in the control group did not generate adequate saccadic eye movements to facilitate saccadic substitution to prevent oscillopsia during fast head movements.

Patients with VOR-gain dysfunction present with an inability to keep their gaze stable in space during head motion (Schubert *et al* 2008:500). Impaired gaze stability results in a retinal slip which leads to a reduction in dynamic visual acuity compared to static visual acuity when the head is kept still (Schubert *et al* 2008:500). Patients with vestibular dysfunction may thus present with oscillopsia that is defined as blurred vision (decreased visual acuity) during fast head movements and may thus experience difficulty during ADLs such as difficulty reading signs or recognise faces when walking (Lambert *et al* 2010:820).

Results of the single-blind cluster randomised controlled trial demonstrated that *within* the two intervention groups, the experimental group presented with statistically significant improved dynamic visual acuity post-intervention. Results of the current study are supported by Schubert, Migliaccio, Clendaniel, Allak and Carey (2008:500). Schubert *et al* (2008:500) showed that VRT specifically gaze stability exercises may improve visual acuity during active head rotation (dynamic visual acuity). Improvement in dynamic visual acuity is achieved through two mechanisms that include an improvement in active angular VOR gain and an increase in the number of compensatory saccades generated during active head rotation.

Findings of the study demonstrates that patients with central vestibular dysfunction post-stroke may benefit from a treatment approach such VRT integrated with task-specific activities that focusses on the integration and re-weighting of multisensory information during sensorimotor adaptation following vestibular loss (Carriot, Jamali and Cullen, 2015:1). Saccadic eye movement training with VSEs and gaze stability exercises delivered as part of the VRT-programme may improve patients' VOR-gain independent of peripheral angular VOR gain recovery and the ability to generate compensatory saccadic eye movements to improve gaze stability during active head rotation (Schubert *et al* 2008:500).

The effect of the interventions on the saccule and inferior vestibular nerve function as well as utricle and superior vestibular nerve function of patients in the experimental group and control group are discussed in Section 6.7.3.

6.7.3. The effect of intervention on patients' saccule, inferior vestibular nerve function and utricle, superior vestibular nerve function

The saccular and inferior vestibular nerve function, as well as utricle and superior vestibular nerve function of patients *within* the experimental and control groups, remained relatively unchanged following the two-week intervention period. When *between-group* difference in otolith function was assessed with adjusting for confounding factors of age, gender and race; results indicate that the intervention of VRT integrated with task-specific activities received by patients in the experimental group did not improve the outcome of otolith function compared to the patients in the control group who received task-specific activities alone.

The findings of the current study are supported by Rosengren and Colebatch (2018:481). Rosengren and Colebatch (2018:481) indicate that although recovery of otolith function quantified by air conduction VEMPs may occur following a peripheral vestibular nerve disorder such as vestibular neuritis (Figure 1.1), saccule and inferior vestibular nerve function, as well as utricle and superior vestibular nerve function in patients with central vestibular dysfunction, may remain abnormal or absent even after central vestibular compensation has occurred (Rosengren and Colebatch 2018:481). It is important to emphasise that although otolithic function may remain unchanged

following VRT integrated with task-specific activities, the assessment of saccule and inferior vestibular nerve function, as well as utricle and superior vestibular nerve function using air conduction VEMPs, may aid therapists to localise the lesions in the central vestibular system to facilitate the specific management of these patients post-stroke (Rosengren and Colebatch 2018:481). The effect of the interventions on the higher vestibular function of patients in the experimental group and control group are discussed in Section 6.7.4.

6.7.4. The effect of intervention on patients' higher vestibular function

Results of the single-blind cluster randomised clinical trial demonstrated that *within* the two intervention groups, the experimental group presented with statistically significant improved: (a) *velocity* and *accuracy* of residual oculomotor visual performance; (b) visual-perceptual function; and (c) cognitive function. In contrast, the control group showed no statistically significant improvement in higher vestibular function, which includes residual oculomotor visual performance, visual-perceptual function and cognitive function post-intervention.

When *between-group* difference in higher vestibular function was measured with adjusting for confounding factors of age, gender and race, results indicated that the VRT-intervention integrated with task-specific activities received by patients in the experimental group did not improve the outcome of residual oculomotor visual performance, visual-perceptual function and cognitive function compared to the patients in the control group who received task-specific activities alone.

The findings of the study are supported by research conducted by Dai *et al* (2013:477) and Van Wyk *et al* (2014:856). Dai *et al* (2013:477) indicated that no statistically significant difference were noted *between* the experimental group that received 'conventional rehabilitation' and VRT compared to the control group that received 'conventional rehabilitation' only. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. The physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training (Dai *et al* 2013:477). Occupational therapy included endurance and balance training aimed to improve

independence in ADLs such as bathing, toileting and dressing (Dai *et al* 2013:477). Although no statistically significant difference was noted *between* the groups, significant *within* group improvement was observed post-intervention. Both intervention groups demonstrated statistically significant improved (P<0.000) visual-perceptual function measured by the Rivermead Behavioural Inattention test, functional balance measured by the PASS and functional ability measured by the FIM (Dai *et al* 2013:477).

The study by Dai *et al* (2013:477) posed several limitations. Although the assessment of clinical features and activity limitations associated with central vestibular dysfunction included the assessment of higher vestibular function, functional balance and functional ability using the Rivermead Behavioural Inattention test, PASS and FIM respectively, Dai *et al* (2013:477) did not assess the study samples' oculomotor control (smooth pursuit eye movements, saccadic eye movements and static visual acuity), reflexive control of gaze (VOR-gain dysfunction and dynamic visual acuity), saccule, inferior vestibular nerve function, utricle and superior vestibular nerve function, higher vestibular function (residual oculomotor visual performance and cognition), level anxiety and/or depression.

Findings of the study by Van Wyk *et al* (2014:856) demonstrated statistically significant improvement of residual oculomotor visual performance function (P=0.021) measured by the King-Devick Test©, visual-perceptual function (P=0.016) measured by the Star Cancellation Test and functional ability (P=0.004) measured by the BI *between* the experimental group that received saccadic eye movement training with VSEs integrated with task-specific activities compared to the control group that received task-specific activities only. Although Van Wyk *et al* (2014:856) did not include adaptation exercises aimed to improve VOR-gain, the intervention did include substitutional and habitual exercises aimed to facilitate sensory substitution, improve patients' functional balance and postural control and habituate patients to movement (Alghadir *et al* 2013:1). The intervention of saccadic eye movement training with VSEs integrated with task specific activities implemented may be considered as a component of the VRT-approach (Section 1.1.4). The process of 'substitution' facilitates the use of individual or combinations of sensory input such as visual or somatosensory (including proprioceptive) information to facilitate vestibular compensation through the process of sensory re-weighting due to dysfunctional

vestibular input (McDonnell and Hillier 2015:3). Saccadic eye movement substitution may be achieved by the implementation of VSEs integrated with task-specific activities (Van Wyk *et al* 2014:856). Progression of these exercises is guided by the patient's ability to (a) allocate information-processing resources between two tasks; (b) maintain sufficient attention on the visual scanning task during the dual-task performance of horizontal and vertical saccadic eye movements; and (c) head movement while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856). The rehabilitation programme also included substitution exercises that may alter somatosensory cues, for example, let the patient stand on different surfaces such as standing on foam with eyes open and closed; challenges the vestibular system by letting the patient perform activities with and without visual input; modified center of gravity exercises; and weight-shifting exercises (Whitney *et al* 2016:13). By removing or altering visual/somatosensory cues, the patient is forced to use remaining sensory–motor cues which may result in the fostering of responses by reacting on mainly vestibular cues (Herdman and Whitney 2007:311).

The effect of the interventions on the level of anxiety and depression of patients in the experimental and control groups are discussed in Section 6.7.5.

6.7.5. The effect of intervention on patients' level of anxiety and depression post-stroke

Results of the single-blind cluster randomised controlled trial demonstrated that *within* the two interventions groups, the experimental group presented with statistically significant improved level of anxiety and depression post-intervention. The median and interquartile range for anxiety was 4.00 (2.00-9.00) and depression was 4.00 (2.00-7.00) for the experimental group which indicates that the experimental group's perceived level of anxiety and depression had decreased to within 'normal' range post-intervention compared to pre-intervention (Table 5.14). In contrast, patients in the control group showed no statistically significant difference in their level of anxiety and depression pre-intervention compared to post-intervention. The median and interquartile range for anxiety was 10.00 (6.00-13.00) and depression was 9.00 (5.00-

13.00) for the control group which indicates that their level of anxiety and depression remained largely unchanged after the two (2)-week intervention period (Table 5.14).

During the data base searches, the researcher could not identify any studies that investigated the effect of VRT on patients' level of anxiety and depression as result of central vestibular dysfunction in the sub-acute phase post-stroke.

The effect of the interventions on the activity limitations associated with central vestibular dysfunction on the levels of activity and participation are discussed in relation to the literature in Section 6.8.

6.8. ACTIVITY LEVEL

The effect of the interventions on the sensorimotor control of balance, mobility and gait of patients in the experimental and control groups are discussed in Section 6.8.1.

6.8.1. The effect of intervention on patients' sensorimotor control of balance, mobility and gait

Results of the single-blind cluster randomised controlled trial demonstrated that *within-group* comparison demonstrated statistically significant improvement in the functional balance post-intervention of both the experimental and control groups. Results of the study also indicated that the *between-group* comparison, the experimental group's functional balance (P=0.000) improved significantly more than in the control group post-intervention (Wilcoxon rank-sum test). Although both groups demonstrated a statistically significant improvement in functional balance as measured by the BBS, the median and interquartile range for the experimental group 37.50 (29.00-47.00) compared to the control group 9.50 (3.00-25.00) indicated that the fall risk of patients in the experimental group improved to a medium fall risk compared to the control group that remained a high fall risk pre-intervention compared to post-intervention.

Within-group results further indicated that the experimental group demonstrated a statistically significant greater ability to modify gait in response to changing task demands (P=0.04) post-intervention. The control group showed no statistically

significant difference in the ability to modify gait in response to changing task demands (P=0.47) pre-intervention compared to post-intervention.

Findings of the study is supported by Brown *et al* (2006:76), Balci *et al* (2013:259), Dai *et al* (2013:47), Grill *et al* (2013:1), Schow *et al* (2016:333) and Gimmon *et al* (2017:3347). Findings of Grill *et al* (2013:1) and Gimmon *et al* (2017:3347) indicate that vestibular, visual and proprioceptive (somatosensory system) information is processed by the central vestibular pathways and integrated within the sensorimotor cortex to maintain an individual's sense of balance and position.

Brown *et al* (2006:76) and Balci *et al* (2013:259) administered VRT that consisted of a programme of adaptation, substitutional and/or habitual exercises aimed to re-adjust the gain of the VOR, habituate the patient to movement, facilitate sensory substitution and improve patients' functional balance and postural control (Alghadir *et al* 2013:1). The VRT programme administered by Dai *et al* (2013:477) consisted of vestibular adaptation exercises aimed to improve patients' gaze stability post-stroke. The VRT programme did not include substitutional and/or habitual exercises aimed to facilitate sensory substitution, habituate patients to movement and/or improve their functional balance and postural control (Alghadir *et al* 2013:1).

Findings of Brown *et al* (2006:76) demonstrated statistically significant improvement (P<0.05) of sensorimotor control of balance, mobility and gait specifically functional balance quantified by FTSTS and the ability to modify gait in response to changing task demands quantified by the DGI in patients (N=10) that received VRT post-stroke (Brown *et al* 2006:76). Findings of Balci *et al* (2013:259) indicated that although the sensorimotor control of balance, mobility and gait performance measured by the BBS, TUG, DGI and DHI improved significantly in all patients (within-group), no statistically significant difference were noted *between* the groups that received VRT, visual feedback posturography training or a home exercise programme.

As previously discussed in Section 6.6.4., the findings of the study by Dai *et al* (2013:477) indicated although higher vestibular function specifically visual-perceptual function, functional balance and functional ability improved significantly (P<0.000) in patients (*within-group*) following a right hemispheric stroke, no statistically significant difference were noted *between* the control group (N=24) that received 'conventional rehabilitation' and the experimental group (N=24) that received 'conventional

rehabilitation' and VRT as an add-on intervention over a four-week intervention period. The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai et al (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training.

Findings by Schow *et al* (2016:333) demonstrated statistically significant improvement in functional balance measured by the BESTest ($P<0.001$), gait velocity ($P<0.001$) and binocular visual dysfunction specifically stereopsis ($P=0.0017$), residual ocular visual performance measured by the King-Devick Test ($P<0.001$), near point convergence ($P<0.001$), binocular fusion ($P<0.001$), positive relative vergence distance ($P=0.03$) and positive relative vergence near ($P=0.03$) in patients that received a four-month rehabilitation program that consisted of a combination of balance training and visual therapy. Balance training incorporated individualised vestibular and proprioceptive exercises aimed to improve sensory integration in patients post-stroke. Visual therapy included training of binocularity, visual fixation, visual tracking, convergence, divergence, visual attention, accommodation, eye-hand coordination and binocularity. It is important to highlight that although Schow *et al* (2016:333) incorporated processes of the vestibular rehabilitation approach into the delivered intervention, these authors did not specify the administered intervention as VRT.

Similarly to VOR-gain dysfunction previously discussed (Section 6.6.2), it is postulated that the statistically significant improvement in functional balance and ability to modify gait in response to changing task demands demonstrated by patients in the experimental group may be attributed to the processes of **sensory** and **behavioural substitution** (Lacour *et al* 2016:54). The process of **sensory substitution** refers to the process of sensory re-weighting by substituting lost or diminished vestibular function with other sensory input such as visual and somatosensory information (Lacour *et al* 2016:54; Whitney *et al* 2016:13). Sensory re-weighting is a powerful mechanism of recovery and may play a key role in vestibular compensation because vestibular function is based on multisensory input and requires the integration of vestibular, visual, and somatosensory information (Lacour *et al* 2016:54; Whitney *et al* 2016:13). **Behavioural substitution** is based on the ability of the CNS to reorganise functionally through the processes of learning and to mimic lost or diminished

vestibular functions. An example of behavioural substitution is the generation of saccadic eye movements during fast head movement, which is a saccadic substitution of the normally slow phase eye movement to prevent oscillopsia during head rotation towards the side of the lesion (Lacour *et al* 2016:54).

Findings from a recent study by Lacour, Dosso, Heuschen, Thiry, Van Nechel and Toupet (2018:1) demonstrated statistically significant improved postural control and functional balance measured by the Postural Instability Index ($P<0.05$), Power Spectral Density in the visual frequency part ($P<0.001$) and the fractional Brownian-motion analysis (stabilogram-diffusion analysis, Hausdorff fractal dimension) ($P<0.0001$) during performance of smooth pursuit eye movement, saccadic eye movement and fixation on a visual target in patients with bilateral vestibular hypofunction (N=21). Lacour *et al* (2018:1) hypothesised that improved postural control and functional balance were achieved by the process of **compensatory sensorimotor substitution** by using smooth pursuit eye movement, saccadic eye movement and visual fixation to substitute for the deficient vestibular function. In the current study, the experimental group demonstrated statistically significant improved: (1) gain of smooth pursuit eye movement of both eyes into the left visual field, (2) latency and accuracy of left eye saccadic movement into the left visual field and (3) velocity of right eye saccadic movement into the right visual field. The control group showed no statistically significant difference in the latency, velocity and accuracy of saccadic eye movement of both eyes into both visual fields following the two-week intervention period. The researcher thus hypothesises that the intervention of VRT integrated with task-specific activities administered to patients in the experimental group resulted in statistically significant improved functional balance and ability to modify gait in response to changing task demands through the process of sensory re-weighting (sensory substitution). The researcher further hypothesises that the inclusion of saccadic eye movement substitution through VSEs integrated with task-specific activities may further improve patients' functional balance through the process of behavioural substitution.

The effect of the interventions on the functional ability of patients in the experimental and control groups are discussed in Section 6.8.2.

6.8.2. The effect of intervention on patients' functional ability

Based on the interpretation of the BI, the median and interquartile range for the experimental group's 40.00 (15.00--55.00) compared to the control group's 37.50 (10.00--50.00) at baseline, indicated that patients in both groups presented with **severe dependence** during completion of ADLs prior to the intervention period. *Within-group* results of both the experimental and control groups in the single-blind cluster randomised controlled trial demonstrated statistically significant improvement in their functional ability post-intervention. *Between-group* results of the study also demonstrated that the experimental group demonstrated better functional ability (P=0.04) compared to the control group post-intervention based on logistic regression adjusted for confounding factors of age, gender and race. Although both groups demonstrated a statistically significant improvement in functional ability as measured by the BI, the median and interquartile range for the experimental group 82.50 (70.00--90.00) compared to the control group's 37.50 (20.00--65.00), indicated that the functional ability of patients in the experimental group changed from severe to **moderate dependence** during performance of ADLs compared to patients in the control group that remained severely dependent during ADLs post-intervention.

Findings of the study is supported by Dai *et al* (2013:477) and Van Wyk *et al* (2014:856). Dai *et al* (2013:477) investigated the effect of VRT on patients' functional ability in the sub-acute phase post-stroke. Findings of the study by Dai *et al* (2013:477) indicated that although the functional ability improved significantly (P<0.000) in all patients that presented with visual-perceptual dysfunction following a right hemispheric stroke (*within-group*), no statistically significant differences were noted *between* the groups that received 'conventional rehabilitation' and VRT (N=24) or 'conventional rehabilitation' (N=24). The 'conventional rehabilitation' programme consisted of one (1) hour of physiotherapy and one (1) hour of occupational therapy for five (5) days per week. Dai et al (2013:477) indicated that physiotherapy treatment sessions included active and passive exercises, resistance exercises and ambulation training. Findings of the study by Van Wyk *et al* (2014:856) demonstrated statistically significant improvement of residual oculomotor visual performance function (P=0.021)

measured by the King-Devick Test©, visual-perceptual function (P=0.016) measured by the Star Cancellation Test and functional ability (P=0.004) measured by the BI *between* the experimental group that received saccadic eye movement training with VSEs integrated with task-specific activities compared to the control group that received task-specific activities only.

The researcher thus hypothesises that the significantly improved clinical features associated with central vestibular dysfunction such as oculomotor function (gain of smooth pursuit eye movement, saccadic eye movement [latency, velocity and accuracy]), reflexive control of gaze (dynamic visual acuity), higher vestibular function (residual oculomotor visual performance, visual-perceptual function, cognitive function), anxiety and depression, functional balance and ability to modify gait in response to changing task demands translated to a significantly improved ability to perform ADLs post-stroke in patients in the experimental group that received VRT integrated with task-specific activities.

In summary, *within-group comparison* in patients from the experimental group presented with improved (1) oculomotor function (smooth pursuit eye movements, saccadic eye movements [latency, velocity and accuracy]), (2) reflexive control of gaze (dynamic visual acuity), (3) higher vestibular function (residual oculomotor visual performance, visual-perceptual function, cognitive function), (4) anxiety, (5) depression, (6) sensorimotor control of balance, mobility and gait (functional balance and ability to ability to modify gait in response to changing task demands), and (6) functional ability post-intervention. Patients from the control group presented with improved (1) oculomotor function (smooth pursuit eye movements); (2) reflexive control of gaze (VOR-gain); (3) sensorimotor control of balance, mobility and gait (functional balance); and (4) functional ability following the two (2) week intervention period.

Between-group comparison based on logistic regression adjusted for age, gender and race, patients in the experimental group improved significantly more than the control group in oculomotor function specifically saccadic movement (velocity and accuracy), depression and functional ability.

6.9. SUMMARY

Results of the cross-sectional survey demonstrated a high prevalence of clinical features (97.1%-99.0%) and activity limitations (87.3%-98.0%) associated with central vestibular dysfunction in patients. A high prevalence of clinical features associated with central vestibular dysfunction included impairment of smooth pursuit eye movement, utricle and superior vestibular nerve function and higher vestibular function, were observed. A high prevalence of activity limitations associated with central vestibular dysfunction included impaired functional ability, ability to modify gait in response to changing task demands and functional balance, were observed in the current study. Due to the high prevalence of clinical features and activity limitations associated with central vestibular dysfunction identified in patients who are in the sub-acute phase post-stroke, it is recommended that all post-stroke patients in the sub-acute phase should undergo an assessment of the central vestibular system to determine the extent to which the clinical features and activity limitations associated with central vestibular dysfunction are present in the patient.

Results of the single-blind cluster randomised controlled trial demonstrated that *between-group comparison,* based on logistic regression adjusted for age, gender and race, patients in the experimental group who received VRT integrated with task-specific activities improved significantly more in oculomotor function, specifically saccadic movement (velocity and accuracy), level of depression and functional ability compared to the control group who received task-specific activities alone. Statistically significant improved functional capacity following VRT may be attributed to central compensation mechanisms due to active neuronal changes in the cerebellum and brainstem in response to sensory conflict produced by vestibular pathology. Statistically significantly improvement observed may also have occurred through the process of sensory substitution. Sensory substitution is the mechanism that involves the reweighting of extra-vestibular input facilitated by VRT. The activation of the combination of the superior rectus and inferior oblique extraocular muscles that have reflexogenic connections to the cerebellum may be associated with neural recovery and better functional outcomes post-stroke. Input from the visual system may compensate for the loss of vestibular information and is thus a substitute as a reference for Earth Vertical in controlling posture and trunk stability resulting in improved functional balance.

The conclusion and limitations of the current study are discussed in Chapter 7. The recommendations for further studies are also discussed in Chapter 7.

CHAPTER 7

CONCLUSION, LIMITATIONS OF THE CURRENT STUDY AND SUGGESTIONS FOR FURTHER STUDIES

7.1. INTRODUCTION

In Chapter 7, the conclusion and limitations of the current study are discussed. Suggestions for further studies are also discussed in this chapter.

7.2. CONCLUSION

Post-stroke patients are diagnosed with central vestibular dysfunction when they present with lesions in the brain regions, which involve the vestibular nuclei in the pontomedullary brainstem and the vestibular pathways that project from the vestibular nuclei via the cerebellar peduncles to the vestibulocerebellum. Central vestibular dysfunction is also diagnosed when post-stroke patients suffered lesions in the brainstem, thalamus and multisensory vestibular cortex areas which includes the PIVC and the MST of the visual cortex (Brandt and Dieterich 2017:352). The central vestibular system has a bilateral structural organization with four crossings between the bilateral vestibular nuclei pathways and cortical areas observed. The first two crossings are observed between the vestibular nuclei and at the lower pontine level, superior to the vestibular nuclei. The third and fourth crossings are observed at the midbrain tegmentum and between the PIVC or the MST of the right and left hemispheres through the splenium of the corpus callosum via transcallosal connections.

In the current study, the ICF was selected as the model of disablement within which the patients' levels of impairment, functional activity and participation as a result of the presence of clinical features associated with central vestibular dysfunction, were determined and documented. The clinical features associated with central vestibular dysfunction based on the anatomy and functional role of the bilateral structure and organisation of the central vestibular system were categorised by impairment on the level of body structure and function that included impairment of (1) oculomotor control; (2) reflexive control of gaze; (3) saccule and inferior vestibular nerve function; (4)

utricle and superior vestibular nerve function; (5) higher vestibular function, and (6) anxiety and/or depression. Impairment on activity and participatory level associated with central vestibular dysfunction were categorised by; (1) impaired sensorimotor control of balance, mobility and gait; (2) impaired functional ability; and (3) participation in physical activity post-stroke.

A cross-sectional survey was conducted to achieve the first aim of the study, namely to determine the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke (N=102). Findings of the study indicated a high prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the sub-acute phase post-stroke. A high prevalence of clinical features associated with central vestibular dysfunction, including impairment of smooth pursuit eye movement (97.1%-99.0%), utricle and superior vestibular nerve function (97.1%) and higher vestibular function (97.1%), were observed. A high prevalence of activity limitations associated with central vestibular dysfunction, including impaired functional ability (98.0%), ability to modify gait in response to changing task demands (97.1%) and functional balance (87.3%), were observed in the current study. A summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey which is based on the ICF-model (Lazaro *et al* 2013:187), are presented in Table 7.1.

Table 7.1.: Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function					**Activity and participation level**	
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**			**Activity limitations associated with central vestibular dysfunction**	**Prevalence (%)**
OCULOMOTOR FUNCTION	**Smooth pursuit eye movements**	97.1%-99.0%		**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT**	**Functional balance**	87.3%
	Saccadic eye movements	Latency	56.9%-70.6%		**Ability to modify gait in response to changing task demands**	97.1%
		Velocity	7.8%-27.5%			
		Accuracy	53.9%-70.6%			
	Static visual acuity	Left eye	25.5%			
		Right eye	18.6%			
		Both eyes	11.8%			
REFLEXIVE CONTROL OF GAZE	**VOR-gain**	Left Gain	41.2%	**FUNCTIONAL ABILITY**	**Functional ability**	98.0%
		Right Gain	59.8%			
	Dynamic visual acuity	58.8%-65.7%				

Table 7.1.: (continued) Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey.

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**		
SACCULE AND INFERIOR VESTIBULAR NERVE FUNCTION	**cVEMP**	61.8%-65.7% %		
UTRICLE AND SUPERIOR VESTIBULAR NERVE	**oVEMP**	97.1%		
HIGHER VESTIBULAR FUNCTION(S)	**Residual oculomotor visual performance**	Velocity	88.2%-90.2%	
		Accuracy	76.5%-85.3%	
	Visual-perceptual function	97.1%		
	Cognition	82.4%		

Table 7.1.: (continued) Summary of the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who participated in the cross-sectional survey.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction		**Prevalence (%)**			
ANXIETY AND/OR DEPRESSION	**Level of anxiety and depression**	Anxiety	66.7%		
		Depression	56.9%		

Results indicated that irrespective of the side and area of stroke, a high prevalence (>97%) of impairment of smooth pursuit eye movement, utricle and superior vestibular nerve function and visual-perceptual function were observed in patients in the sub-acute phase post-stroke. As the brain regions responsible for the various clinical features associated with central vestibular dysfunction that include oculomotor control (smooth pursuit eye movement), otolithic function (utricle and superior vestibular nerve function) and higher vestibular function (visual-perceptual function) overlap, the high prevalence of impairment of smooth pursuit eye movement, utricle and superior vestibular nerve function and visual-perceptual function, may indicate the presence of central vestibular dysfunction in post-stroke patients.

After central vestibular dysfunction was diagnosed based on the outcome of the assessment of smooth pursuit or saccadic eye movement using VNG or the assessment of VOR-gain using vHIT during the cross-sectional survey, 60 patients (N=60) were randomly allocated to either an experimental group (N=30) or control group (N=30). Patients in the experimental group received a combination of VRT integrated with task-specific activities as part of the treatment as an “add-on” intervention compared to patients in the control group who received task-specific activities alone during the two (2) week intervention period. Vestibular rehabilitation therapy (VRT) received by the experimental group consisted of an exercise programme that aimed to: (1) improve gaze stabilisation; (2) improve postural stabilisation and sensorimotor control of balance, mobility and gait; and (3) improve functional activities. The main components of the VRT programme were (a) gaze stabilisation exercises to retrain VOR function; (b) VSE integrated with task-specific activities aimed to facilitate saccadic eye movement substitution (Van Wyk *et al* 2014:856); (c) balance retraining exercises as substitution exercises to retrain VSR function; and (d) habituation exercises to reduce motion induced dizziness or vertigo (Balci *et al* 2013:259).

Findings of the single-blind cluster randomised controlled trial demonstrated that within-group, VRT integrated with task-specific activities resulted in statistically significantly improved clinical features associated with central vestibular dysfunction on body structure and function level that includes improved oculomotor function (gain of smooth pursuit eye movements and saccadic eye movements [latency, velocity and accuracy]). The intervention of VRT integrated with task-specific activities resulted in

statistically significant improved reflexive control of gaze (dynamic visual acuity), higher vestibular function (residual oculomotor visual performance, visual-perceptual function and cognitive function), anxiety and depression post-stroke. Findings of the single-blind cluster randomised controlled trial also indicated that within-group, VRT integrated with task-specific activities resulted in statistically significantly improved activity limitations associated with central vestibular dysfunction on activity level that includes improved sensorimotor control of balance, mobility and gait (functional balance and ability to modify gait in response to changing task demands) and functional ability.

Between-group comparison based on logistic regression adjusted for age, gender and race, indicated that patients in the experimental group that received VRT integrated with task-specific activities improved significantly more in oculomotor function, specifically saccadic movement (velocity and accuracy), level of depression and functional ability, compared to patients in the control group who received task-specific activities alone. A summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention, are presented in Table 7.2.

Table 7.2.: Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)									
Level of body structure and function						**Activity and participation level**			
Clinical features associated with central vestibular dysfunction						**Activity limitations associated with central vestibular dysfunction**			
OCULOMOTOR FUNCTION: **Smooth pursuit eye movements**			**Within-group comparison**	**Between-group comparison**		**SENSORIMOTOR CONTROL OF BALANCE, MOBILITY AND GAIT AND FUNCTIONAL ABILITY**		**Within-group comparison**	**Between-group comparison**
Experimental group (N=29)	Left Visual field	Gain of Right Eye	P=0.004	P=0.17		Experimental group (N=30)	Functional balance: Berg Balance Scale	P=0.000	-
Control group (N=28)			P=0.20			Control group (N=30)		P=0.001	
Experimental group (N=28)	Left Visual field	Gain of Left Eye	P=0.04	P=0.32		Experimental group (N=30)	Ability to modify gait in response to changing task demands: Dynamic Gait Index	P=0.04	-
Control group (N=28)			P=0.03			Control group (N=30)		P=0.47	
Experimental group (N=27)	Right Visual field	Gain of Right Eye	P=0.35	P=0.24		Experimental group (N=30)	Functional ability: Barthel Index	P=0.000	P=0.04
Control group (N=28)			P=0.05			Control group (N=30)		P=0.004	
Experimental group (N=27)	Right Visual field	Gain of Left Eye	P=0.81	P=0.16					
Control group (N=28)			P=0.08						

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
OCULOMOTOR FUNCTION: **Saccadic eye movements**			**Within-group comparison**	**Between-group comparison**	
Experimental group (N=26)	Left Visual field	Latency of Left Eye	P=0.01	P=0.75	
Control group (N=30)			P=0.78		
Experimental group (N=28)	Left Visual field	Latency of Right Eye	P=0.70	P=0.13	
Control group (N=30)			P=0.21		
Experimental group (N=27)	Right Visual field	Latency of Left Eye	P=0.13	P=0.90	
Control group (N=30)			P=0.52		
Experimental group (N=29)	Right Visual field	Latency of Right Eye	P=0.08	P=0.85	
Control group (N=29)			P=0.13		

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function						
Clinical features associated with central vestibular dysfunction						
OCULOMOTOR FUNCTION: **Saccadic eye movements**			**Within-group comparison**	**Between-group comparison**		
Experimental group (N=26)	Left Visual field	Velocity of Left Eye	P=0.08	P=0.01		
Control group (N=30)			P=0.53			
Experimental group (N=28)	Left Visual field	Velocity of Right Eye	P=0.06	P=0.08		
Control group (N=30)			P=0.81			
Experimental group (N=27)	Right Visual field	Velocity of Left Eye	P=0.13	P=0.02		
Control group (N=30)			P=1.00			
Experimental group (N=29)	Right Visual field	Velocity of Right Eye	P=0.02	P=0.01		
Control group (N=29)			P=0.90			

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function						
Clinical features associated with central vestibular dysfunction						
OCULOMOTOR FUNCTION: **Saccadic eye movements**			**Within-group comparison**	**Between-group comparison**		
Experimental group (N=26)	Left Visual field	Accuracy of Left Eye	P=0.02	P=0.03		
Control group (N=30)			P=0.92			
Experimental group (N=28)	Left Visual field	Accuracy of Right Eye	P=0.78	P=0.80		
Control group (N=30)			P=0.28			
Experimental group (N=27)	Right Visual field	Accuracy of Left Eye	P=0.15	P=0.18		
Control group (N=30)			P=0.39			
Experimental group (N=27)	Right Visual field	Accuracy of Right Eye	P=0.08	P=0.32		
Control group (N=29)			P=0.22			

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
OCULOMOTOR FUNCTION: **Static visual acuity**			**Within-group comparison**	**Between-group comparison**	
Experimental group (N=26)	Static visual acuity	Left Eye	P=0.53	P=0.53	
Control group (N=29)			P=0.06		
Experimental group (N=27)	Static visual acuity	Right Eye	P=0.66	P=0.61	
Control group (N=27)			P=0.36		
Experimental group (N=28)	Static visual acuity	Both Eyes	P=0.78	P=0.34	
Control group (N=30)			P=0.88		

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
REFLEXIVE CONTROL OF GAZE: Vestibulo-ocular reflex-gain and dynamic visual acuity			**Within-group comparison**	**Between-group comparison**	
Experimental group (N=30)	VOR-gain	Left	P=0.18	P=0.47	
Control group (N=30)			P=0.02		
Experimental group (N=30)	VOR-gain	Right	P=0.44	P=0.70	
Control group (N=30)			P=0.15		
Experimental group (N=26)	Dynamic visual acuity: > 0.5 LogMAR score during ≥ 2Hz horizontal head rotation		P=0.00	P=0.33	
Control group (N=26)			P=0.11		
Experimental group (N=27)	Dynamic visual acuity: Line difference - DVA minus SVA: Decrease of ≥0.2 LogMAR		P=0.11	P=0.45	
Control group (N=26)			P=0.49		

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION: cVEMP		**Within-group comparison**	**Between-group comparison**		
Experimental group (N=14)	cVEMP LEFT P1	P=0.53	P=0.53		
Control group (N=10)		P=0.06			
Experimental group (N=14)	cVEMP LEFT N1	P=0.66	P=0.61		
Control group (N=10)		P=0.36			
Experimental group (N=14)	cVEMP LEFT Amplitude	P=0.78	P=0.34		
Control group (N=10)		P=0.88			

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)				
Level of body structure and function				
Clinical features associated with central vestibular dysfunction				
SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION: cVEMP		**Within-group comparison**	**Between-group comparison**	
Experimental group (N=13)	cVEMP RIGHT P1	P=0.20	P=0.76	
Control group (N=10)		P=0.72		
Experimental group (N=13)	cVEMP RIGHT N1	P=0.48	P=0.53	
Control group (N=10)		P=0.26		
Experimental group (N=13)	cVEMP RIGHT Amplitude	P=0.86	P=0.97	
Control group (N=10)		P=0.72		

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
UTRICLE AND SUPERIOR VESTIBULAR NERVE FUNCTION: oVEMP		**Within-group comparison**	**Between-group comparison**		
Experimental group (N=4)	oVEMP LEFT and RIGHT P1	Due to the high number of patients that presented with an absent oVEMP, neither a Wilcoxon matched-pair signed-rank test nor a logistic regression could be applied.			
Control group (N=1)					
Experimental group (N=4)	oVEMP LEFT and RIGHT N1	Due to the high number of patients that presented with an absent oVEMP, neither a Wilcoxon matched-pair signed-rank test nor a logistic regression could be applied.			
Control group (N=1)					
Experimental group (N=4)	oVEMP LEFT and RIGHT Amplitude	Due to the high number of patients that presented with an absent oVEMP, neither a Wilcoxon matched-pair signed-rank test nor a logistic regression could be applied.			
Control group (N=1)					

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function						
Clinical features associated with central vestibular dysfunction						
HIGHER VESTIBULAR FUNCTION: **Residual oculomotor visual performance**			**Within-group comparison**	**Between-group comparison**		
Experimental group (N=30)	King Devick Sub-test 1:	Time	P=0.004	P=0.23		
Control group (N=30)			P=0.76			
Experimental group (N=30)	King Devick Sub-test 1:	Errors	P=0.01	P=0.82		
Control group (N=30)			P=0.40			
Experimental group (N=30)	King Devick Sub-test 2:	Time	P=0.00	P=0.47		
Control group (N=30)			P=0.60			

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)						
Level of body structure and function						
Clinical features associated with central vestibular dysfunction						
HIGHER VESTIBULAR FUNCTION: **Residual oculomotor visual performance**			**Within-group comparison**	**Between-group comparison**		
Experimental group (N=30)	King Devick Sub-test 2:	Errors	P=0.03	P=0.46		
Control group (N=30)			P=0.41			
Experimental group (N=30)	King Devick Sub-test 3:	Time	P=0.00	P=0.82		
Control group (N=30)			P=0.27			
Experimental group (N=30)	King Devick Sub-test 3:	Errors	P=0.01	P=0.12		
Control group (N=30)			P=0.23			

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
HIGHER VESTIBULAR FUNCTION: **Visual-perceptual function and cognitive function**			**Within-group comparison**	**Between-group comparison**	
Experimental group (N=30)	Star Cancellation Test:	Time	P=0.93	P=0.21	
Control group (N=30)			P=0.14		
Experimental group (N=30)	Star Cancellation Test	Errors	P=0.00	P=0.17	
Control group (N=30)			P=0.14		
Experimental group (N=30)	Cognitive function: Mini-Mental State Examination		P=0.00	P=0.56	
Control group (N=30)			P=0.25		

Table 7.2.: (continued) Summary of the within-group comparison based on the Wilcoxon matched-pair signed-rank test and between-group comparison based upon logistic regression adjusted for age, gender and race between the experimental and control groups pre and post intervention.

International Classification of Functioning, Disability and Health (ICF)					
Level of body structure and function					
Clinical features associated with central vestibular dysfunction					
LEVEL OF ANXIETY AND/ OR DEPRESSION			**Within-group comparison**	**Between-group comparison**	
Experimental group (N=30)	Hospital Anxiety and Depression Scale	Anxiety sub-scale	P=0.001	P=0.32	
Control group (N=30)			P=0.97		
Experimental group (N=30)	Hospital Anxiety and Depression Scale	Depression sub-scale	P=0.003	P=0.003	
Control group (N=30)			P=0.52		

It is postulated that the statistically significantly improvement observed in the experimental group that received VRT integrated with task-specific activities occurred through the process of sensory substitution (sensory re-weighting). Sensory substitution is the mechanism that involves the re-weighting of extra-vestibular input facilitated by VRT (Lacour *et al* 2016:54). One of the main components of the VRT programme received by patients in the experimental group included VSEs integrated with task-specific activities aimed to facilitate saccadic eye movement substitution (Van Wyk *et al* 2014:856). The VSEs integrated with task-specific activities consisted of the performance of horizontal, vertical and dynamic saccadic eye movements (visual scanning) while performing a static or dynamic motor (balance) activity (Van Wyk *et al* 2014:856). Saccadic eye movement training activates the superior and inferior rectus, medial and lateral rectus, inferior and superior oblique extraocular muscles that have reflexogenic connections to the cerebellum. Findings of the study are supported by previously published literature that the activation of the extraocular muscles through eye movement training may be associated with neural recovery and better functional outcomes post-stroke (Carrick *et al* 2016:3). Statistically significant improved functional capacity measured by postural and balance outcomes following VRT may be attributed to central compensation mechanisms due to active neuronal changes in the cerebellum and brainstem in response to sensory conflict produced by vestibular pathology (Balci *et al* 2013:259).

Vestibular rehabilitation therapy integrated with task-specific activities are a low cost, safe and effective complement to standard treatment of stroke patients and provides a functional application in the treatment of patients' post-stroke. The high prevalence of clinical features and activity limitations associated with central vestibular dysfunction on body structure and function, as well as activity level in patients post-stroke, may suggest that the measurement of these clinical features and activity limitations associated with central vestibular dysfunction might be a robust biomarker that may be applied in the guidance and interpretation of treatment outcomes post-stroke.

Findings of the study adds to an increasing body of evidence that the CNS has the capability to compensate for central vestibular dysfunction and re-weight sensory inputs post-stroke (Whitney *et al* 2016:13). Finally, Smith (2018:1) postulates that due to the important role the vestibular system plays in the detection of gravity followed by the extensive transmission of vestibular information across many brain areas, VRT has an

effect on the electrophysiological rhythms and pathophysiological activity of the CNS which ultimately results in improved function.

The limitations of the study are discussed in Section 7.3.

7.3. LIMITATIONS OF THE CURRENT STUDY

The limitations identified throughout the study are:

(1) During the cross-sectional survey, 20% of patients' information on the type of stroke and area of stroke (31%) were unavailable in their medical records. This lack of detailed information resulted in the researcher not being able to differentiate patients with regards to the type and anatomical location of the stroke during the data analysis in phase 1 of the study. It is recommended that future studies should consider stratifying their study samples based upon the type and anatomical location of the stroke. Through stratification of the study samples, the prevalence of the clinical features associated with central vestibular dysfunction based on the type and anatomical location of the stroke, may be determined.

(2) During the single-blind cluster randomised controlled trial, 17% of patients' information on the type of stroke and area of stroke (28%) were unavailable in their medical records. This lack of detailed information resulted in the researcher not being able to differentiate patients with regards to the type and anatomical location of the stroke during the data analysis in phase 2 of the study. It is recommended that future studies should consider stratifying their study samples based upon the type and anatomical location of the stroke. Through stratification of the study samples, the type and anatomical location of the stroke can be taken into consideration when the effect of the interventions on the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients in the sub-acute phase are determined.

(3) The absent data of the clinical features and activity limitations associated with central vestibular dysfunction of the patients in the single-blind cluster randomised controlled trial were presented in Table 5.3. Reasons for the absent data of the clinical feature of oculomotor control were the inability to obtain reliable measurements of these patients due to failure to maintain a steady level of alertness during the measurement of smooth pursuit eye movement using VNG (Table 5.4) or that patients presented with a static visual acuity score > 1.3 LogMAR of the left or right eye respectively.

It is recommended that the specific medication used by patients in future studies should be recorded. Specific medication may have sedative and analgesic effects that may influence the level of alertness during the measurement of smooth pursuit and saccadic eye movements using VNG. Collection of specific medication and the strength of their effects may enable researchers to control for the effects of medication in future studies (Sloane, Ivey, Roth, Roederer and Williams 2008:140).

Reliable measurements of the gain of smooth pursuit eye movements that could not be obtained in the experimental group at pre- and post-intervention, include: (a) gain of right eye in the left visual field (pre-intervention: N=1, post-intervention: N=1); (b) gain of left eye in the left visual field (pre-intervention: N=2, post-intervention: N=2); (c) gain of right eye in the right visual field (pre-intervention: N=2, post-intervention: N=2); and (d) gain of left eye in the right visual field (pre-intervention: N=3, post-intervention: N=2).
Reliable measurements of the gain of smooth pursuit eye movements that could not be obtained in the control group at pre- and post-intervention, include: (a) gain of right eye in the left visual field (pre-intervention: N=2, post-intervention: N=0); (b) gain of left eye in the left visual field (pre-intervention: N=2, post-intervention: N=0); (c) gain of right eye in the right visual field (pre-intervention: N=2, post-intervention: N=1); and (d) gain of left eye in the right visual field (pre-intervention: N=2, post-intervention: N=1).

Reasons for the absent data of the clinical feature of oculomotor control were the inability to obtain reliable measurements in these patients due to failure to maintain a steady level of alertness during the measurement of saccadic eye movement using VNG (Table 5.5a., Table 5.5b. and Table 5.5c.) or that patients presented with a static visual acuity score > 1.3 LogMAR of the left or right eye respectively. Reliable measurements of the latency, velocity and accuracy of saccadic eye movements that could not be obtained in the experimental group at pre- and post-intervention, include: (a) latency of left eye in the left visual field (pre-intervention: N=4, post-intervention: N=2); (b) latency of right eye in the left visual field (pre-intervention: N=3, post-intervention: N=1); (c) latency of left eye in the right visual field (pre-intervention: N=2, post-intervention: N=2); (d) latency of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=1); (e) velocity of left eye in the left visual field (pre-intervention: N=2, post-intervention: N=4); (f) velocity of right eye in the left visual field (pre-intervention: N=3, post-intervention: N=1); (g) velocity of left eye in the right visual field (pre-intervention: N=2, post-intervention: N=2);

(h) velocity of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=1); (i) accuracy of left eye in the left visual field (pre-intervention: N=4, post-intervention: N=2); (j) accuracy of right eye in the left visual field (pre-intervention: N=3, post-intervention: N=1); (k) accuracy of left eye in the right visual field (pre-intervention: N=2, post-intervention: N=2); and (l) accuracy of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=1).

Reliable measurements of the latency, velocity and accuracy of saccadic eye movements that could not be obtained in the control group at pre- and post-intervention, include: (a) latency of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=0); (b) velocity of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=0); and (c) accuracy of right eye in the right visual field (pre-intervention: N=1, post-intervention: N=0).

Reasons for the inability to obtain a measurement of static visual acuity (Table 5.6) in the experimental and control groups, were a static visual acuity score of higher than 1.3 LogMAR of the left or right eye respectively. Reasons for the inability to obtain a measurement of dynamic visual acuity (Table 5.8) in these patients, were a dynamic visual acuity score > 1.3 LogMAR during ≥ 2Hz horizontal head rotation or a static visual acuity score > 1.3 LogMAR. As dynamic visual acuity is indicated by a decrease of ≥0.2 LogMAR when the dynamic visual acuity LogMAR score is subtracted from the static visual acuity LogMAR score, the inability to obtain a static visual score at baseline results in the inability to obtain a dynamic visual acuity score.

Measurements of the static and dynamic visual acuity that could not be obtained in the experimental group at pre- and post-intervention, include: (a) static visual acuity of the left eye (pre-intervention: N=4, post-intervention: N=3); (b) static visual acuity of the right eye (pre-intervention: N=2, post-intervention: N=2); (c) static visual acuity of both eyes (pre-intervention: N=1, post-intervention: N=1); (d) dynamic visual acuity (>0.5 LogMAR score during ≥ 2Hz horizontal head rotation) (pre-intervention: N=4, post-intervention: N=1); and (e) dynamic visual acuity (line difference of a decrease of ≥0.2 LogMAR) (pre-intervention: N=4, post-intervention: N=1).

Measurements of the static and dynamic visual acuity that could not be obtained in the control group at pre- and post-intervention, include: (a) static visual acuity of the left eye (pre-intervention: N=0, post-intervention: N=1); (b) static visual acuity of the right eye

(pre-intervention: N=1, post-intervention: N=3); (c) dynamic visual acuity (>0.5 LogMAR score during ≥ 2Hz horizontal head rotation) (pre-intervention: N=4, post-intervention: N=4); and (e) dynamic visual acuity (line difference of a decrease of ≥0.2 LogMAR) (pre-intervention: N=4, post-intervention: N=4).

(4) Findings of the current study indicated that although statistically significant *within-group* improvement was observed in multiple clinical features and activity limitations associated with central vestibular dysfunction, statistically significant differences *between* the two interventions groups were only observed in the clinical features and activity limitations associated with central vestibular dysfunction that include saccadic eye movement (velocity and accuracy), depression and functional ability. The absence of statistically significant differences between the groups may be attributed to the small sample size of the experimental group (N=30) and control group (N=30).

Although the sample size of phases 1 and 2 were calculated based on a study by Van Wyk *et al* (2014:856) with the assistance of a statistician (Section 3.1.3.1.), the researcher acknowledges the fact that a small sample size may result in a reduction of statistical power (Ferreira, Pintoa, Veleza, Leffa, Piza and Fregni 2019:1). Latif, Amadera, Pimentel, Pimentel and Fregni (2011:306) indicate that patients in the field of physical medicine and rehabilitation such as post-stroke patients, are often more complex as these patients present with multiple impairments. As result of the multiple impairments present in post-stroke patients, the homogeneity of a study sample is more difficult and the precise calculation of the sample size are increasingly important when the potential limited number of patients for recruitment are considered (Latif *et al* 2011:306). Borschmann, Hayward, Raffelt, Churilov, Kramer and Julie Bernhardt (2018:1) also recommended that patient selection and stratification of study samples based upon infarct volume, initial level of impairment and biomarkers of recovery may be considered in the selection of an adequate sample size to achieve statistical power.

(5) Findings by Kim *et al* (2016:2424) indicated that 93% of patients with isolated lateral medullary infarction (LMI) demonstrated at least one (1) clinical feature of otolithic dysfunction that includes either an ocular tilt reaction (OTR) (N=29/45, 64%) or SVV tilt (N=37/44, 84%). Abnormalities of oVEMPs (27%) and cVEMPs (29%) were less common than OTR and SVV tilt (Kim *et al* 2016:2424). Kim *et al* (2016:2424) suggest that the discrepancy in otolithic dysfunction indicate that different anatomical substrates and/or

dissimilar reciprocal modulation for processing of each otolithic signal in central vestibular structures are in the dorsolateral medulla.

During the planning of the study protocol, the researcher did not consider the inclusion of the assessment of perception of verticality using SVV tilt in the battery of objective measures. Dieterich and Brandt (2019:1) indicate that tilts of the SVV are the most frequent clinical feature of an acute tone imbalance of the bilateral vestibular system in the frontal (roll) plane. Tilts of the SVV may be observed in patients with acute unilateral lesions of the graviceptive pathways that originate from the otolith organs and the *vertical* semi-circular canals and travel via the vestibular nuclei and the dorsolateral thalamic nuclei to the multisensory vestibular cortex areas that include the PIVC (Figure 1.2) (Section 1.1.1.2) (Dieterich and Brandt 2019:1). Patients with acute unilateral lesions of the vestibulo-cerebellar loop (Section 1.1.5.1) may also present with either ipsilateral or contralateral SVV tilts depending on location of the cerebellar lesion (Dieterich and Brandt 2019:1). The researcher acknowledges that the measurement of perceived visual vertical using SVV tilt can provide additional information on acute unilateral vestibular dysfunction in patients who are in the sub-acute phase post-stroke.

(6) Findings by Miller *et al* (2014:2070) suggest that stroke patients may present with unilateral disruption of inhibitory corticobulbar projections to the vestibular nuclei that may result in an asymmetry in descending vestibular drive to motor neuron pools. Miller *et al* (2014:2070) hypothesise that the asymmetry in descending vestibular drive to motor neuron pools may result in spastic hypertonia observed in patients post-stroke. Miller *et al* (2014:2070) demonstrated a strong positive relationship between the degree of asymmetry and the severity of spasticity in the study sample (N=17). In the current study, the presence of spastic hypertonia in the study sample was not assessed. Neither the Modified Ashworth Scale (MAS) nor the Antigravity Spasticity Index (AGSI) to measure the probable presence of spastic hypertonia, were included in the battery of objective measures used in the current study.

(7) A recent study by Mitsutake, Sakamoto, Ueta and Horikawa (2020:110) investigated the relationship between standing body sway responses during galvanic vestibular stimulation and motor function of the hemiplegic lower extremity of post-stroke patients (N=30) compared to healthy controls (N=49). Postural stability was assessed during galvanic vestibular stimulation while quietly standing with eyes closed using a C7-

mounted accelerometer. Lower extremity function of the post-stroke patients was measured using the Fugl-Meyer Assessment scale (FMA-LE). Results of the study by Mitsutake *et al* (2020:110) demonstrated that post-stroke patients present with lower standing body sway test scores during galvanic vestibular stimulation compared to the control group (P=0.010). Correlation analysis demonstrated that the standing body sway test scores were significantly associated with the FMA-LE (r=0.374, P=0.021). Findings of the study indicated that even in individuals with normal peripheral vestibular function, the presence of motor impairment was associated with standing postural instability during galvanic vestibular stimulation (Mitsutake *et al* 2020:110). Mitsutake *et al* (2020:110) concluded that motor impairment of the hemiplegic lower extremity as measured by the FMA-LE might lead to inhibition of normal standing postural stability. In the current study, the presence of motor impairment in the study sample was not assessed. The Fugl-Meyer scale to measure the probable presence of motor impairment post-stroke (Fugl-Meyer, Jääskö, Leyman, Olsson and Steglind 1975:13) were not included in the battery of objective measures used in the current study.

(8) Vestibular, visual and proprioceptive (somatosensory system) information is processed by the central vestibular pathways that include the vestibular nuclear complex and integrated within the sensorimotor cortex to maintain an individual's sense of balance and position (Grill *et al* 2013:1; Gimmon *et al* 2017:3347). The vestibular nuclei complexes are closely connected and are responsible for the integration of semicircular canal and otolith information from the vestibular periphery and other sensory systems that include the somatosensory, optokinetic, visual and neck proprioceptive systems. Although the visual system and vestibular system function in intimate integration with the somatosensory (proprioceptive, cutaneous, and joint receptors) system in maintaining postural orientation and stability during functional movement, the researchers did not measure proprioception with any specific objective measures during the current study.

(9) The researcher did not collect the specific medication used by patients in the current study. The researcher was therefore unable to adjust for the overall effects or changes in medications (Sloane *et al* 2008:140) during the data analysis in the current study. It is recommended that future studies should collect the use of medication by their study samples to enable researchers to control for drug effects (Sloane *et al* 2008:140) when the effect of interventions on the clinical features and activity limitations associated with central vestibular dysfunction in post-stroke patients in the sub-acute phase are determined.

(10) Findings by D'Silva, Lin, Staecker, Whitney and Kluding (2016:400) indicated that individuals with diabetes mellitus often develop multi-organ anatomic, structural and functional changes due to microvascular complications such as peripheral neuropathy, retinopathy and vestibular dysfunction that may result in impaired balance and increased risk of falls. D'Silva *et al* (2016:400) indicated that a recent epidemiological study by Agrawal, Carey, Della Santina, Schubert and Minor (2009:938) demonstrated that vestibular dysfunction was 70.0% higher in individuals with diabetes mellitus compared to age-matched controls (N= 5086). Despite the increased prevalence of vestibular dysfunction in individuals with diabetes, it is also important to highlight that people with diabetes may also present with somatosensory and visual impairment that may limit their ability to reweigh sensory information (D'Silva *et al* 2016:400). In the current study, the researcher did not record the number of patients in the study sample which had diabetes. The researcher was therefore unable to adjust for diabetes and diabetic complications during the data analysis in the current study. The Michigan Neuropathy Screening Instrument (Feldman, Stevens, Thomas, Brown, Canal and Greene 1994:1281) to assess patients for diabetic complications such as peripheral neuropathy and lower extremity pain were also not included in the battery of objective measures used in the current study.

Suggestions for future research are discussed in Section 7.4.

7.4. SUGGESTIONS FOR FUTURE RESEARCH

Suggestions for future research are:

(1) Dieterich and Brandt (2019:1) demonstrated that measurement of the perceived visual vertical using SVV tilt identify the presence of acute tone imbalance of the bilateral vestibular system in the frontal (roll) plane. It is thus recommended that the measurement of SVV tilt be included in the battery of objective measures used to assess otolith function in future research.

(2) Miller *et al* (2014:2070) demonstrated a strong positive relationship between the degree of asymmetry and the severity of spasticity in post-stroke patients. Stroke patients may present with spastic hypertonia attributable to an asymmetry in descending vestibular drive to motor neuron pools as result of the unilateral disruption of inhibitory

corticobulbar projections to the vestibular nuclei. It is thus recommended that the assessment of spastic hypertonia using the MAS or AGSI be included in the battery of objective measures used to assess otolith function in future research.

(3) Mitsutake *et al* (2020:110) demonstrated a relationship between patients' postural control in standing during galvanic vestibular stimulation and the presence of motor impairment of the hemiplegic lower extremity post-stroke. Stroke patients may present with motor impairment that may result in the inhibition of their postural stability in standing. It is thus recommended that the assessment of motor impairment using the Fugl-Meyer scale be included in the battery of objective measures in future research.

(4) Grill *et al* (2013:1) and Gimmon *et al* (2017:3347) indicated that vestibular, visual and proprioceptive (somatosensory system) information is processed by the central vestibular pathways and integrated within the sensorimotor cortex to maintain an individual's sense of balance and position. Stroke patients' functional balance may be improved through the process of sensory substitution. The CNS presents with the capability to compensate for vestibular dysfunction and re-weight sensory inputs through the process of sensory substitution (Lacour *et al* 2016:54; Van Wyk *et al* 2016:140; Whitney *et al* 2016:13). The process of sensory substitution refers to the process of possible sensory re-weighting by substituting lost or diminished vestibular function with other sensory input that includes visual and somatosensory (proprioceptive) information to facilitate vestibular compensation in the 'early re-organisation' (sub-acute) phase post-stroke (Lacour *et al* 2016:54; Van Wyk *et al* 2016:140; Whitney *et al* 2016:13). It is thus recommended that the assessment of proprioception be included in the battery of objective measures in future research.

(5) Agrawal *et al* (2009:938) and D'Silva *et al* (2016:400) demonstrated a relationship between vestibular dysfunction and diabetes mellitus. Stroke patients with diabetes may present with diabetic complications such as peripheral neuropathy and lower extremity pain that may result in balance dysfunction and decreased ability to reweigh sensory information (D'Silva *et al* 2016:400). It is thus recommended that the assessment of peripheral neuropathy using the Michigan Neuropathy Screening Instrument be included in the battery of objective measures in future research.

(6) Findings by Vossel *et al* (2013:1782) indicated that decreased self-awareness of impaired higher vestibular function specifically visuospatial deficits (anosognosia) was the most important predictor for performance in standardised ADLs ($p<0.001$) in right hemispheric stroke patients (N=55). The study highlights the important role of self-awareness of visuospatial deficits for successful ADL performance. The study also emphasised the importance of assessment of higher vestibular function that include visual-perceptual function and anosognosia in right hemispheric stroke patients. It is thus recommended that the assessment of anosognosia be included in the battery of objective measures used in future research.

(7) Due to less optimal spontaneous recovery of the central vestibular system post-stroke, patients may develop maladaptive sensory strategies in the early months post-stroke in response to the absence of specific management (assessment and intervention) to address vestibular dysfunction post-stroke (Bonan *et al* 2015:521; Lacour and Bernard-Demanze 2015:285). A suggestion for future research is to investigate the prevalence of clinical features and activity limitations associated with central vestibular dysfunction in patients who are in the chronic post-stroke phase.

(8) The cerebellum plays an important role in the clinical features and activity limitations associated with central vestibular dysfunction that include oculomotor control, reflexive control of gaze, otolithic function, higher vestibular function functional balance and ability to modify gait in response to changing task demands. Future investigations of the flocculus, intermediate and lateral zones of the cerebellum may reveal pathology and related impairments unique to patients with central vestibular dysfunction in the sub-acute and chronic post-stroke phases (Gimmon *et al* 2017:3347; Schniepp *et al* 2017:87).

7.5. SUMMARY

A stroke may result in a vestibular tone imbalance in the structures that make up the central vestibular system. As result of the vestibular tone imbalance of the central vestibular system and possible interruption of the vestibulo-thalamo-cortical pathways and vestibulo-cerebellar tract, patients may resent with multiple clinical features associated with central vestibular dysfunction in the sub-acute phase post-stroke. Irrespective of the side and area of stroke, the majority of the study sample presented

with a high prevalence (>97%) of clinical features associated with central vestibular dysfunction that included impairment of smooth pursuit eye movement, utricle and superior vestibular nerve function and visual-perceptual dysfunction. It may be assumed that the increased prevalence of the multiple clinical features related to central vestibular dysfunction be associated with the high prevalence (87.3%-98.0%) of activity limitations also characteristic of central vestibular dysfunction post-stroke. The activity limitations associated with central vestibular dysfunction in post-stroke patients included the impairment of functional balance, ability to modify gait in response to changing task demands and functional ability. It may therefore be presumed that the high prevalence of activity limitations associated with central vestibular dysfunction be attributed to the interrelation between impaired smooth pursuit eye movement, utricle and superior vestibular nerve function and visual-perceptual dysfunction in patients in the sub-acute phase post-stroke.

The intervention of VRT integrated with task-specific activities for the rehabilitation of central vestibular dysfunction consisted of a programme of exercises aimed to facilitate the adaptation of the vestibular system and sensory substitution through the process of sensory re-weighting. The intervention of VRT integrated with task-specific activities also aimed to habituate patients to movement and improve their balance and postural control post-stroke. Patients who received VRT integrated with task-specific activities improved significantly more in oculomotor function, specifically saccadic movement (velocity and accuracy), depression and functional ability, compared to patients who received task-specific activities alone. Findings of the study adds to an increasing body of evidence that the CNS has the capability to compensate for central vestibular dysfunction and re-weight sensory information post-stroke. Vestibular rehabilitation therapy integrated with task-specific activities are a low cost, safe and effective complement to standard treatment of stroke patients and provides a functional application in the treatment of patients post-stroke.

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Addendum A: Ethics Approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

28/06/2018

Approval Certificate
Amendment
(to be read in conjunction with the main approval certificate)

Ethics Reference No: 374/2015

Title: PHYSIOTHERAPY FOR CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

Dear Miss Andoret van Wyk

The **Amendment** as described in your documents specified in your cover letter dated 6/05/2018 received on 6/05/2018 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 27/06/2018.

Please note the following about your ethics amendment:
- Please remember to use your protocol number (**374/2015**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committe may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics amendment is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, Tswelopele Building, Level 4-60*

Dr R Sommers; MBChB; MMed (Int); MPharMed; PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

☎ 012 356 3084 deepeka.behari@up.ac.za / fhsethics@up.ac.za http://www.up.ac.za/healthethics
✉ Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60 / 61, 31 Bophelo Road, Gezina, Pretoria

(012-3563084 deepeka.behari@up.ac.za http://www.up.ac.za/healthethics
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YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

30-Jul-2018

Approval Certificate

New Application

Ethics Reference No.: 374/2015

Title: New Title: PHYSIOTHERAPY FOR CENTRAL VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE. dd 06/05/2018.

OLD TITLE: THE PREVALENCE AND MANAGEMENT OF VISUAL IMPAIRMENTS AND VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

Dear Miss Andoret van Wyk

The **New Application** as supported by documents specified in your cover letter for your research received on the , was approved by the Faculty of Health Sciences Research Ethics Committee on the 27-Jun-2018.

Please note the following about your ethics approval:

- Ethics Approval is valid from to .
- Please remember to use your protocol number (374/2015) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed(Int) MPharMed
Deputy Chairperson: Faculty of Health Sciences Research Ethics Committee

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
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Faculty of Health Sciences Research Ethics Committee

27/08/2015

Approval Certificate
New Application

Ethics Reference No.: 374/2015

Title: THE PREVALENCE AND MANAGEMENT OF VISUAL IMPAIRMENTS AND VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

Dear Andoret Van Wyk

The **New Application** as supported by documents specified in your cover letter dated 24/07/2015 for your research received on the 30/07/2015, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 26/08/2015.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**374/2015**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

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Addendum B: PACTR Registration

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

SOUTH AFRICAN COCHRANE CENTRE

PO Box 19070, Tygerberg, 7505, South Africa;
Francie van Zijl Drive, Parow Valley, Cape Town
Tel: +27 21 938 0438; Fax: +27 21 938 0836
E-mail: cochrane@mrc.ac.za

THE SOUTH AFRICAN COCHRANE CENTRE

THE COCHRANE COLLABORATION

03 September 2015

To Whom It May Concern:

RE: The prevalence and management of visual impairments and vestibular dysfunction in post-stroke patients in the sub-acute phase.

As project manager for the Pan African Clinical Trial Registry (www.pactr.org) database, it is my pleasure to inform you that your application to our registry has been accepted. Your unique identification number for the registry is **PACTR201509001223262**

Please be advised that you are responsible for updating your trial, or for informing us of changes to your trial.

Additionally, please provide us with copies of your ethical clearance letters as we must have these on file (via email, post or fax) at your earliest convenience if you have not already done so.

Please do not hesitate to contact us at +27 21 938 0835 or email epienaar@mrc.ac.za should you have any questions.

Yours faithfully,

Elizabeth D Pienaar
www.pactr.org Project Manager
+27 021 938 0835

PACTR
PAN AFRICAN CLINICAL TRIALS REGISTRY

Addendum C: Letters of Permission from the Rehabilitation Centres

Life Rehabilitation

National Rehabilitation office
Oxford Manor, 21 Chaplin Road, Illovo, 2196
Private Bag X13, Northlands, 2116, South Africa
Telephone +27 11 219 9620
Facsimile +27 86 686 0441
www.rehab.co.za

15 June 2015

Ms Andoret van Wyk

Faculty of Health Sciences, University of Pretoria

Request for permission to conduct research

Dear Ms van Wyk

Many thanks for the request for permission to conduct research at our Life Rehabilitation Units at Life New Kensington Clinic and Life Riverfield Lodge on the topic: **The prevalence and management of visual impairments and vestibular dysfunction post-stroke.** Life Rehabilitation supports the development of the field of rehabilitation through evidence-based research and we welcome any research projects being conducted at our units.

I hereby grant permission to you to access the 2 Life Rehabilitation facilities for the purpose of conducting your research under the following conditions:

- Patient confidentiality is to be respected at all times, and therefore:
  - All appropriate patients admitted to the aforementioned facilities will be presented with a letter from the researcher requesting the patient's participation in the research project. Patients who are willing to participate are required to make contact with the researcher directly.
  - Data on patients have to be depersonalised and managed in accordance with the Protection of Private Information Act.
- You may only access information and use it for the purposes outlined in your research proposal
- Patients have the right to refuse participation in the research study.
- No official Life Healthcare documentation (or photocopies) may leave Life Healthcare premises, and all patient files must remain on Life Healthcare property at all times.
- The unit is not to be named in your research documents.
- Access to patients and information are dependent upon permission by the relevant managers to limit disruption to the unit routine.
- Life Healthcare takes no responsibility for any personal equipment used on Life Healthcare premises

Please liaise directly with Ms Ida Groenewald at Life Riverfield Lodge, and Ms Danny Joelson at Life New Kensington Clinic to arrange your visits. I wish you success with your research, and look forward to the results. We would appreciate a copy of your research upon completion.

Sincerely,

Nina Strydom
Therapy Support Specialist
Acute Rehabilitation and Mental Health

Life Group
HEALTH CARE

21 Chaplin Road, Illovo 2196
Private Bag X13, Northlands 2116
Tel: + 27 31 536 3812
Cell: + 27 84 566 1281
Fax: 086 678 1450
Email: nina.strydom@lifehealthcare.co.za
Website: www.lifehealthcare.co.za

Permission to access Records / Files / Data base at the Life Riverfield Lodge

To: Clinic Manager
Life Riverfield Lodge

Dr Marinda Overbeek

Department of Physiotherapy
Faculty of Health Sciences
University of Pretoria

Me A van Wyk
Dr CA Eksteen

From: The Investigator
Department of Audiology
Faculty of Humanities
University of Pretoria

Dr B Heinze

Re: Permission to do research at Life Riverfield Lodge

Drs CA Eksteen, Dr B Heinze and I are researchers working at the Department of Physiotherapy and Department of Audiology at the University of Pretoria. I am requesting permission on behalf of all of us to conduct a study on the Life Riverfield Lodge grounds that involves access to patient records.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

The title of the study is: The prevalence and management of visual impairments and vestibular dysfunction post-stroke.

The researchers request access to the following information:

Access to patient scans and X-Rays once written permission has been obtained from patients who are willing to participate in the research project. .

We intend to publish the findings of the study in a professional journal and/ or at professional meeting like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Signature of the Principle Investigator

Permission to do the research study at this hospital and to access the information as requested, is hereby approved.

Clinic Manager

Life Riverfield Lodge

Dr Marinda Overbeek

Signature

Hospital Official Stamp

Riverfield Lodge (Pty) Ltd.
P.O. Box 67372
Bryanston
2021

Addendum D: Informed Consent and Patient Information Sheet

PATIENT / PARTICIPANT'S INFORMATION & INFORMED CONSENT DOCUMENT

(Each patient must receive, read and understand this document before the start of the study)

If a child is 18 years or younger and is requested to partake in a research study, the parent /legal guardian must give consent. However children from 7-18 years must also sign an <u>ASSENT FORM</u> (This form must be written in layman's language/terms to enable a grade 5 learner to understand.)

THE PREVALENCE AND MANAGEMENT OF VISUAL IMPAIRMENTS AND VESTIBULAR DYSFUNCTION IN POST-STROKE PATIENTS IN THE SUB-ACUTE PHASE

Principal Investigators: Andoret van Wyk

Supervisor: Dr Carina A Eksteen

Co-supervisor: Dr Barbara Heinze

Institution: University of Pretoria

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S):

Daytime numbers: 082 7111 774

Afterhours: 082 7111 774

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION:

			:	
dd	**mmm**	**ivy**	**Time**	

Dear Patient

INTRODUCTION

You are **invited** to volunteer for a research study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about all the procedures involved in the study. In the best interests of your health, it is strongly recommended that you discuss with or inform your personal doctor of your possible participation in this study, wherever possible.

WHAT IS THE PURPOSE OF THE RESEARCH TRIAL?

You had recently suffered a stroke and the investigator would like you to consider taking part in the first phase of a research study on the assessment of patients post stroke. The assessment of visual impairments and vestibular dysfunction will provide evidence on the prevalence of visual-and ocular impairments and vestibular dysfunction in patients post-stroke. The research will contribute to an evidence based holistic understanding of visual- and vestibular system dysfunction that possibly present in patients following a stroke. The study will further contribute to the diagnosis and treatment strategies that should be implemented in the rehabilitation of visual- and vestibular system dysfunction following a stroke.

During the study an audiologist and physiotherapist will perform tests and outcome measures to determine if you present with a visual-and ocular impairment and/or vestibular dysfunction. The tests and outcome measures are a standard form of assessment nationally and internationally and are not something “strange”.

The investigator would like you to also consider taking part in the second phase of the research study on the rehabilitation of patients post-stroke. The rehabilitation will consist of activities that you have to re-learn to perform in order to resume functional activities in everyday life (task-specific activities). Vestibular physiotherapy and visual scanning exercises (specific eye movements) together with above-mentioned activities also form

part of the intervention. We know that this treatment has a positive effect on the functional outcome of people who sustained a stroke.

During the study you will receive either vestibular physiotherapy and visual scanning exercises (specific eye movements) together with task-specific activities or task-specific activities without vestibular physiotherapy and visual scanning exercises (specific eye movements). Both interventions are a standard form of treatment nationally and internationally and are not something “strange”.

WHAT IS THE DURATION OF THIS TRIAL?

If you decide to take part in the first phase of the research study, you will be one of approximately 100 patients. The assessment session will last approximately two hours. You will be asked to visit the audiologist and physiotherapist respectively so that they may complete the tests and outcome measures.

If you decide to take part in the second phase of the study (after participating in the first phase of the research study), you will be one of approximately 60 patients. The study will last for 2 weeks. You will be asked to visit the audiologist and physiotherapist after 2 weeks as per the following schedule:

↓ ↓

Day 1---------- Day 15

The assessment during each visit will last approximately three hours. You will be asked to visit the audiologist and physiotherapist respectively so that they may complete the tests and outcome measures.

DESCRIPTION OF PROCEDURES

This study involves answering some questions with regard to your illness and examination of yourself. The audiologist will use Video Nystagmography (VNG), EyeSeeCam vHIT, Vestibular evoked myogenic potential (VEMP), Snellen chart and dynamic visual acuity to assess your visual system (eye movements) and vestibular system.

The physiotherapist will ask you to complete outcome measures and to fill in forms with questions pertaining to your; (1) cognitive function; (2) residual oculomotor visual performance; (3) unilateral spatial neglect and visual-perceptual function; (4) functional balance; (5) the ability to modify gait in response to changing task demands; (6) functional ability; (7) post-stroke depression; and (8) anxiety.

At twenty (20) weeks after your admission to the rehabilitation facility, the investigator will contact you telephonically and complete a questionnaire over the phone. The investigator will ask questions pertaining to your participation in physical activity following the stroke.

HAS THE TRIAL RECEIVED ETHICAL APPROVAL?

This clinical trial Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, telephone numbers 012 3541677 / 012 3541330 and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October 2008), which deals with the recommendations guiding doctors in biomedical research involving human/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT IN THIS TRIAL?

Your participation in this trial is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to other medical care. The investigator retains the right to withdraw you from the study if it is considered to be in your best interest. If it is detected that you did not give an accurate history or did nor follow the guidelines of the trial and the regulations of the trial facility, you may be withdrawn from the trial at any time.

IS ALTERNATIVE TREATMENT AVAILABLE?

Alternative treatment in the form of general exercise therapy is often used to treat patients with stroke. If you decide not to take part in this study it is possible that your physiotherapist may treat you with other forms of exercise therapy.

MAY ANY OF THESE TRIAL PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

None of the trial procedures will result in discomfort or inconvenience to you.

WHAT ARE THE BENEFITS TO YOU

This research will contribute to an evidence based holistic understanding of visual- and vestibular system dysfunction that possibly present in patients following a stroke. The study will further contribute to the diagnosis and treatment strategies that should be implemented in the rehabilitation of visual- and vestibular system dysfunction. It may also provide valuable direction in the development of a comprehensive approach to assessment and treatment of patients post-stroke that considers all the multiple contributing factors that are essential to optimise post-stroke rehabilitation to improve patients' functional outcome post-stroke and improve the provision of evidence based post-stroke care.

WHAT ARE THE RISKS INVOLVED IN THIS TRIAL?

There are no risks involved in this trial.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS TRIAL?

Other co-morbid disease or disability such as cancer or amputation that will prevent or limit assessment as well as the participation in other pharmacological or rehabilitation intervention studies which can lead to confounding of the results of this study will restrict your participation in this study. Also if you have a history of neck surgery, recent neck trauma, severe rheumatoid arthritis, atlanto-axial and occipito-atlantal instability, cervical myelopathy or radiculopathy, carotid sinus syncope, Chiari malformation and vascular dissection syndromes you will be excluded from the study.

DISCONTINUATION OF TRIAL TREATMENT

The investigator will supervise any discontinuation with your health as first priority.

INSURANCE AND FINANCIAL ARRANGEMENTS

Neither you nor your medical scheme will be expected to pay for any study medication or trial procedures assessments and treatment during the course of the trial. You will not be paid to participate in this trial. The investigator will determine if you are eligible to receive reimbursement for out-of-pocket and/or travel expenses.

SOURCE OF ADDITIONAL INFORMATION

For the duration of the trial, you will be under the care of the Tshwane Rehabilitation Center (TRC) / Tshwane District Hospital (TDH) / Life Riverfield Lodge / Life New Kensington Clinic. If at any time between your visits you feel that any of your symptoms are causing you any problems, or you have any questions during the trial, please do not hesitate to contact the investigator. The 24 hour telephone number is 082 7111 774, through which you can reach him/her or another authorized person.

CONFIDENTIALITY

All information obtained during the course of this trial is strictly confidential. Data that may be reported in scientific journals will not include any information which identifies you as a patient in this trial.

INFORMED CONSENT

I hereby confirm that I have been informed by the investigator, Andoret van Wyk about the nature, conduct, benefits and risks of clinical trial I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical trial.

I am aware that the results of the trial, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a trial report.

I may, at any stage, without prejudice, withdraw my consent and participation in the trial. I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the trial.

Patient's name _____

(Please print)

Patient's signature _____ Date _____

I, Andoret van Wyk herewith confirm that the above patient has been informed fully about the nature, conduct and risks of the above trial.

Investigator's name _____

(Please print)

Investigator's signature _____ Date _____

Witness's name* _____Witness's signature _____ Date _____

(Please print)

*Consent procedure should be witnessed whenever possible.

VERBAL PATIENT INFORMED CONSENT (applicable when patients cannot read or write)

I, the undersigned, Andoret van Wyk, have read and have explained fully to the patient, named …….. and/or is/her relative, the patient information leaflet, which has indicated the nature and purpose of the trial in which I have asked the patient to participate. The explanation I have given has mentioned both the possible risks and benefits of the trial and the alternative treatments available for his/her illness. The patient indicated that he/she understands that he/she will be free to withdraw from the trial at any time for any reason and without jeopardizing his/her access to other medical care, assessment and treatment strategies used in the clinical trial, to which he/she agrees.

I hereby certify that the patient has agreed to participate in this trial.

Patient's Name _____

(Please print)

Investigator's Name _____

(Please print)

Investigator's Signature _____ Date _____

Witness's Name _____ Witness's Signature _____ Date _____

(Please print)

(Witness - sign that he/she has witnessed the process of informed consent)

Addendum E: Data collection sheet

Data collection sheet

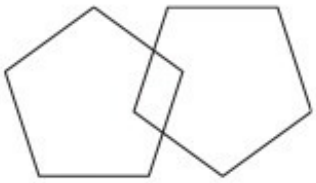
1. Stroke type:
   - Ischeamic ☐
   - Haemorrhagic ☐
2. Age: 19 – 84 years ☐
3. Sub-acute phase: physiologically stable to six months post-stroke ☐
4. Ability to follow instructions and the capacity to provide informed consent ☐
5. Mini-Mental State Examination: Score of seven or higher ☐
6. History of:
   - Organic disorder ☐
   - Major psychiatric impairment ☐
   - Cancer ☐
   - Amputation ☐
   - History of neck surgery ☐
   - Recent neck trauma ☐
   - Severe rheumatoid arthritis ☐
   - Atlanto-axial and occipito-atlantal instability ☐
   - Cervical myelopathy or radiculopathy ☐
   - Carotid sinus syncope ☐
   - Chiari malformation ☐
   - Vascular dissection syndromes ☐
   - Vertebral artery syndrome ☐
7. Positive Dix-Hallpike test ☐
8. Participation in other pharmacological or rehabilitation intervention studies ☐

Addendum F: Mini-Mental State Examination

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



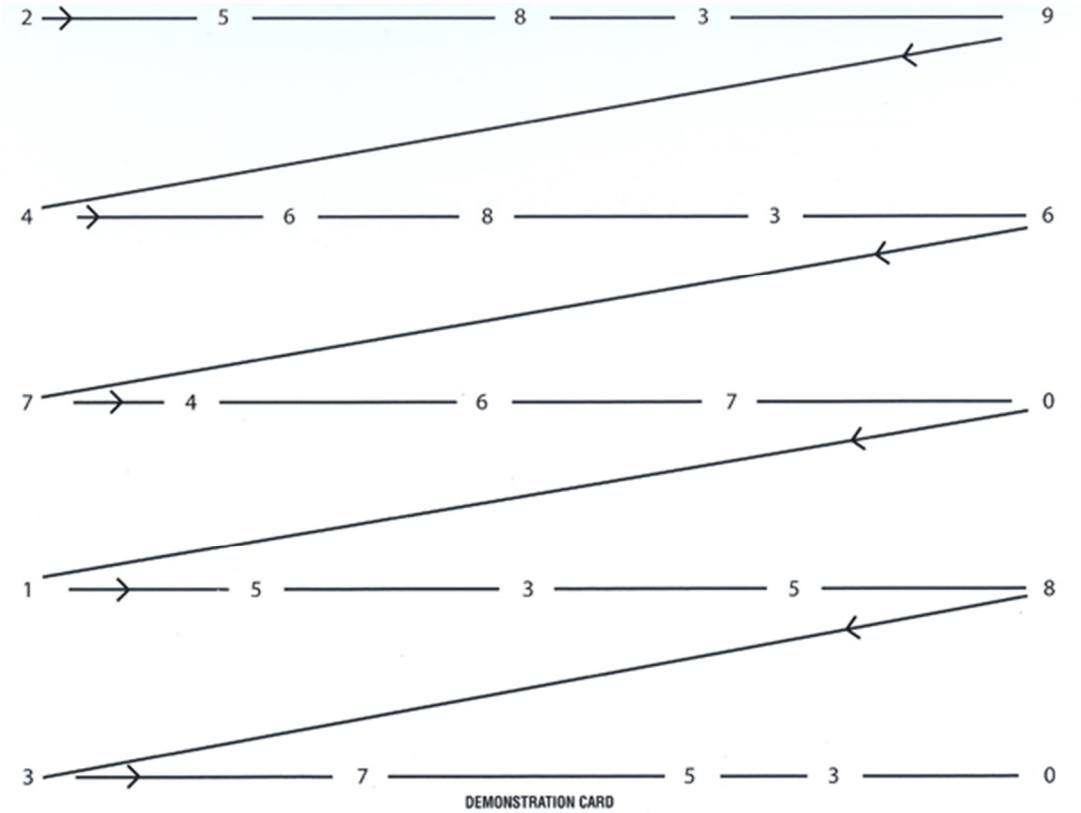
_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

[1]MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

Addendum G: King-Devick Test©



DEMONSTRATION CARD

TEST CARD I

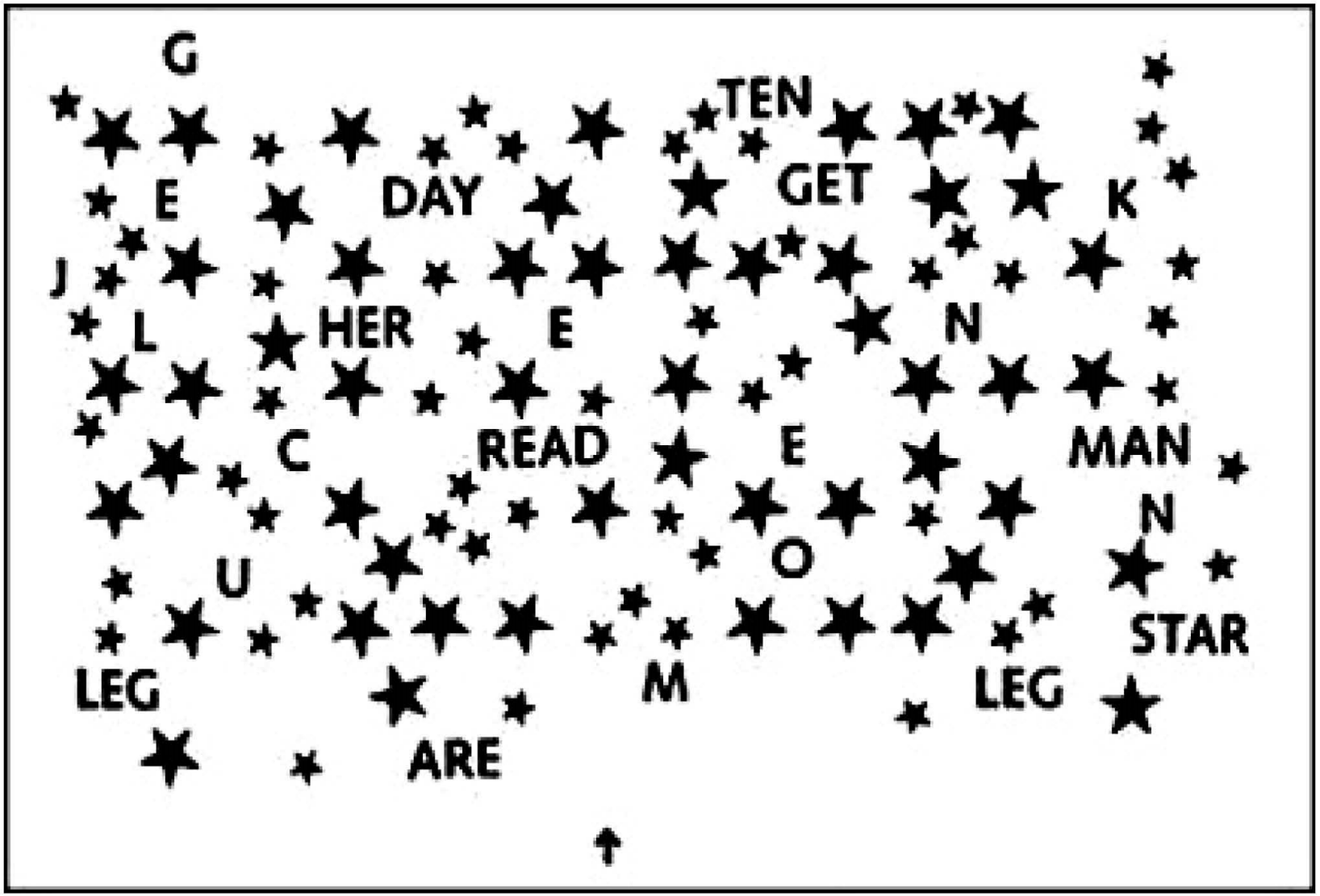
3			7			5		9		0
2		5			7			4		6
1		4				7			6	3
7				9				3	9	0
4		5				2			1	7
5				3			7	4		8
7		4				6			5	2
9			0				2	3		6

TEST II

5			4			1			8	0
4		6					3		5	9
7			5					4	2	7
3		2				6			9	4
1			4				5		1	3
9				3		4			8	5
5	1						6		3	1
4				3			5		2	7

TEST III

Addendum H: Star Cancellation Test


G
TEN
E
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J
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STAR
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M
LEG
ARE

Addendum I: Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Addendum J: Berg Balance Scale

Berg Balance Scale

The Berg Balance Scale (BBS) was developed to measure balance among older people with impairment in balance function by assessing the performance of functional tasks. It is a valid instrument used for evaluation of the effectiveness of interventions and for quantitative descriptions of function in clinical practice and research. The BBS has been evaluated in several reliability studies. *A recent study of the BBS, which was completed in Finland, indicates that a change of eight (8) BBS points is required to reveal a genuine change in function between two assessments among older people who are dependent in ADL and living in residential care facilities.*

Description:
14-item scale designed to measure balance of the older adult in a clinical setting.

Equipment needed: Ruler, two standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway

Completion:

Time: 15-20 minutes

Scoring: A five-point scale, ranging from 0-4. "0" indicates the lowest level of function and "4" the highest level of function. Total Score = 56

Interpretation:
41-56 = low fall risk
21-40 = medium fall risk
0 –20 = high fall risk

A change of 8 points is required to reveal a genuine change in function between 2 assessments.

Berg Balance Scale

Name: _____ Date: _____

Location: _____ Rater: _____

ITEM DESCRIPTION	SCORE (0-4)
Sitting to standing	_____
Standing unsupported	_____
Sitting unsupported	_____
Standing to sitting	_____
Transfers	_____
Standing with eyes closed	_____
Standing with feet together	_____
Reaching forward with outstretched arm	_____
Retrieving object from floor	_____
Turning to look behind	_____
Turning 360 degrees	_____
Placing alternate foot on stool	_____
Standing with one foot in front	_____
Standing on one foot	_____

Total _____

GENERAL INSTRUCTIONS

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject's performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

Berg Balance Scale

SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

TRANSFERS
INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays safely
( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

Berg Balance Scale continued…

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in > 20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding on.
( ) 4 able to lift leg independently and hold > 10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold ≥ 3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall

( ) TOTAL SCORE (Maximum = 56)

Addendum K: Dynamic Gait Index

Dynamic Gait Index (DGI)

1. Gait level surface _____

Instructions: Walk at your normal speed from here to the next mark (20')

20′ = **6 METRES**

Grading: Mark the lowest category that applies.

(3) Normal: Walks 20', no assistive devices, good sped, no evidence for imbalance, normal gait pattern

(2) Mild Impairment: Walks 20', uses assistive devices, slower speed, mild gait deviations.

(1) Moderate Impairment: Walks 20', slow speed, abnormal gait pattern, evidence for imbalance.

(0) Severe Impairment: Cannot walk 20' without assistance, severe gait deviations or imbalance.

2. Change in gait speed _____

Instructions: Begin walking at your normal pace (for 5'), when I tell you "go," walk as fast as you can (for 5'). When I tell you "slow," walk as slowly as you can (for 5').

5′ = **1.5 METRES**

Grading: Mark the lowest category that applies.

(3) Normal: Able to smoothly change walking speed without loss of balance or gait deviation. Shows a significant difference in walking speeds between normal, fast and slow speeds.

(2) Mild Impairment: Is able to change speed but demonstrates mild gait deviations, or not gait deviations but unable to achieve a significant change in velocity, or uses an assistive device.

(1) Moderate Impairment: Makes only minor adjustments to walking speed, or accomplishes a change in speed with significant gait deviations, or changes speed but has significant gait deviations, or changes speed but loses balance but is able to recover and continue walking.

(0) Severe Impairment: Cannot change speeds, or loses balance and has to reach for wall or be caught.

3. Gait with horizontal head turns _____

Instructions: Begin walking at your normal pace. When I tell you to "look right," keep walking straight, but turn your head to the right. Keep looking to the right until I tell you, "look left," then keep walking straight and turn your head to the left. Keep your head to the left until I tell you "look straight," then keep walking straight, but return your head to the center.

Grading: Mark the lowest category that applies.

(3) Normal: Performs head turns smoothly with no change in gait.

(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.

(1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, staggers but recovers, can continue to walk.

(0) Severe Impairment: Performs task with severe disruption of gait, i.e., staggers outside 15" path, loses balance, stops, reaches for wall.

15" = **38.1 CM**

4. Gait with vertical head turns _____

Instructions: Begin walking at your normal pace. When I tell you to "look up," keep walking straight, but tip your head up. Keep looking up until I tell you, "look down," then keep walking straight and tip your head down. Keep your head down until I tell you "look straight," then keep walking straight, but return your head to the center.

Grading: Mark the lowest category that applies.

(3) Normal: Performs head turns smoothly with no change in gait.

(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.

1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, staggers but recovers, can continue to walk.

(0) Severe Impairment: Performs task with severe disruption of gait, i.e., staggers outside 15" path, loses balance, stops, reaches for wall.

15" = **38.1 CM**

5. Gait and pivot turn _____

Instructions: Begin walking at your normal pace. When I tell you, "turn and stop," turn as quickly as you can to face the opposite direction and stop.

Grading: Mark the lowest category that applies.

(3) Normal: Pivot turns safely within 3 seconds and stops quickly with no loss of balance.

(2) Mild Impairment: Pivot turns safely in > 3 seconds and stops with no loss of balance.

(1) Moderate Impairment: Turns slowly, requires verbal cueing, requires several small steps to catch balance following turn and stop.

(0) Severe Impairment: Cannot turn safely, requires assistance to turn and stop.

6. Step over obstacle _____

Instructions: Begin walking at your normal speed. When you come to the shoebox, step over it, not around it, and keep walking.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to step over the box without changing gait speed, no evidence of imbalance.

(2) Mild Impairment: Is able to step over box, but must slow down and adjust steps to clear box safely.

(1) Moderate Impairment: Is able to step over box but must stop, then step over. May require verbal cueing.

(0) Severe Impairment: Cannot perform without assistance.

7. Step around obstacles _____

Instructions: Begin walking at normal speed. When you come to the first cone (about 6' away), walk around the right side of it. When you come to the second cone (6' past first cone), walk around it to the left.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to walk around cones safely without changing gait speed; no evidence of imbalance.

(2) Mild Impairment: Is able to step around both cones, but must slow down and adjust steps to clear cones.

(1) Moderate Impairment: Is able to clear cones but must significantly slow, speed to accomplish task, or requires verbal cueing.

(0) Severe Impairment: Unable to clear cones, walks into one or both cones, or requires physical assistance.

8. Steps _____

Instructions: Walk up these stairs as you would at home, i.e., using the railing if necessary. At the top, turn around and walk down.

Grading: Mark the lowest category that applies.

(3) Normal: Alternating feet, no rail.

(2) Mild Impairment: Alternating feet, must use rail.

(1) Moderate Impairment: Two feet to a stair, must use rail.

(0) Severe Impairment: Cannot do safely.

TOTAL SCORE: ___ / 24

References

1. Herdman SJ. Vestibular Rehabilitation. 2nd ed. Philadelphia, PA: F.A.Davis Co; 2000.
2. Shumway-Cook A, Woollacott M. Motor Control Theory and Applications, Williams and Wilkins Baltimore, 1995: 323-324

Addendum L: Barthel Index

THE BARTHEL INDEX

Patient Name: _____

Rater Name: _____

Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
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Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
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Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
***Arch Phys Med Rehabil.* 1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study.*1988;10:61-63.**

Copyright Information

Addendum M: Telephonic-administered international physical activity questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Addendum N: Supplementary data

Table (a).: Comparison of patients' smooth pursuit eye movement gain between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' SMOOTH PURSUIT EYE MOVEMENT GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Left Visual field	Gain of Right Eye	-6.48 (10.63)	0.19	0.21	0.12	0.11	0.28	0.21
Control group (N=28)			-2.60 (11.51)						
Experimental group(N=28)	Left Visual field	Gain of Left Eye	-4.45 (9.35)	0.87	0.58	0.64	0.31	0.95	0.83
Control group (N=28)			-4.89 (11.37)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (a).: (Continued) Comparison of patients' smooth pursuit eye movement gain between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' SMOOTH PURSUIT EYE MOVEMENT GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Right Visual field	Gain of Right Eye	-1.94 (9.83)	0.54	0.54	0.93	0.84	0.52	0.60
Control group (N=28)			-3.61 (10.24)						
Experimental group(N=28)	Right Visual field	Gain of Left Eye	0.27 (9.82)	0.13	0.17	0.10	0.16	0.12	0.20
Control group (N=28)			-3.76 (9.69)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (b).: Comparison of patients' latency of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' LATENCY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Left Visual field	Latency of Left Eye	16.50 (34.01)	0.11	0.17	0.10	0.17	0.12	0.08
Control group (N=28)			-1.10 (45.50)						
Experimental group(N=28)	Left Visual field	Latency of Right Eye	-5.81 (64.39)	0.39	0.80	0.35	0.57	0.39	0.38
Control group (N=28)			6.29 (40.68)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (b).: (Continued) Comparison of patients' latency of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' LATENCY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Right Visual field	Latency of Left Eye	10.23 (42.88)	0.82	0.50	0.80	0.46	0.78	0.94
Control group (N=28)			13.61 (63.11)						
Experimental group(N=28)	Right Visual field	Latency of Right Eye	2.68 (62.83)	0.54	0.47	0.69	0.62	0.50	0.63
Control group (N=28)			11.54 (44.52)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (c).: Comparison of patients' velocity of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' VELOCITY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Left Visual field	Velocity of Left Eye	-23.92 (62.37)	0.08	0.08	0.01*	0.001**	0.08	0.02*
Control group (N=28)			14.80 (92.41)						
Experimental group(N=28)	Left Visual field	Velocity of Right Eye	-33.16 (91.08)	0.16	0.19	0.01*	0.06	0.15	0.30
Control group (N=28)			-5.61 (52.09)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (c).: (Continued) Comparison of patients' accuracy of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' VELOCITY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Right Visual field	Velocity of Left Eye	-26.54 (78.91)	0.19	0.25	0.002**	0.005**	0.52	0.35
Control group (N=28)			-0.55 (69.52)						
Experimental group(N=28)	Right Visual field	Velocity of Right Eye	-21.16 (77.96)	0.21	0.04*	0.17	0.008**	0.53	0.51
Control group (N=28)			1.45 (54.71)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (d).: Comparison of patients' accuracy of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' ACCURACY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Left Visual field	Accuracy of Left Eye	-3.31 (12.07)	0.36	0.16	0.36	0.14	0.44	0.37
Control group (N=28)			-0.15 (13.55)						
Experimental group(N=28)	Left Visual field	Accuracy of Right Eye	-0.03 (12.23)	0.51	0.59	0.85	1.00	0.51	0.64
Control group (N=28)			-2.24 (13.18)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level				** = Significant at the 1% level		

Table (d).: (Continued) Comparison of patients' accuracy of saccadic eye movements between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' ACCURACY OF SACCADIC EYE MOVEMENTS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION									
Intervention groups	Objective measure		Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
				P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=29)	Right Visual field	Accuracy of Left Eye	-2.46 (10.59)	0.81	0.71	0.39	0.24	0.78	0.89
Control group (N=28)			-3.36 (16.93)						
Experimental group(N=28)	Right Visual field	Accuracy of Right Eye	-4.58 (12.94)	0.75	0.74	0.06	0.09	0.77	0.85
Control group (N=28)			-3.45 (14.33)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level			

Table (e).: Comparison of patients' static visual acuity between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' STATIC VISUAL ACUITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=26)	Left eye	0.09 (0.12)	0.08	0.17	0.23	0.40	0.10	0.04*
Control group (N=29)		0.01 (0.18)						
Experimental group(N=27)	Right eye	0.06 (0.18)	0.61	0.70	0.75	0.85	0.51	0.56
Control group (N=27)		0.04 (0.20)						
Experimental group(N=28)	Both eyes	0.09 (0.13)	0.17	0.14	0.39	0.31	0.15	0.15
Control group (N=30)		0.02 (0.22)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (f).: Comparison of patients' vestibulo-ocular reflex-gain between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' VESTIBULO-OCULAR REFLEX-GAIN BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	VOR-gain: Left	-0.1 (0.3)	0.36	0.37	0.39	0.34	0.36	0.19
Control group (N=30)		-0.1 (0.3)						
Experimental group(N=30)	VOR-gain: Right	-0.1 (0.3)	0.65	0.67	0.56	0.64	0.65	0.47
Control group (N=30)		-0.1 (0.4)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (g).: Comparison of patients' dynamic visual acuity between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' DYNAMIC VISUAL ACUITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=26)	> 0.5 LogMAR score during ≥ 2Hz horizontal head rotation	0.16 (0.21)	0.10	0.09	0.16	0.16	0.14	0.19
Control group (N=26)		0.06 (0.23)						
Experimental group(N=27)	Line difference: DVA minus SVA: Decrease of ≥0.2 LogMAR	0.81 (2.79)	0.35	0.41	0.24	0.20	0.32	0.39
Control group (N=26)		0.16 (1.99)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (h).: Comparison of patients' saccular and inferior vestibular nerve function between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=14)	cVEMP LEFT P1	-0.46 (2.26)	0.05*	0.04*	0.46	0.45	0.06	0.10
Control group (N=10)		1.43 (2.01)						
Experimental group(N=14)	cVEMP LEFT N1	-0.34 (2.05)	0.37	0.38	0.76	0.83	0.41	0.78
Control group (N=10)		0.35 (1.42)						
Experimental group(N=14)	cVEMP LEFT Amplitude	-3.71 (24.55)	0.66	0.61	0.56	0.36	0.61	0.97
Control group (N=10)		3.00 (49.37)						

cVEMP = Cervical Vestibular Evoked Myogenic Potential	P1 = First positive peak on wave form	N1 = First negative deflection on wave form
[1] = P-value: Exceedance probability	* = Significant at the 5% level	** = Significant at the 1% level

Table (h).: (Continued) Comparison of patients' saccular and inferior vestibular nerve function between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' SACCULAR AND INFERIOR VESTIBULAR NERVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=14)	cVEMP RIGHT P1	0.6 (2.2)	0.76	0.72	0.45	0.49	0.42	0.37
Control group (N=10)		0.4 (2.0)						
Experimental group(N=14)	cVEMP RIGHT N1	-0.4 (2.6)	0.96	0.76	0.05*	0.01*	0.97	0.57
Control group (N=10)		-0.4 (2.5)						
Experimental group(N=14)	cVEMP RIGHT Amplitude	-0.5 (22.5)	0.79	0.95	0.47	0.42	0.93	0.93
Control group (N=10)		-3.6 (31.9)						

cVEMP = Cervical Vestibular Evoked Myogenic Potential	P1 = First positive peak on wave form	N1 = First negative deflection on wave form
[1] = P-value: Exceedance probability	* = Significant at the 5% level	** = Significant at the 1% level

Table (i).: Comparison of patients' residual oculomotor visual performance between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' RESIDUAL OCULOMOTOR VISUAL PERFORMANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	King Devick Sub-test 1: Time	33.73 (59.64)	0.03*	0.02*	0.16	0.11	0.02*	0.17
Control group (N=30)		1.96 (43.05)						
Experimental group(N=30)	King Devick Sub-test 1: Errors	4,54 (8.08)	0.24	0.09	0.55	0.36	0.20	0.08
Control group (N=30)		1.11 (12.25)						
Experimental group(N=30)	King Devick Sub-test 2: Time	29.54 (39.71)	0.001**	0.001**	0.01*	0.05*	0.00*	0.04*
Control group (N=30)		-14.48 (49.39)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (i).: (Continued) Comparison of patients' residual oculomotor visual performance between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' RESIDUAL OCULOMOTOR VISUAL PERFORMANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	King Devick Sub-test 2: Errors	2.88 (6.01)	0.96	0.33	0.92	0.37	0.89	0.27
Control group (N=30)		2.74 (11.40)						
Experimental group(N=30)	King Devick Sub-test 3: Time	28.08 (43.53)	0.001**	0.002**	0.02*	0.07	0.00*	0.01*
Control group (N=30)		-21.67 (56.89)						
Experimental group(N=30)	King Devick Sub-test 3: Errors	3.88 (6.78)	0.89	0.47	0.47	0.12	0.81	0.44
Control group (N=30)		3.56 (10.64)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (j).: Comparison of patients' visual-perceptual function between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' VISUAL-PERCEPTUAL FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Star Cancellation Test: Time	-8.73 (84.54)	0.32	0.26	0.40	0.31	0.32	0.48
Control group (N=30)		10.43 (62.02)						
Experimental group(N=30)	Star Cancellation Test: Errors	6.10 (9.63)	0.44	0.15	0.36	0.17	0.43	0.02*
Control group (N=30)		3.97 (11.35)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (k).: Comparison of patients' cognitive function between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' COGNITIVE FUNCTION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Mini-Mental State Examination	-3.13 (3.77)	0.01	0.01	0.18	0.20	0.14	0.09
Control group (N=30)		-0.63 (2.81)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level

Table (I).: Comparison of patients' level of anxiety and/ or depression between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' LEVEL OF ANXIETY AND/ OR DEPRESSION BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Hospital Anxiety and Depression Scale: Anxiety sub-scale	4.13 (5.10)	0.02*	0.01*	0.25	0.15	0.01*	0.01*
Control group (N=30)		0.8 (5.45)						
Experimental group(N=30)	Hospital Anxiety and Depression Scale: Anxiety sub-scale	3.83 (4.47)	0.003**	0.001**	0.04*	0.01*	0.002**	0.001**
Control group (N=30)		-0.07 (5.38)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (m).: Comparison of patients' functional balance between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' FUNCTIONAL BALANCE BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Berg Balance Scale	-7.00 (9.73)	0.000	0.000	0.000	0.000	0.000	0.000
Control group (N=30)		-22.83 (10.93)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (n).: Comparison of patients' ability to modify gait in response to changing task demands between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' ABILITY TO MODIFY GAIT IN RESPONSE TO CHANGING TASK DEMANDS BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Dynamic Gait Index	-7.40 (4.34)	0.41	0.50	0.19	0.14	0.48	0.56
Control group (N=30)		-3.00 (10.17)						
[1] = P-value: Exceedance probability			* = Significant at the 5% level			** = Significant at the 1% level		

Table (o).: Comparison of patients' functional ability between the experimental group and control group pre and post intervention

COMPARISON OF PATIENTS' FUNCTIONAL ABILITY BETWEEN THE EXPERIMENTAL GROUP AND CONTROL GROUP PRE AND POST INTERVENTION								
Intervention groups	Objective measure	Mean Difference (SD) (Pre-Post)	Comparison between-group experimental : control group (Linear regression on differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, unadjusted)	Comparison between-group experimental : control group (Linear regression on differences, adjusted)	Comparison between-group experimental : control group (Linear regression on rank of differences, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on intervention over time, adjusted)	Comparison between-group - experimental : control group (Mixed-effect model on rank of intervention over time, adjusted)
			P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]	P-value[1]
Experimental group(N=30)	Barthel Index	-40.33 (16.91)	0.000	0.000	0.000	0.000	0.000	0.000
Control group (N=30)		-8.50 (15.32)						

[1] = P-value: Exceedance probability | * = Significant at the 5% level | ** = Significant at the 1% level