A critical analysis of the functional outcome of people with spinal cord injuries who have received stem cell therapy

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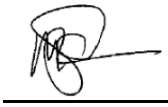
Statement

I, Melanie Skeen, declare that the dissertation which I hereby submit for the degree M PhysT at the University of Pretoria is my own work and has not been previously submitted by myself for a degree at another tertiary institution.

Where secondary material has been used, this has been carefully acknowledged and referenced in accordance with university requirements. I am aware of university policies and implications regarding plagiarism.



28/04/2014

Melanie Skeen Date:

Expression of thanks

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A word of thanks to Barbara English for the language editing.

To Prof Becker, a word of thanks for the statistical advice and analysis during the study.

Letter from the language editor

TO WHOM IT MAY CONCERN

I, Barbara English, confirm that Melanie Skeen (student number 02450194; University of Pretoria) had her dissertation for the degree M Phys T in the School of Health Care Sciences language edited by me.

The title of the dissertation concerned was “A critical analysis of the functional outcome of people with spinal cord injuries who have received stem cell therapy”.

Barbara English
Director of Wordsmiths English Consultancy

27 November 2014

Abstract

A spinal cord injury (SCI) can result in severe dysfunction and disability. Stem cell therapy is seen as a potential means of promoting healing and improving function in patients with SCIs and several early-phase clinical trials are underway. Treatment for SCIs using stem cells is also being offered in some countries and patients who had received these treatments were participants in this study. The aim of the study was to determine the functional outcomes of persons with SCIs who have undergone stem cell therapy.

Methods and Patients: Eleven (11) persons with SCIs who had received stem cell therapy in various forms were identified. Informed consent was obtained from all participants. A survey was carried out using a questionnaire and the Spinal Cord Independence Measure (SCIM) III to collect data on the nature of the injury, the nature of the treatment and its cost, and measurement of the person's functional status.

Results: Comparisons were drawn between the impairment and functional ability pre- and post stem cell therapy and expected outcomes of people with SCIs, using the SCIM III. Four (4) of the participants SCIM III scores remained unchanged. One (1) participant's score fell by ten (10) points after the stem cell therapy. One (1) participant improved by one (1) point and then returned to his previous level of dependency once back home again. Of the six (6) participants who improved post stem cell therapy three (3) achieved their expected SCIM III scores. On average the participants SCIMs improved by 6 points, which is to be expected post-acute rehabilitation as described by Ackerman et al. (2010). No new muscle innervation was reported. Sources of stem cells were autologous, xenogeneic and allogeneic. Stem cells were administered orally, subcutaneously, intravenously, intramuscularly. Cost of the treatment ranged from R0 - R700 000.

Conclusion: There is no evidence that the forms of stem cell therapies utilised by these people with SCIs and administered outside of registered clinical trials are beneficial. Education is needed both for people with SCIs and rehabilitation health professionals working with these people to enable the latter group to make informed decisions based on research evidence. Correct ethical research is to be encouraged in the field and patients should be selected for trials using well defined criteria. Only safe and clinically verified procedures should be carried out on patients once the required research has

been completed. People with SCIs should be warned about the presence of stem cell tourism that is still a common occurrence.

Table of contents

List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ADL	Activities of daily living
ASIA	American Spinal Injury Association
AFO	Ankle foot orthosis
BDNF	Brain-derived neurotrophic factor
BMSC	Bone marrow stem cells
BPI	Brief pain inventory
C	Cervical
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CISC	Clean intermittent self-catheterisation
CNS	Central nervous system
CPD	Continued Professional Education
ESC	Embryonic stem cell
FDA	Federal Drug Administration
FIM	Functional Independence Measure
FPS-R	Faces Pain Scale-Revised
GCP	Graded chronic pain questionnaire
GDNF	Glial-cell-derived neurotrophic factor
GSW	Gun shot wound
ISCoS	International Spinal Cord Society
ICCP	The International Campaign for Cure for Spinal Cord Paralysis
ICF	International classification of functioning, disability and health
ICORD	International collaboration on repair discoveries
L	Lumbar
LEMS	Lower extremity motor score
MBA	Motorbike accident
MPSS	Methylprednisolone sodium succinate
MVA	Motor vehicle accident

NASIS	National Acute Spinal Injury Studies
NGF	Nerve growth factor
NRS	Numeric rating scale
OEC	Olfactory ensheathing cells
Para	Paraplegic
PEDro	Physiotherapy Evidence DSCIREatabase
Quad	Quadriplegic/tetraplegic
QASA	Quad Para Association of South Africa
SASCA	Southern African Spinal Cord Association
SC	Schwann cell
SCI	Spinal cord injury
SCIM	Spinal Cord Independence Measure
SCIRE	Spinal Cord Injury Rehabilitiation Evidence
SCOPE	Spinal Cord Outcomes Partnership Endeavor
SD	Standard deviation
RAF	Road Accident Fund of South Africa
RCT	Randomised controlled trial
RSA	Republic of South Africa
T	Thoracic
TB	Tuberculosis
TRH	Thyrotropin releasing hormone
UCB	Umbilical cord blood
UEMS	Upper extremity motor score
USA	United States of America
UTI	Urinary tract infection
VAS	Visual analogue scale
VRS	Visual rating scale
WHO	World Health Organization
ZPP	Zone of partial preservation

List of definitions

Activities of daily living (ADL): "*activities involved in self-care, communication and mobility, such as dressing, eating and other skills necessary for independent living"* (Steeves JD, Fawcett JW, Tuszynski MH, Lammertse D, Curt AEP, Ditunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, Havton LA, Grossman R, Short DJ, Nakamura M, Katoh H, Coleman WP, Gaviria M, Privat A, Kalichman MW, Rask C, 2007 pg. 34).

ASIA impairment scale (AIS): "*describes the completeness or severity of the spinal injury*" – see ASIA learning centre http://www.asia-spinalinjury.org/elearning/elearning.php

ASIA A: "*no motor or sensory function at the level of S4 & S5 sacral segments"*
ASIA B: "*sensory sparing below the injury including S4 & S5 but no motor sparing"*
ASIA C: "*some motor function below the neurological level but more than half of the key muscles have muscle strength less than 3/5 (non-functional)* "
ASIA D: "*motor function below the lesion level but more than half the muscles have a muscle strength of 3 or more out of 5 (functional)"*
ASIA E: "*normal motor and sensory function" (Steeves et al., 2007, pg. 34)*

ASIA motor score: "is *calculated on an ASIA chart, by assigning to one muscle group, innervated and primarily identified with a specific level, a score between 0 (no detectable contraction) and 5 (active movement and a full range of movement against maximum resistance). C5-T1 and L2-S1 are tested giving 10 levels on each side of the body for a possible maximum score of 100"* (Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, Bartlett PF, Blight AR, Dietz V, Ditunno J, Dobkin BH, Havton LA, Ellaway PH, Fehlings MG, Privat A, Grossman R, Guest JD, Klietman N, Nakamura M, Gaviria M, Short D. 2007, pg. 204).

Central nervous system (CNS): "*The CNS consists of the brain and spinal cord. Information coming to and from the CNS is conducted via the peripheral nervous system* (PNS)" (Steeves et al., 2007, pg. 35).

Complete and incomplete SCI: *"are other terms used to describe the overall severity of SCI. Technically, SCI is classified as complete if there is no motor or sensory function preservation in the sacral (most caudal) segments. Thus, incomplete SCI is where there is some preserved motor or sensory function at the lowest sacral spinal level (S4/S5). There can be extensive variability in the degree of preserved function after incomplete SCI" (Fawcett et al., 2007, pg. 204).*

Functional independence measure (FIM):"*records the severity of disability of people after a disabling disorder. The 18 FIM items define two statistically and clinically different indicators. Thirteen items define disability in motor functions. Five items define disability in cognitive functions. FIM was not specifically designed for any single disability situation such as spinal injury" (Steeves et al., 2007, pg. 36)*

Helsinki Declaration: "*the Helsinki Declaration was developed by the World Medical Association and is a set of ethical principles for the medical community regarding human experimentation. It was originally adopted in June 1964 and has since been amended multiple times."* Recommendations can be found at www.wma.net/e/policy/b3.htm

Paraplegia: *"… term used to refer to functional loss* (paralysis) *below the level of the upper extremities, which may involve loss of motor and/or sensory function within the trunk, and/or the lower extremities. This implies damage to the spinal cord* (either by disease or injury) *below the level of C8 and may include damage to conus medullaris or cauda equina (i.e. neural tissue within the spinal canal)*" (Fawcett et al., 2007 pg. 204).

Spinal cord independence measure (SCIM): *"a scale* (outcome measure) *for assessing function and activities of daily living that appears to be more sensitive and accurate for assessing SCI than the Functional independence measure (FIM). The*

SCIM is a 100-point disability scale developed specifically for SCI with an emphasis on 18 activities associated with:

1. *Self-care (feeding, bathing, dressing, grooming) max 20 points*
2. *Respiration and sphincter management (breathing, bladder, bowel, use of toilet) max 40 points*
3. *Mobility (in bed, transfers, indoors and outdoors, wheelchair, walking) max 40 points"* (Steeves et al., 2007, pg. 37).

Stem cell: "*Stem cell is a term used to describe a specific type of cell with two major characteristics: the capability to differentiate into multiple cell types and the ability to maintain a self-renewing population."(Donnelly, Lamanna and Boulis 2012 pg 1)*

Tetraplegia / quadriplegia: "*the term used to refer to loss of motor and/or sensory function due to damage (either by injury or disease) to the spinal cord, the impairment of the upper extremities as well as trunk, legs and pelvic organs. This implies damage to the spinal cord at or above the C8 level*" (Fawcett et al., 2007 pg. 203).

Zone of partial preservation (ZPP): "only used when SCI is complete and refers to those segments below the neurological level of injury where there is some preservation of impaired motor or sensory function (usually, but not always, within a few segments of the neurological level)" (Fawcett et al., 2007 pg. 204).

List of tables

List of Figures

Chapter 1

Introduction and problem identification

1.1. Introduction

Spinal cord injury (SCI) is a devastating and debilitating injury. The first record of a SCI is to be found in the Edwin Smith Egyptian Papyrus written in approximately 1700BC and it is described as an injury to the neck vertebrae accompanied by paralysis and as "an ailment not to be treated" (Elsberg 1931). By the middle of the 20th century the standard treatment entailed the repositioning of the spine and either surgical or non-surgical fixation, followed by rehabilitation of the residual abilities (Eltorai 2003, pg.4). Since then many new alternative therapies have been proposed, one of which is stem cell therapy.

The incidence and prevalence of SCI have been published and figures vary. The published data estimating the worldwide prevalence of SCI, although insufficient, when reviewed by Wyndaele and Wyndaele (2006, pg. 532) was found to be in the range of 223–755 per million inhabitants. Wyndaele and Wyndaele (2006) reported incidence of SCI lies between 10.4 and 83 per million inhabitants per year. Lim and Tow (2007, pg. 49) report that traumatic SCI occurs at a high incidence of between 15-40 per million population worldwide. The World Health Organization's fact sheet N°384 of November 2013 reports that "around the world between 250 000 and 500 000 people suffer a spinal cord injury every year." (http://www.who.int/mediacentre/factsheets/fs384). The only South African data available indicates an incidence of 104 per million inhabitants (Theron and Burger, 2003), which is well above the worldwide incidence. Although South Africa has no spinal cord register, the CEO of the Quad Para Association of South Africa (QASA) states that over 750 SCIs are sustained per year, giving an incidence of 14.48 per million (Seirlis in personal email, 2013). The same author also indicated that the South African Road accident fund (RAF) reported 150 new SCIs over the months of December 2012

and January 2013 which, if taken over a year, would amount to 900 SCIs per year in road traffic accidents alone, or an incidence of 17.32 per million population. These statistics are both presumed to be underestimates, as their data collection methods are not faultless. Other traumatic causes of SCI in South Africa are interpersonal violence, industrial accidents and sporting activities (Theron and Burger 2003).

There are non-traumatic causes of SCI and in South Africa the major cause would be Tuberculosis (TB) often associated with Acquired Immunodeficiency syndrome (AIDS). This dissertation focuses on persons with traumatic injuries who have received stem cell therapy. Persons with non-traumatic causes of SCI such as TB, spine and tumours have not been included because nobody in the sample of volunteers had non traumatic SCI.

One-third of patients with SCI worldwide, regardless of the cause, are reported to be tetraplegic and around 50% of patients with SCI are reported to have a complete lesion (Wyndaele and Wyndaele 2006). The mean age at which patients sustain a SCI is reported to be 33 years, although a bimodal distribution is beginning to emerge with a second incidence peak in older adults primarily due to injuries as a result of falls in the older population. The gender ratio between men and woman in the population is reported to be 3.8/1 (Nandoe Tewarie Rishi, Hurtado, Bartels, Grotenhuis and Oudega, 2010). In this study the average age was 36.9 years, with a male/female ratio of 2.6/1 and 2/3 of the patients sustaining tetraplegic lesions.

1.2. Pathophysiology of SCI

A SCI results in both primary and secondary tissue damage. Primary tissue damage to the spinal cord is the result of the primary mechanical injury while secondary damage results from ischemia, anoxia, free radical formation and excitetoxicity, lipid peroxidation, and an inflammatory response that occurs after the injury (Mothe and Tator 2012). Macrophages and other cells form an extracellular matrix resulting in glial scar tissue that forms a physical and chemical barrier to regeneration of axons at the site of the injury in the spinal cord. The process of scar-tissue formation leads to the presumption that central nervous system (CNS) axons do not regenerate, unlike axons in the peripheral

nervous system, which do regenerate post-trauma. When a peripheral nerve graft was transplanted into a rat's spinal cord it resulted in robust growth of the spinal cord axons into the graft, suggesting that the lack of recovery in the CNS is due to the hostile environment that is created by the glial scar and that inhibits regeneration (Thuret, Moon and Gage 2006). To counteract this presumed barrier and promote endogenous neuroregeneration, biologic therapies such as Condriotinase ABC, Anti Nogo, inhibition of Rho activation and stem cells are being studied. Pharmaceutical drugs are also being investigated as potential treatment to enhance endogenous neuroregeneration. These will be described more fully in Chapter 2.

The primary argument behind the use of biological and pharmaceutical inhibition of glial scar tissue is that if the inhibitory factors for axonal growth are limited then the possibility of using stem cells as a further regenerative treatment becomes viable. Garbossa, Boido, Fontanella, Fronda, Ducati and Vercelli (2012) suggest that stem cells can provide trophic and immunomodulatory factors to stimulate axonal growth, to modulate the injured spinal cord environment and to reduce inflammation to preserve function and promote healing of the SCI.

The impairments following SCI are loss of motor, sensory and autonomic function (Anderson 2004). These impairments are the result of damage to the spinal cord axons, loss of neurons, the activation of astrocytes and microglia and demyelination and degeneration of oligodendrocytes (Tator 2006).

The SCI leads to impairments in body functions and structure (incontinence, paralysis, poor balance, spasticity, contractures) and these lead to activity limitation such as bed mobility, balance, gait, transfers, dressing, and washing. SCI also leads to decreased participation in activities of normal life such as work, recreation, sport and all levels of social interaction and community reintegration, which are all affected by the person's environmental and personal factors as well (International Classification of Function, Disability and Health ICF, WHO 2001).

1.3. Medical management and rehabilitation of SCI

Historically, treatment of a person with an SCI includes emergency medical care, resuscitation and stabilisation of the injury, prevention of secondary injury, surgical decompression and fusion. Once the patient is stabilised rehabilitation can commence (Garbossa et al., 2012). The epidemiology of SCI changed drastically after the Second World War. The last few decades people sustain more incomplete injuries, more specialised rehabilitation centres are available to these patients and patients have longer survival periods post injury and post rehabilitation (Krause, Carter, Pickelsimer and Wilson 2008). The longer survival periods post SCI are mainly due to better understanding and management of patients, such as preventing pressure sores and improving bladder and bowel management. The primary aim in treatment of SCI at present is to decrease levels of mortality and numbers of complications. Another aim is optimisation of residual function of body structures so that the patients' activity limitation is reduced. This optimisation of functional ability occurs during participatory activities in daily life to reduce the burden of care of the patient (Garbossa et al., 2012).

The cost of management of an SCI are high and rehabilitation is recommended as an integral part of an effective treatment regime (Krause et al., 2008). The recovery and rehabilitation period is long and the lesion only stabilises neurologically at 18-24 months post injury. Munce, Wodchis, Guilcher, Couris, Verrier, Funq, Craven and Jaqlal (2013) describe the cost of SCI as $123,674 (R1, 138 963.41) for the first year post injury per patient. In paragraph 2.2.1 the treatment of SCI is discussed in more depth.

One of the new and popular possible biological treatments for SCI is stem cell therapy. However, up to the present time there is not yet any research-based evidence that stem cell therapy results in a cure for SCI. Despite this fact, stem cell therapy is being offered on Internet websites as a SCI cure or as treatment to improve functional ability of patients' with SCIs.In paragraphs 1.4 & 1.5 the potential of stem cell therapy as a treatment for SCIs is discussed in more detail.

1.4. Stem cells

1.4.1. Stem cells as treatment of SCI

Stem cells have been demonstrated to be beneficial in terms of motor and functional improvement in rodent models of spinal cord disease and injury (Bregman, Kunkel-Bagden, Reier, Dai, McAtee and Gao 1993; Lau, Ogbogu, Taylor, Stafinski, Menon and Caulfield 2008; Curt, JA Van Hedel, Klaus and Dietz 2004; and Lukovic, Stojkovic, Moreno-Manzano, Bhattacharya and Erceg 2014). However, the associated risks of experimental therapy, the differences between rat and the human locomotor and corticospinal systems, the injury models used in experimental SCI rat models were different from the average traumatic SCI sustained in the population of people with SCI. (Dobkin, Curt and Guest 2006, Lukovic et al., 2014), These differences are facts that make the translation of experimental research to clinical medicine difficult. Despite this difficulty in translation from research in rodent models into treatment of human SCI, the cell transplantation industry continues to expand, with international commercial clinics offering stem cell therapy for a variety of diseases including SCI (Chhabra, Lima, Sachdeva, Mittal, Nigam, Chaturvedi, Arora, Aggarwai, Kapur and Khan 2009). These clinics are advertised widely on the Internet and many persons with SCI are being encouraged through the promises on these sites and family and friends, to seek this treatment. People with SCI visit these clinics in search for a cure of the SCI or improvement of their functional capacity resulting in a phenomenon known as stem cell tourism. Stem cell tourism is discussed further in paragraph 2.2.3.

According to Donnelly, Lamanna and Boulis (2012) recent advances in stem cell technology have opened up a new avenue for the treatment of SCI and spinal cord disease. Should it be possible for stem cells to grow into new neurons in the spinal cord then this would bring about a possible cure for SCI. Stem cell therapy still needs to be proven through ethical scientific trials in humans before it can potentially become a recommended or recognised treatment for SCI.

1.4.2. What are stem cells?

Stem cells are cells in the body that have the ability to divide autonomously and to differentiate into the more that 200 cell types that constitute the body. These cells maintain and repair the body tissue (Mothe and Tator 2012, pg 3825). Stem cells can be obtained from many sources: embryonic cells, foetal tissue, umbilical cord blood, adult bone marrow (mesenchymal tissue), adult central nervous system tissue and induced pluripotent stem cells created from the skin or other tissue such as adipose tissue. However, there are ethical questions regarding the use of stem cells (Donnelly et al., 2012).

1.4.3 Ethical issues regarding the use of stem cells as treatment modality for injury, pathology or disease

The use of human embryos to obtain stem cells is an ethical choice that depends on one's belief concerning the beginning of human life. Many people believe that life begins at conception and, therefore, preparing stem cells from the inner cell mass of a blastocyst would be considered destroying human life (Ertelt 2009).

A further ethical dilemma presents when people with SCI who are seeking alternative treatment procedures are misled by clinics that offer recovery after stem cell therapy on the Internet. Cures for hundreds of dreaded incapacitating conditions and diseases are offered on the Internet. This advertising results in patients then travelling the world to far off places for therapy offered to cure their condition. Currently, there is no scientific published evidence that stem cell therapy can cure SCI in humans. It is therefore unethical for hospitals, clinics and doctors to make such claims over the Internet when there is no evidence to support their statements (Fawcett et al., 2007; Lukovic et al., 2014).

1.4.4. Other sources of stem cells

There are other sources of stem cells to avoid the use of human embryonic stem cells and in this way bypass the ethical dilemma. Some centres are reportedly using stem cells other than of human origin – called "xenogeneic" stem cells – such as cells from rabbits or sheep (Mills 2009). The question

arises as to whether these xenogeneic stem cells are effective to use in humans to grow human tissue or whether rejection of these stem cells is to be expected.

Another practice that has recently begun is the use of a nutritional supplement to enhance the body's production of stem cells. These supplements are advertised to enable the body to maintain and repair tissue and organs (Pienaar 2012). This type of advertising, however, is a contentious issue and no scientific published article on human trials was found on a PubMed data base. There are websites warning people against the lack of evidence and potential harm of these supplements, such as liver failure and tumour formation. (Peterson 2007 np.)

There are also methods of stimulating stem cell release from the bone marrow into peripheral blood before harvesting cells from the blood (Kawada 2006, Jensen, Hart, Zaske, Drapeau, Gupta, Schaeffer and Cruickshank 2007).

Researchers have also shown that it is possible to engineer stem cells back to the pluripotent state. These stem cells called "induced pluripotent stem cells" are now being used (Yu, Vodyanik, Smuga-Otto, Antosiewicz-Bourget, Frane, Tian, Nie, Jonsdottir, Ruotti, Stewart, SlukvinII and Thomson 2007).

1.4.5. The challenges of stem cell therapy for SCI

In the population group of people with SCI, the injuries are often more severe than laboratory-induced injuries to rat models as mentioned above. SCI in humans is the result of a combination of severing of the spinal cord, pressure and loss of blood supply to the spinal cord. The severity of such an SCI will affect the outcome of the stem cell therapy at structural and functional level, as well as the levels of activity and participation. For example, if the spinal cord is completely severed the chances of recovery are reduced; an incomplete injury has a better chance of recovery (Lukovic et al., 2014).

There is the associated risk of tumour growth after stem cell transplantation, especially if undifferentiated embryonic stem cells are transplanted into an injury site (Ronsyn, Berneman, Van Tendeloo, Jorens, Ponsaerts 2008).

Another reported complication is that stem cell transplants could give rise to increased neuropathic pain or allodynia as a result of aberrant axonal sprouting (Mothe and Totor 2012, pg 3826).

1.4.6. Present recommendations by international bodies

At present no form of stem cell therapy is recommended for the treatment of SCI by the International spinal cord society (ISCoS), according to Blight, Curt, Ditunno, Dobkin, Ellaway, Fawcett, Fehlings, Gossman, Lammertse, Privat, Steeves, Tuszynski, Kalichman and Guest 2009, or by the International Campaign for Cure for Spinal Cord Paralysis (ICCP) (Steeves et al., 2007; Garbossa et al., 2012.)

1.4.7. Rehabilitation and stem cell treatment

The persons in this study who received stem cell therapy were all encouraged by the clinics where they received the stem cell therapy to undergo at least a three-month period of rehabilitation post stem cell therapy. Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical-, sensory-, intellectual-, psychological- and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination (WHO website January 2014). Rehabilitation as a therapy for people with SCI endeavours to harness the residual function after an impairment, which is not a cure as such but is based instead on the harnessing of residual function on body structure and function level. Rehabilitation retrains muscles, skills and function so as to enable resumption of activities and then to optimise the patient's participation in activities of daily life (ADL) in their environment.

If stem cell transplant can result in reconnection of neurons and enable re-innervation of muscles and dermatomes and new function can be brought about, intensive rehabilitation will be required to harness the new muscle power and increase it and rehabilitate it into functional activities.

1.5. Clinical implications of stem cell therapy and rehabilitation

In the technological age in which we live, the majority of patients experiencing an SCI have access to the Internet and a vast amount of information at their fingertips: be it from the print media, television, Internet or by word of mouth. Persons suffering a traumatic SCI are bombarded with information concerning possible cures from well-meaning friends and/or family members. People are desperate for a cure that would improve their ability to walk following a devastating SCI (Anderson 2004). Many are willing to pay large sums of money for the promise of a cure, especially when their doctor and therapeutic team cannot offer the recovery they seek. A Google search of the words: stem cells for spinal cord injuries, resulted in 1 940 000 hits (6 January 2013). The first link reads: ”walking after SCI”; after such an introduction words such as “hope” and “cure” are used regularly on sites. Other websites use phrases such as “embryonic stem cells and SCI cure” and “Stem cell cure”.

Some information on the web appears to be biased, anecdotal, unscientific and misleading, especially information placed onto Internet websites by centres offering stem cell therapy. Internet websites often have patient testimonies of their improvement, videos and non-scientific proof of the efficacy of stem cell transplant instead of non-biased evidence-based information based on recognised randomised controlled trials. The videos and testimonials give limited information and show snippets of information aimed at encouraging others to seek the treatment.

Doctors and specialists citing years of experience and large numbers of successful procedures are also displayed on these websites (Dobkin et al., 2006). Many sites speak of research being done and success rates for procedures but there are no scientific results and no peer-reviewed research published in scientifically recognised journals or literature that back up their claims (Nelson 2008). Many clinics worldwide and especially in India and China and at one stage even in a clinic active in Germany are offering cures for SCI using stem cells (Tator 2006).

The fact that people with SCI obtain knowledge about the sites / venues where stem cell therapy is provided result in the emerging phenomenon “stem cell

tourism" where people travel to far-off countries to seek treatment for their SCI (Nelson 2008, Lau et al., 2008, Kiatpongsan and Sipp 2008).

In private rehabilitation units in South Africa, patients that hail from the higher economic strata of society who have the financial means to afford this stem cell therapy are targets of this World Wide Web advertising campaign. These people with SCI fly to distant locations for treatment that is not available in recognised Western specialist SCI evidence rehabilitation centres (Amadour 2005). Fawcett et al. (2007) comment on these experimental therapies, writing that they have been included into clinical practice without clinical trial completion (Lukovic et al., 2014).

Rehabilitation professionals working in a spinal unit encounter large numbers of patients enquiring about the possibility of stem cell therapy as a cure for their injury. It is therefore essential that accurate and updated information is given to these patients. However, despite the provision of accurate information on the lack of benefit from this form of intervention, patients are not deterred from seeking out stem cell therapy with the hope of recovery. The role of rehabilitation professionals in providing people with SCI with evidence-based information to allow them to make informed decisions cannot be overemphasised (Amadour 2005). There is, however, no concise, appropriate and practical summary that can be used by health professionals to provide patients who enquire about stem cell therapy with evidence-based information in order to make an informed decision regarding stem cell therapy.

1.6. Recovery from SCI and outcomes and efficacy of treatments for SCI

The main concern about stem cell therapy being given as treatment is the lack of research evidence of efficacy of treatment. A complicating factor in proving the effectiveness of rehabilitation or treatment for SCI is the fact that after an SCI there is a natural recovery response in a percentage of subjects. This makes the study of efficacy of any, but specifically stem cell therapy treatment, more difficult (Fawcett et al., 2007). The natural recovery process after SCI will be discussed further in Chapter 2.

In assessing the outcome or efficacy of therapeutic interventions, a combination of both the assessment of neurological deficits and remaining spinal conductivity (impairment) is required as well as the person's functional outcome (functional ability or activity level and participation in their home, family roles and socio-economic environment) (Curt, JA Van Hedel, Klaus and Dietz 2004). Re-assessment of a patient participating in a trial should be done at regular pre-determined intervals to monitor change. Without the assessment of the outcome of interventions on a regular basis, reports and claims of improvement are merely anecdotal and hearsay. The fact that a person with SCI says he/she "feels better" after a procedure is not sufficient evidence of an actual improvement or efficacy and may, on further investigation, reveal a placebo effect.

Improvement in an impairment level (level of body function and structure; i.e. sensation or muscle strength) does not necessarily reflect in changes in the person's level of ability to perform functional activities (activity level) and participation in daily community life and vice versa. Improved function may not necessarily be due to nerve regeneration but, instead, to skills learnt or neural plasticity (Wirth, van Hedel, Kometer, Dietz and Curt, 2008).

Neurophysiological recordings such as neurography, somato-sensory-evoked potential and motor-evoked potentials are done to test spinal tract function (Curt et al., 2004) but were not used on participants in this study.

Objective prediction of patients' functional outcome after an SCI and the assessment of their functional outcome post rehabilitation is a topic that is addressed extensively in the literature (Formal, Cawley and Stiens 1997, Aidinoff, Front, Itzkovich, Bluvshtein, Gelernter, Hart, Beiring-Sorensen, Weeks, Laramee, Craven, Hitzig, Glazer, Zeilig, Aito, Scivoletto, Mecci, Chadwick, El Masry, Osman, Glass, Soni, Gardener, Savic, Bergstrom, Silva and Catz, 2011). Based on the validity of assessment scales (outcome measures) it is possible to predict the functional outcome of patients post SCI. The most recognised, valid and reliable outcome measures for assessing impairment and function as well as activity in participation levels are the ASIA scale and the SCIM III respectively (Formal et al., 1997, Adinoff et al., 2011).

There are many ways of predicting patients' functional outcomes, one being the accurate neurological assessment using the ASIA scale as soon as possible after the injury (Maynard, Bracken, Creasey, Ditunno, Donovan, Ducker, Garber, Marino, Stover, Tator, Waters, Wilberger and Young, 1997). In the current study the ASIA and SCIM III were used to assess change in participants' motor strength (impairment-level assessment) and activity and participation level functional ability post intervention. The validity and reliability of the outcome measures is discussed at length in the following chapter.

1.6.1. Assessment of functional outcomes

Functional outcome can be assessed by scoring the ADL using the SCIM outcome measure (Itzkovich, Gelernter, Biering-Sorensen, Weeks, Laramee, Craven, Tonack, Hitzig, Glaser, Zeilig, Aito, Scivoletto, Mecci, Chadwic, El Masry, Osman, Glass, Silva, Soni, Gardiner, Savic, Bergstrom, Bluvshtein, Ronen and Catz 2007; Catz, Itzkovich, Tesi, Biering-Sorensen, Weeks, Chadwick, El Masry, Osman, Glass, Silva, Soni, Gardner, Savic, Bergstrom, Bluvshtein and Ronen 2007). The SCIM III reflects the level of independence or participation of people with SCI, which is not necessarily demonstrated in the results of the neurological assessment (Hall, Cohen, Wright, Call and Werner 1999; Wirth et al., 2008). The SCIM shows how the muscle strength and sensation measured in the neurological assessment are used functionally in ADL. Fawcett et al. (2007) also state that no SCI therapy can be considered effective for the treatment of patients unless the therapy improves the abilities of the patients to function in their daily activities and routines.

1.7. Research problem

The researcher, having worked in a spinal rehabilitation unit for many years and having been asked to rehabilitate 3 patients after their stem cell therapy, realised that although the patients showed good motivation and were committed to their rehabilitation programme, no obvious improvement in their neurological status and functional ability (more than what was expected for the type and level of lesion they sustained) was noticed. The lack of functional improvement and the false expectations generated by the Internet websites and centres that performed the stem cell therapy stimulated the study in this area.

Another factor was the importance of conducting a study to investigate this subject and to limit if not prevent harm and abuse of those with SCI who find themselves in an emotionally vulnerable position and seeking a cure. Another fact that stimulated the study was the large amount of money being asked by the clinics for the stem cell therapy. The apparent lack of results and an ethical concern about unfounded promises of cures being promised and not delivered were additional motivatination to carry out this study. The fact that these so-called “cures” were not being recommended by professionals in the field and that there was no evidence that they could cure SCI also concerned the author. Another concern was the possibility of complications from the stem cell therapy that was not communicated on the website such as pain, loss of function, tumour growth or even no change, which could have devistationg emotional side effects. Patients have the right to receive accurate information from their health care professionals and the website information regarding stem cell therapy is apparently not correct / accurate. The only way to obtain evidence on the outcome of these stem cell treatments that patients were being given was to carry out a study of these patients and their functional outcomes after the treatment and to document the results.

1.7.1. Aims of the study

The primary aim of the study was to perform a critical survey of persons who received stem cell therapy following their traumatic SCI to determine whether the stem cell therapy had any influence on their level of functional ability as measured on the SCIM III.

The secondary aims were
To use the findings from this research-evidence-based study to inform and educate health professionals and potential patients who might consider stem cell therapy so that they can make an informed decision about the potential effect of the treatment based on research evidence.

1.7.2. The objectives of the study were:

To obtain the following information from patients who had undergone stem cell therapy:

a) The level of the SCI;

b) Their perceived outcomes;

c) The nature of the stem cell therapy;

d) The costs involved in the stem cell therapy (direct and indirect); and

e) The patients' experiences of the stem cell therapy.

To use the SCIM III to compare the functional ability of persons who had undergone stem cell therapy with the functional outcomes expected for the same level of injury based on the current literature.

To compile an information leaflet that provides guidelines to health care practitioners and their patients who consider stem cell therapy to assist them in making an informed, evidence-based decision regarding stem cell therapy.

To make results of the study available via presentation of papers at conferences and talks at rehabilitation workshops or continual professional development workshops (CPD) to professionals in the field of SCI to assist them in giving information to the patients they work with.

1.8. Layout of this dissertation

In Chapter 1, the background to this study and the core problem were discussed. The aims and objectives of the study were set out.

In Chapter 2, the literature on the subject of SCI, recognised treatments, rehabilitation, treatment and stem cell therapy is set out, as is the recovery after SCI and sample sizes required for SCI trials. Present and future possible treatment for SCIs and stem cells in particular are described. Stem cell trials and tourism and the translation from laboratory research to treatment of patients are set out. The ASIA, SCIM III and VAS and NRS outcome measures that were used in this study and their reliability and validity are described.

In Chapter 3 a detailed report is given as to how the research was undertaken. The study design and methodology are described.

In Chapter 4 the biographical data and results are tabulated and presented. The data is analysed and the results described and explained. The demographic data of the participants of the study are also tabulated.

In Chapter 5 the results of the research are discussed and a conclusion on the research is given. Limitations of the study are set out and suggestions for further research are made.

Chapter 2

Literature Study

2.1. Introduction

The aim of this chapter is to summarise the current literature on the subject of this dissertation, describe how the literature was sourced and analysed and set out the current information on the topics set out below.

- The current internationally recognised SCI treatment is presented. Patient's potential recovery after SCI and appropriate issues regarding studies in the SCI population are described. New treatment possibilities for SCI are investigated in rehabilitation-, surgical- and biological areas.
- Stem cell therapy for SCI is looked at under the following headings: what are stem cells?; stem cell trials that are currently taking place; and stem cell tourism.
- The translation of laboratory research to bedside implementation of the results is investigated.
- The assessment tools are described for determining:
    - a patient's baseline impairment at body and structure level,
    - functional ability on the level of participation
    - the identification of potential change in these levels based on any type of intervention.

The outcome measures used in this study were the

- ASIA scale
- SCIM III
- VAS & NRS

The literature search strategy that was followed to identify the relevant literature was an electronic literature search using Google as well as the electronic library data bases of the University of Pretoria. The initial search was done in January 2010 and then follow-up searches were done with the final one carried out in August 2014 to update the literature The following key words were used:

- Spinal cord injury
- Stem cells
- Stem cell therapy
- Outcome measures for SCI
- SCIM III
- ASIA
- Spinal cord injury rehabilitation
- Stem cell treatment
- Spinal cord injury treatment

On the 20 August 2014 a search was done by using the following key words:

- Spinal cord injury, human stem cell therapy, outcomes.
- SCIM, spinal cord injury and ASIA motor scores
- Visual analog scales, numeric rating scales

The search requested publications from the last 5 years only (2009-2014)

The following search engines were used:

- Science Direct
- PubMed
- Medline
- CINAHL

- Scopus
- PEDro
- Google scholar
- Google

The original literature included animal trials where relevant and articles from 1960 to 2014 were used and they were included to get the full history of the use of stem cells in SCI and get a historical prospective of changes in SCI treatment over the last 50 years.

The search included only: 1) RCTs; 2) case studies; 3) position statements; 4) clinical observation studies; 5) systematic literature reviews; and 6) retrospective case reviews.

Searches were also done on Google to see the specific stem cell therapy offered by clinics and to assess the information persons with spinal cord injuries are exposed to. The key words used in this search were “stem cells for spinal cord injury”.

The following websites were also visited:

ASIA: http://www.asia-spinalinjury.org/

SCIRE: http://www.scireproject.com/

ISCOS: http://www.iscos.org.uk/

Miami project: http://www.miamiproject.miami.edu/

QASA: http://www.qasa.co.za/

ICCP: http://www.campaignforcure.org/

Beike: http://beikebiotech.com/

Christopher Reeve Foundation: http://www.christopherreeve.org

The Spinal cord injury zone: http://www.spinalcordinjuryzone.com/

Rehab measures:http://www.rehabmeasures.org/Lists/RehabMeasures/

International collaboration on repair discoveries [ICORD]:www.icord.org

These websites were either known to the researcher because of her experience in the field or websites she came across in articles used in her research or found on the Internet during her research.

Firstly, all titles of articles were scanned and the most appropriate ones' abstracts were read and evaluated to see if the articles were appropriate for shortlisting. Following this process the full articles of the shortlisted abstracts were then sourced. Relevant articles were then appraised according to relevance to the study subject matter and PEDro guidelines for assessing clinical trials. Bibliographies of useful and appropriate articles were also scanned for further relevant articles on the subject matter (snowballing). If these articles were found to be relevant and or useful they were also included.

2.2. SCI treatment and recovery

2.2.1. Historical and current recognised SCI treatment

The first recorded mention of an SCI is to be found in an Egyptian Papyrus scroll written in approximately 1700BC as an injury to the neck vertebrae accompanied by paralysis. In 1927 Harvey Cushing described the outcome for soldiers with SCI sustained during World War I: "Fully 80 percent died in the first few weeks in consequence of infection from bedsores and catheterization" (Cushing 1927, pg 749).

The management of SCI changed radically during World War 2. At this present stage the treatment of SCI, according to Brown, Deriso and Tansey (2012), involves acute / emergency intervention to treat and limit the initial injury, followed by the prevention of secondary complications and followed by rehabilitation to maximise on residual function and improve independence and quality of life. Acute or emergency treatment involves accurate assessment of the lesion and medical stabilisation haemodynamically, mechanically through surgery, and monitoring and preventing secondary complications.

Acute care includes maintaining adequate spinal perfusion and surgical intervention, which do not necessarily improve the final functional outcome of the patients but allow for shorter rehabilitation periods and shorter hospitalisation. Besides surgical intervention, pharmacological treatment that is said to limit the secondary injury are sometimes administered. The most common treatment is a high dose of the glucocorticosteroid, methylprednisolone sodium succinate (MPSS) within 8 hours after the injury. This treatment is disputed in some research and many SCI centres are no longer administering it. According to Nandoe Tewarie Rishi et al. (2010), there is still insufficient evidence to support standards of care in the acute phase of treatment of SCI (Nandoe Tewarie Rishi et al., 2010).

As yet there is no known cure for SCI. As the patient moves from acute to sub-acute care the following needs to be monitored and complications prevented: skin for pressure sores, respiratory system to prevent collapse, autonomic nervous system dysfunction, spasticity, pain, gastrointestinal tract slowing, incontinence and constipation, deep venous thrombosis or other circulatory problems such as hypotension and bradycardia, line infections, urinary tract infections (UTIs) and bladder or kidney problems. Contractures and muscle wasting also need to be monitored (Brown 2012). Long-term care can also involve treatment for pain, fertility, autonomic dysreflexia, myositis, contractures, septicaemia, osteoporosis, fractures and depression (Nandoe Tewarie Rishi et al., 2010).

Rehabilitation should start almost immediately after the injury and includes in the acute-care phase harnessing of the person’s residual function, teaching compensatory strategies, promoting neural plasticity, limiting functional loss and complications and in the sub-acute-care phase improving functional outcomes and independence. Improving functional outcomes and independence facilitates independence systematically to higher outcome levels within the patient’s pathophysiology and precautions relevant to the sub-acute phase.

Rehabilitation post the sub-acute phase focuses on functional retraining in ADL such as eating, dressing, grooming, bathing, toileting, mobility and self-care.

Assistive devices and mobility aids are often required, recommended and the patient is taught how to apply these aids correctly and efficiently to optimise his/her functional ability.

The rehabilitation therapists decide together with the patient, how best to combine these different methods of both substitution and neural recovery when possible, to suit the level of injury and the needs of each patient in his or her environment. How independent people with SCI become may depend on their length of stay in rehabilitation, which may be determined by outside factors such as financial constraints or the person's age at the time of the injury (Scivoletto, Morganti, Ditunno, Ditunno and Molinari 2003). There is level 4 research evidence that individuals initially cared for in interdisciplinary, specialist acute care SCI units show more efficient functional gains during rehabilitation and have reduced levels of mortality than individuals who are not rehabilitated in specialised spinal units (Heineman, Yarkony, Roth, Lovell, Hamilton, Ginsburg, Brown and Meyer 1989). Factors such as later age, less function or more severe injury, prior contact with the health system, funding, rural habitation and being unmarried are associated with a greater chance of hospital re-admissions. However, with the improved treatment and management post injury of people with SCI means their their life expectancy now approaches that of the able-bodied population (Fawcett et al., 2007).

In relation to stem cell therapy, if the stem cell therapy can result in development of new neural pathways and reinnervation of muscles or dermatomes, then rehabilitation would be required to harness the newly formed pathways and to teach the patient to use them for improved function. This rehabilitation would then result in improved functional ability at participation level and improved independence. Such an improvement would be evident when the patient is assessed on the SCIM III outcomes measure.

2.2.2. Recovery after SCI and sample size requirements in research trials

The outcomes of an SCI can be quite accurately predicted within the first week of injury (Burns and Ditunno 2001), and most complete injuries recover at least 1 neurological level below their actual level of injury. Patients with incomplete injuries can recover even more neurological levels below the level of injury

within the first year to 18 months after injury (Burns, Lee, Ditunno and Tessler 2003). People with a tetraplegic SCI who are conservatively treated have a 70%-80% chance of recovering one (1) further neurological level after their injury. People with tetraplegia with their pin prick sensation is spared below the level of the lesion of SCI, have a 92% chance of recovery to a 3/5 Oxford muscle strength for first level of 0/5 strength muscles below the injury. Neurological improvement occurs during the first 6-8 months after an acute injury and then plateaus at about 18 months post injury. Fawcett et al. (2007) report that 10% of ASIA A patients get some sensory recovery and another 10% gain some motor and sensory recovery during the 1st year post injury.

In people with incomplete SCI there is an even better chance of improvement. Almost 60% (57%) to 80% of central cord injuries ambulate independently and almost all people with brown sequard lesions walk again (Burns and Ditunno 2001).

Owing to this spontaneous recovery in SCI, large sample groups of patients are required to participate in randomised clinical trials to provide statistical significant research evidence that one type of treatment / rehabilitation is more effective than another. According to Fawcett et al., (2007), the number of persons required for statistically significant results in a randomised clinical trial on patients classified as ASIA A should at least be 480 patients. If a randomised clinical trial is performed on patients classified as ASIA B, at least 2200 participants will be required to participate in the trial.

The time of the application of the treatment procedure, after the SCI, needs to be noted because of the spontaneous recovery in SCI within the first 18 months. Eighty percent of the recovery takes place in the 1st three months and the rest in the 1st year after injury. So fewer participants will be required if the trial takes place in the more chronic phase of the injury; that is after the first 18 months. The acute phase after a SCI is regarded as the period within the first three (3) days after injury and the chronic phase of a SCI is regarded as the period as later than a year after the injury.

2.3. New treatment possibilities for SCI

Many new treatment possibilities are suggested for SCI but none can be recommended without it having undergone sound clinical trials. In the rehabilitation field of SCI the following are being investigated:

2.3.1. Rehabilitation wise

The following modalities have been investigated and are now used in the rehabilitation of SCI:

Functional Electrical Stimulation (where paralysed muscles are stimulated electrically to promote muscle contraction and create muscle bulk). This is often done in conjunction with activity such as cycling or walking. Should the transplanted stem cells form new neural pathways in the spinal cord, then this form of stimulation of muscles would maintain the muscle bulk and contractibility of muscles and result in faster return-to-normal function.

Gravity-assisted ambulation or locomotor training (where assisted walking is performed with robotic or mechanical assistance on a treadmill, to retrain gait patterns). This form of gait retraining will enhance the memory pattern of gait should the neural pathways of gait re-innervate the muscles and dermatomes, which would result in faster recovery of functional gait.

Electrical stimulation of the spinal cord (where the spinal cord itself is stimulated electrically) to re-establish spinal tracts (Tator 2006). This form of stimulation would be advantageous to assist in the development of new spinal tracts should the stem cells be able to develop new neurons.

The use of robotics to enable execution of some motor tasks is also being researched, as well as investigation into the use of cortical control of the robot to perform functional tasks (Nandoe Tewarie Rishi et al., 2010). Robotics is being investigated to assist patients with an SCI to regain a variety of functional tasks because SCI is devastating and that lost motor function is limiting.

Other surgical and biological therapies are also being investigated. These are described in the following paragraph.

2.3.2. Surgical and biological treatments for SCI

Drs Brian Kwon, Okon, Plunet, Baptiste, Fouad, Hillyer, Weaver, Fehlings and Tetzlaff (2011) describe the barrier to neuroregeneration at the level of the SCI. The authors further describe the various directly applied biologic therapies (in contrast to systemically applied therapies) that have been studied to promote endogenous neuroregeneration. They include the following therapies:

Chondriotinase ABC assists with the degradation of inhibitory chondroitin sulphate proteoglycans. This therapy would promote neuroregeneration should the stem cells be effective in the formation of new neurons.

Anti Nogo therapy has been shown through clinical trials to neutralise myelin-mediated inhibition of neural outgrowth (Kwon et al., 2011). So should the stem cell therapy be effective and myelin-mediated inhibition can be inhibited, more neural outgrowth would be possible.

Inhibiting Rho activation: Rho activation affects axonal sprouting and secondary damage at the injury site. So by inhibiting the Rho activation this hopes to have a neuroprotective effect and and in this way reduces scar tissue formation. Cethrin is being used in human clinical trials. If less scarring can take place at the site of the injury the regrowth of new neuron pathways would be facilitated.

Pharmaceutical treatment that has also been investigated for its effect on SCI recovery in animal and human trials includes (Kwon et al., 2011):

ChABC used as an adjunct to stem cell transplant because it promotes axonal sprouting, reduces cystic cavity, suggesting that it can provide a neuroprotective effect to the spinal cord.

Steroids such as Methylprednisolone and Tirilazad to improve neurological recovery, but their use is controversial. These drugs have been used in human trials and are used therapeutically in some centres. Three National Acute spinal injury studies were done (NASIS) where

neurological improvement was shown to occur within 6 months after the SCI. A review of these studies, however, showed myelopathy and increased infections and since then many centres have stopped the use of this drug (Nandoe Tewarie Rishi et al., 2012).

Naloxone, a non-specific opioid receptor antagonist has been shown to reduce allodynia and improve spinal cord conduction and oedema. Researchers failed to show therapeutic effects during a clinical trial.

The controversial evidence on the effect of GM1 Ganglioside, which is a sialic acid containing glycosphingolipids and is effective in preventing demyelination and may contribute to motor function recovery in rats. The first trial was positive but the second not – for this reason the controversy.

Thyrotropin releasing hormone (TRH) administered to reduce secondary injury to the spinal cord. However, the positive results in the first trial have not been replicated in follow-up trials. Should it be possible to reduce the secondary injury to the spinal cord it would open up an avenue for recovery of more function post SCI.

Nimodipine, which is a calcium channel blocker, administered to patients to reduce vasospasm, ischaemia and infarction in the cord post injury. The reasoning behind the administration of this drug was that if vascularisation is enhanced and the injury to the cord due to diminished blood supply reduced, secondary injury would reduce and result in more incomplete spinal lesions which would leave patients with a higher functional level.

Gacyclidine (an aD-aspartate NMDA receptor antagonist) administered to diminish the excitotoxicity from excessive glutamates in the spinal cord. One trial was performed with poor results.

Erythropoietin – a drug containing hematopoietic growth factor – also might have neuroprotective abilities. Its effect in SCI has still to be evaluated.

Anti-CD11d antibodies found to decrease neutrophil and macrophage activity and inflammation and to improve tissue sparing in rat models.

Minocycline, a long-acting, broad-spectrum antibiotic that may inhibit oligodendrocytes and microglia. If such is possible Minocycline can reduce axonal dieback and in this way reduce spinal cord damage. Human clinical trials by administering Minocycline to patients post SCI have started.

Progesterone for improving gene and protein expression and thought to potentially be neuro-protective and prevent spinal cord damage and promote healing. Ten (10) rat studies have been done, where the spinal cords of the rats were transected, with no behavioural improvement after the administration of the progesterone. In rats whose spinal cords were only contused the rats showed behavioural improvements (Kwon et al 2011, pg 1559).

Oestrogen for decreasing tissue damage and apoptosis. However, in these trials the oestrogen was given pre-injury or at the time of injury, which would be almost impossible to do in human SCI. Oestrogen studies in animal trials (rats and mice) reported less autonomic dysreflexia post injury (Kwon et al., 2011, pg 1571).

Magnesium, reputed to improve tissue sparing and decrease apoptosis, which would then reduce SCI deficits. Eight (8) studies were performed on small mammals and magnesium showed an effect when administered up to eight (8) hours after the injury (Kwon et al 2011, pg 1571).

Riluzole (abenzothiazole an anti convulsant that works as a sodium channel blocker) is meant to inhibit excitotoxicity. Eight (8) studies were done on rats, some of which showed reduced spasticity in the tail post trial. The dosages in these animals could not be increased because large doses had systemic side effects. One human trial has been initiated and results are awaited (Kwon et al 2011, pg 1571).

Polyethylene glycol is a drug with fusiogenic properties and has the potential ability to contribute to the repair of damaged axons. As such it

may improve tissue sparing in the spinal cord post injury. A study on rats and guinea-pigs and one (1) canine study was completed. Some other studies showed that neuroprotection took place while others showed behavioural improvement and reduction in allodynia (Kwon et al 2011, pg 1571).

Atorvastatin, found to decrease inflammatory cytokines and increase tissue sparing in the spinal cord. Three studies were done on rats, which showed significant behavioural recovery in the course of these studies (Kwon et al 2011, pg 1579).

The neucleoside Inosine, often taken by athletes as a dietary supplement. It is said to decrease apoptosis and increase sprouting of ascending and descending tracts in the spinal cord. No behavioural outcomes were reported and as yet there is little pre-clinical evidence to support the use of it in acute treatment phase of SCI (Kwon et al 2011, pg 1579).

Pioglitazone, a nuclear hormone receptor and regulator of gene expression and neuroprotection because it has anti-inflammatory effects and anti-neoplastic properties. Researchers claim that it is possible that the drug can bring about neuroprotection and lessen secondary damage in the spinal cord. Two small studies were done to investigate the appropriate dosage (Kwon et al 2011, pg 1579).

The use of growth factors such as brain-derived neurotrophic factor (BDNF), glial-cell-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) have also been administered in clinical trials in animal models. Stem cell therapy was also used in conjuction with the growth factors to determine if the growth factors improve recovery after SCI. The animal trials showed better motor recovery (Thuret, Moon and Gage 2006, pg 635; Tator 2006, pg

972).

Systemic hypothermia, where cooling the body to between 30ºC-35ºC has also been explored and was found to have a neural sparing effect on the injured spinal cord (Hawryluk, Rowland, Kwon and Fehlings, 2008, pg 8).

These aforementioned therapies are being investigated and trials are being done but as of yet none have been recommended as an indicated or recognised treatment for SCI. The use of these biological agents and drugs in SCI still requires further investigation.

One field in which much research is being done is the area of stem cell therapy.

2.4. Stem cell therapy for SCI

2.4.1. What are stem cells?

Stem cells are cells in the body that have two distinct capabilities: firstly, the ability to differentiate into more than 200 cell types that constitute the body and therefore maintain and repair the body tissue (Mothe and Tator 2012, pg 3625-2628). Secondly stem cells have the ability to keep replenishing themselves (Donnelly et al., 2012).There are various types of stem cells, classified on the basis of their ability to differentiate into different cell types. Totipotent cells are capable of generating each and every type of cell in the body and is therefore able to generate an entire organism; for example, a fertilised egg. Pluripotent stem cells can develop into all cells of the 3 germ layers; for example, embryonic stem cells. Multipotent stem cells can develop cells only within one germ layer; for example, bone marrow stem cells, which can form certain pre-set types of cells only and not any types of cells in the body (Donnelly et al., 2012).

There are various sources of stem cells:

- Embryonic stem cells harvested from the blastocyst that are pluripotent but present ethical issues as mentioned in Chapter 1.
- Neuronal progenitors harvested from foetal or embryonic tissue, which are multipotent stem cells that also present ethical concerns.
- Adult central nervous system stem cells multipotent and autologous, which can be surgically harvested from the adult central nervous system. These adult central nervous system stem cells are not rejected by the body but need to be surgically harvested and have limited differentiation potential

- Adult mesenchymal stem cells harvested, for instance, from adult bone marrow. These are multipotent, easily harvested and autologous but have limited cell-differentiation potential
- Umbilical cord cells that are harvested from the umbilical cord, are multipotent and the use of which cells raise no ethical concerns but also have a limited cell-differentiation potential.
- Induced pluripotent, autologous stem cells from skin, which are either pluripotent or multipotent. No ethical concerns exist in the way they are harvested. They have the potential for pluripotency but need additional viral vectors to induce the pluripotency (Donnelly et al., 2012)

Theoretically stem cells could be used in the spinal cord to regenerate new neurons that might bridge the gap formed by the SCI and cure or restore the spinal cord, resulting in recovery from the SCI. Donnelly et al. (2012) argue that stem cell transplants could be used to replace lost cells such as oligodendrocytes, neurons, motor neurons and astrocytes.

There are various methods of administrating the stem cells to the spinal cord, which include:

- Intravascular infusion
- Intrathecal infusion
- Direct intraparenchymal injection

The first two methods rely on the stem cells ability' to find and migrate to the area of pathology in the spinal cord. Research evidence of this process happening is lacking in large-animal models. Direct injection delivers the stem cells direct to the injury site but may carry risk in causing further pathology to the injury site by the injection.

These difficulties in administering stem cells to the spinal cord raise the following questions:

Could the stem cells administered through intravascular injection or intrathecal infusion find their way to the SCI (Rosenfeld and Gillet 2004)?

Could the scar tissue present (glial scar) at the site of injury prevent healing from taking place (Rosenfeld and Gillet 2004, Barnabe-Heider and Frisen, 2008)?

Should the administered stem cells start growing at the SCI site, the question that is raised is: will they form neurons at the site of injury in the spinal cord or will they form other cell types like bone, scar or connective tissue (Barnabe, Heider and Frisen 2008)?

Should the stem cells grow and bridge the injury site in the spinal cord will they stop growing at some stage (i.e. when the spinal cord has been restored) or form a tumor at the site of injury due to over growth (Barclay 2009)?

Considering the above, and the fact that most ethically approved research is still only being done on animals or the human trials in phases 1 or 2 studies, presently there is no scientific evidence and no recognised institution doing stem cell therapy as a cure or treatment for SCI (Tator 2006, Blight et al., 2009, Donnelly 2012). Pilot studies consisting of phase 1 and 2 trials have been initiated recently but these trials are purely to determine safety of stem cell therapy for SCI. (Chhabra et al., 2009, Tator 2006, Donnelly 2012). Since 2009 some studies such as the Geron study have also been initiated. This was a phase 1 human clinical trial and was stopped for financial and ethical reasons (Lukovic et al., 2014).

2.4.2. Stem cell trials

Many stem cell trials have shown positive neurobehavioural benefits in rodent models. These positive results have prompted the start of human trials and various scientific and ethically approved trials are now taking place (Garbossa et al., 2012, Donnelly 2012). The first RCT on cell therapy in patients who had sustained an SCI was the Procord trial, which used modified macrophages to promote a controlled inflammatory reaction, in this way initiating healing of the SCI. This trial was stopped for financial reasons although some neural recovery

was reported (Hawryluk, Rowland, Kwon and Fehlings 2008). Clinical trials using bone marrow stem cells (BMSC) have been and are being conducted, some registered, some not. The completed trials that have been published were all phase 1 and II trials, thus only showing safety of the procedure. Some of these trials are continuing, mainly those using autologous BMSC. Most of these trials just indicate the safety of the procedure rather than efficacy of the transplant on the patients' functional ability (Mothe and Tator 2012). Some trials are being done using umbilical cord blood (UCB) as a source of stem cells. Schwann cells (SC) and Olfactory Ensheathing cells (OECs) are not stem cells but are also capable of migration, myelin production and fast amplification. These cells have also been studied (Mothe and Tator 2012). The Geron study carried out in the USA and then stopped used pluripotent-cell-derived human embryonic stem cells, also known as oligodendrite progenitor cells. This trial was cancelled in November 2011, with only 4 candidates enrolled – for financial reasons and the recipients showed no signs of benefit (Wilcox, Cadotte and Fehlings 2012, pg 6; Mothe and Tator 2012 pg 3826; Lukovic et al., 2014, pg 1).

Much preclinical research has been done in the field of cell transplantation therapy. Preclinical research on stem cell transplants have exhibited the dual action of cell rejuvenation as well as trophic support to bring about less cell damage and to create a friendly environment for nerve regeneration. (Garbossa et al., 2012). At present research on stem cell transplantation for SCI focuses on the replacement of damaged cells (neurons and oligodendrocytes), providing trophic support for neurons, and modifying the environment within the spinal cord to facilitate the regrowth of axons (Thuret et al., 2006).

Some preclinical trials have shown the safety of the procedures for the administration of stem cell to the spinal cord; that is, no negative side effects occurred as a result of the administration procedure. As yet no neurological recovery has been demonstrated post stem cell administration (Chharbra et al., 2009; Kiatpongsan et al., 2008; Curt et al., 2006; Mothe and Tator 2012; Wilcox et al 2012, pg 6).

In 2004 Rosefelt and Gillet postulate that future strategies for human spinal cord repair will probably be multifaceted:

- Encouragement of axonal growth and reconnection of spinal cord;

- Replacement of cellular elements in and around the cord; and

- Reversal of demyelination that has taken place (Rosefelt and Gillet 2004, pg 637).

These above-mentioned strategies are being incorporated into the present stem cell therapy trials. The following important vital elements that should be considered before stem cell transplants could be effective are:

- The connective tissue matrix in the spinal cord;

- The degree of glial scarring after the injury; and

- Central myelin inhibitory factors present after the SCI that should be eliminated to facilitate axon outgrowth (Rosenfelt & Gillet 2004, pg 637).

Rosenfelt & Gillet (2004) reported that the balance of these above mentioned factors would be as important for the restoration of the SCI as the administration of the stem cells and this balance would be very difficult to optimise.

Present stem cell therapy offers the following strategies for spinal cord repair: replacement of damaged neuronal and glial cells, remyelination of spared axons, restoration of neuronal circuitry, bridging of lesion cavities, production of neurotrophic factors, anti-inflammatory cytokines and other molecules to promote tissue sparing and neovascularisation, and a permissive environment for plasticity and axonal regeneration (Mothe and Tator 2012). These strategies address the elements listed above.

Cell transplantation is financially highly beneficial to the international clinics already offering stem cell therapy commercially (Mothe and Tator 2012).

2.4.3. Stem cell tourism

Stem cell therapy is big business. Customers from throughout the world are recruited to international clinics in China, Russia, India, Thailand, United States

and Ukraine. The majority of the clinics offer intrathecal or intravascular BMSC or UCB-derived stem cells (Wilcox, Cadotte and Fehlings 2012).

Authors such as Cyranoski 2006; Lau et al. 2008; Barclay 2009 and Creasy & Scott 2009 were the first to discuss stem cell tourism in their publications. These authors describe how non-evidence-based stem cell therapies are offered to the general public as a cure for a large variety of conditions, resulting in people spending large amounts of money to undergo this treatment. In a survey published in "Stem Cell" the authors report that "most people learn about stem-cell treatment offerings from "direct-to-consumer advertising" on the Internet, which often makes claims about the medicine that are optimistic but inaccurate. There is a mismatch between what is being offered and what the existing scientific literature says" (Lau, Ogbogu, Taylor, Stafinski, Menon and Caulfield 2008 pg. 594).

Creasy and Scott describe that individuals with often incurable conditions (like SCI) find information on the Internet about stem cell intervention, are attracted by the promises of improvement and even cure for their condition and act out of determination and sometimes desperation to travel to clinics who offer stem cell transplants -usually at considerable personal cost.

The possible health or functional benefit should be weighed against the medical risks and financial outlay of the stem cell therapy. Information on these websites can range from accurate to anecdotal to misleading and even potentially dangerous due to the fact that the treatments given are not proven to be either effective nor safe (Creasy and Scott 2009).

A position statement on the sale of unproven cellular therapies was published in in 2009 in Spinal Cord journal (Blight et al., 2009). This article discusses the new unproven cell therapy which is being made available to purchase. This stem cell therapy offers hope for improvement, despite this therapy as of yet not being proven by clinical trials. This position statement, sent as a letter to the editor, was an attempt to warn health professionals in the field of rehabilitation practice and to give them information to pass on to their patients. The ICCP has also put together "Advice to people with SCI on Experimental treatment for SCI" by Steeves et al., in 2007 for patients and their families, friends and care givers

about participating in clinical trials. The guideline that was compiled by the authors, was aimed at guiding patients who seek experimental treatment. The guideline warns potential patients on what to look out for and how to evaluate the treatment they intend to enrol for, offered as part of the clinical trial. It also warns people that treatments that don't really work or might even do harm might become standard medical care if they do not adhere to the principles of scientific randomised clinical trials.

2.5. Translation of research to bedside

Translation from basic pre-clinical research in the area of SCI to the bedside or clinical practice is often a time consuming and tedious process. This is probably partly due to:

- The difference between rats and larger mammals, and humans
- The translation process of basic research findings to clinical research via thorough investigation in human clinical trials being a long and complex process. (Wilcox et al., 2012)
- The associated risks of experimental therapy to the patient (such as worsening of the condition or tumours),
- The differences between rat and human locomotor and corticospinal systems (Mothe and Tator 2012),
- The injury models used in experimental SCI rat models being different from the average traumatic SCI sustained in the population group of people with SCI during real life trauma (Nandoe Tewarie Rishi et al., 2010)

In the translation process the timing of treatment post injury needs to be considered as well. The timing of experimental intervention would determine as to whether the effect of the treatment should be neuro-protective (in the acute phase post injury) or neuro-regenerative (post-acute to chronic phase post injury).

From the literature it seems apparent that further pre-clinical trials are required to optimise the treatment algorithms for stem cell therapy on humans with SCI (Wilcox et al., 2012, pg 7).

2.6. Assessment tools for the outcomes of SCI treatment trials

Translating the results of laboratory research trials for SCI to clinical research on human patients is a challenge and will involve good acute medical treatment, rehabilitation and the evidence-based assessment of the outcomes of the treatment techniques to determine the efficacy of the intervention. Rehabilitation units treating patients with SCI should be prepared to include such new therapeutic approaches into their rehabilitation procedures. To investigate new treatment approaches into the rehabilitation procedures it is essential to monitor accurately any change in the patient's signs (i.e. any form of motor or sensory change). These signs could indicate regeneration of spinal cord tracts and conduction of impulses over the injury site and be measured by using clinical, electrophysiological, imaging and behavioural assessment techniques. Steeves et al. (2007) suggest that when planning a trial the most accurate assessment techniques for detecting a change in neurological or functional outcome should be selected. In the selection of these assessment techniques the following factors should be considered:

The phase of clinical trial as the primary and secondary outcome measures and thresholds of change are likely to differ or evolve from phase 1 (safety) to phase 3 (therapeutic confirmatory trials). The outcome measures should therefore be carefully selected to suit the phase of the clinical trial.

Assessment techniques should be selected by taking the level of spinal injury, including the extent of the zone of partial preservation (ZPP) into consideration.

The severity of spinal injury should be considered to ensure that the assessment techniques are sensitive enough to detect varying degrees of incomplete to complete sensory-motor loss.

The time since the SCI will determine the focus of the treatment: whether the patient has an acute or a chronic lesion; whether the lesion is unstable (in the acute phase) or more stable (found more in the chronic phase); as well as the varying functional abilities capacities after SCI.

The appropriateness of the outcome measure to the capacity or capability that is to be evaluated (e.g. sensorimotor impairment, autonomic function, personal functional capacity, performance, or community participation). Different clinical targets normally require distinct outcome assessment tools.

The sensitivity of outcome measure (i.e. detection threshold).

The accuracy and validation of outcome assessment tool.

The reliability of outcomes measures including inter and intra-rater reliability.

The feasibility of using a selected outcome measurement tools in a particular center or across multiple centers.

The adoption of standardised outcome assessment procedures and data sets across multiple trial centres (Steeves et al., 2007).

It is further important to select a combination of clinical assessment measures such as the ASIA assessment scale and neurophysiological assessment techniques for assessing the level of injury on body structure and function level, as well as assessment scales that grade the patients' level of functional ability such as ADL scores, the SCIM III and walking capacity. The application of only one assessment is said to be not sufficient to evaluate the clinical significance of any new treatment (Dawson, Shammley and Jamous 2008).

Functional recovery after SCI can be dependent on the following:

- The extent of the injury;
- Reorganisation of undamaged neural pathways post injury; and

- The development of new pathways (such could be expected if the stem cells grew new neurons).

Spinal cord tracts are capable of significant reorganisation, which is induced by both activity-dependent- and injury-induced plasticity. This plasticity is shown in animals that have had an induced spinal injury and in which a certain degree of motor function was regained (Blesch and Tusynski 2009).

Research in subjects with SCI has demonstrated that rehabilitation improves the patient's functional ability due to muscular and neural plasticity (Curt et al., 2004). The accuracy of initial baseline examinations and assessments in the first days following an injury is critical for detecting and demonstrating changes and prognosis in the body structure and function level (Ditunno et al., 2005). Recovery of just one (1) neurological level in patients with tetraplegia could have a major effect on the patient's functional ability, but this is dependent on the severity of the injury, the level of the injury, and the patient's general strength of muscles below the injury (Ditunno et al., 2005) For example, if a patient recovers from an ASIA B with just sensory sparing to an ASIA D sensory and functional motor sparing he or she will be much more independent than if the injury had stayed an ASIA B lesion. Neurological recovery following SCI is said to correlate with an increase in function and self-care and even walking (Ditunno et al., 2005). This natural recovery and improvement in function as a result of rehabilitation needs to be borne in mind when the efficacy of the treatment is assessed. The fact that rehabilitation brings about an improvement in functional ability without a necessary improvement in neurology also needs to be taken into account.

In people with both paraplegia and tetraplegia, it is possible to predict walking recovery based on the initial one-week post injury's sensory and motor examination using the ASIA assessment scale. Successful trial execution requires a sufficient statistically determined study population, as well as researchers' good understanding of the known functional recovery patterns in patients with SCI to detect a potential change that could be the result of newly implemented treatment techniques.

Uniformity of classification of the SCI based on accurate initial body structure and function assessment post injury is important for standardisation of assessment, prediction and monitoring of patients' impairment and functional ability on activity and participation levels. This assessment requires an accurate baseline and repeated measurements of outcome measures as well as definite meaningful endpoints or outcome levels (Burns and Ditunno 2001; Ditunno et al., 2005; Tator 2006).

The implementation of outcome measures is important for detecting any deterioration in a patient's condition post treatment, especially during clinical trials (Ellaway et al., 2004) in which experimental treatment could cause further damage to the spinal cord. A decrease in only one (1) spinal level especially in persons with cervical injury is likely to have serious repercussions. Slight worsening in the neurological level of a patient with a cervical lesion can result in the loss of finger, hand or arm movements (C5–T1) or even the ability to breathe spontaneously (C3–C5 lesion). Treatment applied to a patient with a thoracic SCI could be seen as safer, as deterioration of one (1) or two (2) spinal levels would have less functional impact, but then improvement in only one (1) thoracic neurological level would result in only very modest or no improvement in functional ability. It is therefore important to use outcomes measures that assess patients on impairment, functional-activity level, as well as participation level for patients who participate in clinical trials and as part of normal rehabilitation practice (Steeves et al., 2007).

2.6.1. Functional outcome measures

Functional outcome measures, which assess a patient's functional independence, are required in a clinical testing protocol. According to Steeves et al. (2007) where an international panel assessed outcome measures relevant to clinical trials in SCI for cell-based- and pharmacological treatments, the authors identified two (2) comprehensive functional outcome measures – the Functional Independence Measure (FIM) and the Spinal Cord Independence Measure (SCIM). Dawson et al. (2008) also compared many outcome measures and found the SCIM III to have superior responsiveness to FIM in terms of assessing functional outcomes in SCI. For assessment of lower limb

function the Walking Index for Spinal Cord Injury (WISCI) was recommended to be done in conjunction with other outcome measures such as the timed up-and-go- or the ten-minute-walk test (Dawson et al., 2008).

For this study the SCIM III was selected because the FIM is not sensitive enough to measure functional change in SCI function especially in tetraplegics. No lower limb function assessment tools were considered appropriate for the study population.

Steeves et al. (2007) also comment that the performance of functional evaluations may be a more direct measurement of a clinically meaningful change in the functional capacity of a patient, although the changes in functional outcomes may not always be the result of a demonstrated change in spinal–neurological activity or connectivity. A change in a person's functional ability after SCI may be due to adaptive changes (or plasticity) within and/or without the central nervous system (CNS). Plasticity without the nervous system entails learning of skills and techniques through improved mobility and strength and endurance. Adaptation of environmental aspects of a patients home, work or social environment can also contribute to more functional ability and/or the patient can learn alternative compensatory strategies or new skills on how to perform certain functional activities. If the expected therapeutic benefit from a treatment is modest, a dramatic improvement in functional performance may not be readily evident. Nevertheless, functional outcome assessments on activity and participation levels should be undertaken as an outcome measure secondary to neurological assessments.

2.6.2. The ASIA scale as an assessment tool:

Curt (2004) describes the ASIA assessment tool as an internationally accepted tool used to measure the neurological deficit caused by SCI. Steeves et al. (2007, pg 209) describe the ASIA impairment scale as a "standardized and routinely adopted classification for most patients suspected of suffering a SCI". The name of the ASIA scale is the standardised neurological examination protocol of the American Spinal Injury Association (ASIA) and the scale derived its name from there. The ASIA scale is a tool to measure motor and sensory neurological deficits quantitatively. The ASIA scale gives the medical- and

rehabilitation teams a picture and an objective measure to describe the level of the lesion and to identify the extent of the patient's neurological deficit. The ASIA scale may also be used to predict, to a certain extent, the functional outcome of a patient with an SCI.

The ASIA scale consists of two sections: a motor assessment and a sensory assessment. The motor part entails individual muscle testing of the 20 key muscles in the body: 5 in each upper limb and 5 in each lower limb. It is recommended that upper-limb- and lower-limb motor scores should be scored separately as the upper-extremity motor score (UEMS) and lower-extremity motor score (LEMS). This layout of the ASIA scale allows rehabilitation professionals to detect a change in motor function to be recorded as specific to either the cervical or lumbar levels. Separation of the motor scores into UEMS and LEMS also reduces the influence that a large change in the functional strength in one or a few muscles may have on the assessment of therapeutic benefit of a treatment. This seperation of motor scores also allows for a distinction between increased strength in innervated muscles and new myotomes becoming re-innervated (ASIA web site).

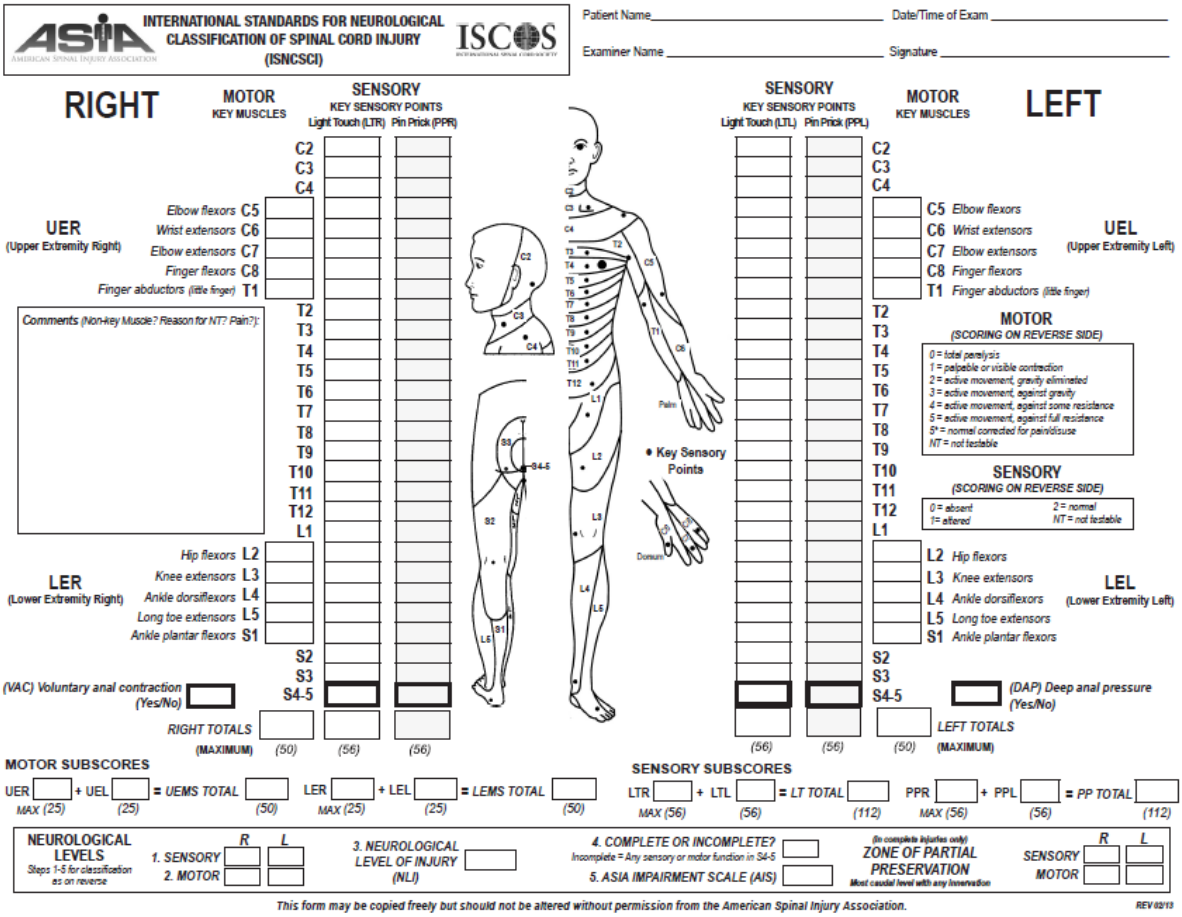

Figure 2.1. The ASIA assessment chart

ASIA sensory and motor assessments are conducted in the supine position. The assessment procedure involves the qualitative grading of sensory responses to touch and pin-prick at each of 28 dermatomes along each side of the body and a qualitative grading of the strength of contraction in 10 representative (key) muscles. These key muscles are primarily identified with a specific spinal level – 5 for the upper extremity (C5–T1) and 5 for the lower extremity (L2–S1) – on each side of the body.

The ASIA motor score is calculated by assigning a score between 0 (no detectable contraction) and 5 (active movement and a full range of movement against maximum resistance) to one muscle group, innervated and primarily identified with a specific spinal level. Spinal levels C5 to T1 and levels L2 to S1 are tested, giving 10 spinal motor levels to be scored on each side of the body for a possible maximum motor score of 100.

Both the LEMS and the UEMS are a maximal 50-point subset of the ASIA motor score for the representative leg and foot muscles and arm and hand muscles respectively. The term 'motor level' is defined as the most caudal spinal level as indexed by the key muscle group for that level having a muscle strength of 3 or above, while the key muscle for the spinal segment above is graded normal (5). (ASIA web site: http://www.asia-spinalinjury.org/)

ASIA sensory score is calculated by testing a point on the dermatome of each spinal level from C2 to S4–5 for both light touch and pin-prick sensation. Each point is assigned a score from 0 (absent sensation) through 1 (abnormal sensation) to 2 (normal sensation). The possible maximum sensory score is 56 on each side for a maximum total for the whole body of 112 for each of light touch and pin-prick sensation. Sensory level is defined as the spinal segment corresponding with the most caudal dermatome having a normal score of 2/2 for both pin-prick and light touch.

Zone of partial preservation (ZPP) is a term that is used only when a SCI is complete. ZPP refers to those segments below the neurological level of injury where there is some preservation of impaired motor or sensory function (usually, but not always, within a few segments of the neurological level). (ASIA web site: http://www.asia-spinalinjury.org/) Below the most caudal 'functional' ASIA motor level (ASIA motor grade of 3, 4, or 5) the ZPP consists of those myotomes and dermatomes that remain partially innervated, but at a level that may not be functionally meaningful (e.g. ASIA motor grade of 1 or 2; i.e. non-functional muscle strength). The exact numbers of segments so affected make up the ZPP. Any improvement in function ascribed to any intervention whether clinical or experimental that is confined to the first two segments caudal to the last functional ASIA motor level may be due to plastic changes within the ZPP rather than to the formation of new spinal connections across the level of injury (Steeves et al., 2007).

It is essential to identify a functionally meaningful ASIA motor score threshold to see the benefit of a therapeutic intervention and this motor score can then show both on the level and severity of the SCI, as well as the degree of spontaneous recovery after SCI with conventional or experimental treatment.

Previous studies (Fawcett et al., 2007) have indicated that a low cervical, ASIA A-injured patient is likely to spontaneously improve about 10 ASIA motor points during the first year after SCI through natural recovery, rehabilitation and functional use of muscles. Thus, to demonstrate the efficacy of a therapeutic intervention, a response to treatment of an additional 10-point improvement in the ASIA motor score (efficacy threshold now being 20 point) might be considered a valid primary outcome end point (Fawcett et al., 2007).

The ASIA score describes the effect of structural deficits after an SCI by indirectly determining the neurological deficit. The timing of the ASIA assessment is important in relation to the date of injury when determining the outcome of the SCI. The first ASIA assessment is aimed to be performed 5-10 days after the injury, the last examinations about 1 year after acute SCI, by which time the condition is said to have stabilised (Fawcett et al., 2007). The time window of 5-10 days post injury also allows the medical and rehabilitation team to distinguish between resolving neuronal conduction blocks that occur during the period of maximal loss (allowing early functional recovery) and post-lesion repair mechanisms (weeks to months after injury). The best time to do the initial assessment is said to be in the first 72 hours after the injury (Burns et al., 2003). The one limitation of the ASIA is that it is unable to determine the motor level of lesions to the thoracic spinal cord (Fawcett et al., 2007).

The ASIA assessment has been widely adopted throughout the world among physicians and rehabilitation team members. This fact makes the ASIA assessment scale an ideal tool because data can be objectively compared between units. The ASIA is an easy assessment procedure to perform, very little equipment is needed and it can be used in different phases of a clinical trial. The ASIA can be used to compare the outcome between patients with similar lesions or comparing the results between clinical trials. The ASIA score is further used to classify motor-complete and sensory-complete SCI (ASIA A) as well as motor complete, sensory-incomplete SCI (ASIA B). In the acute stages of SCI it is reported that the more reliable indicator of a patient's sensory and motor impairment is 72 hours after the injury because the patient is then medically more stable. With chronic patients (more than 12 months after SCI), the ASIA assessment may not necessarily show the most important aspects of

functional changes after SCI (Steeves et al., 2007). Nevertheless, the ASIA is still valuable in determining the extent and level of the injury and identifying any neurological change.

The ASIA motor score is considered more reliable than the ASIA sensory score in predicting functional outcome after SCI (Steeves et al., 2007). Total ASIA scores showed very strong inter-rater reliability correlation with Pearson correlation coefficients and intraclass correlation coefficients exceeding 0.96, $P<0.01$ for total motor, light touch and pin prick scores (Savic, Bergstrom, Frankel, Jamous and Jones 2007). However, sensory scores are reported to be highly variable at different assessment times by the same assessor (interrater) and between different ASIA assessors (interrater). In one study the ICC for total motor score was 0.98; for light touch 0.96, and for pin prick 0.89. The reliability values for patients with incomplete lesions were lower. The lower limits of the confidence interval for sensory scores in patients with incomplete injuries were below 0.75, a value that Marino, Jones, Kirshblum, Tal and Dasgupta (2008) propose as a minimally acceptable level of reliability. The ASIA light touch score does not necessarily correlate with subsequent sensory scores accurately and, according to experts in the field, does not seem to be particularly useful as an SCI clinical trial outcome measure (Steeves et al., 2007). For this reason only the ASIA motor score was used in this study. The aim of only implementing the ASIA motor score in this study was not to underestimate the importance of sensation or sensory recovery in an SCI person. Sensation helps the patient to prevent pressure sores and enables the patient to use his or her limbs more effectively. The rehabilitation process, however, mainly focuses on motor recovery and functional improvement and the researcher had no means of performing evoked potentials on all the participants to accurately assess changes in sensation.

2.6.3. The Spinal Cord Independence Measure (SCIM) as an outcome measurement tool

The spinal cord independence measure (SCIM) is a standardised rating scale of ADL. The SCIM aims to assess the functional impairment in performing a task and not a neurologic deficit. The SCIM has gone through a few alterations and versions. SCIM III was used in this study.

As a functional measure the SCIM appears to be a more sensitive and accurate functional assessment for ADL after SCI than the FIM. Both the FIM and the SCIM detect functional changes but the FIM missed 26% of the changes detected by the SCIM. Consecutive scores on the SCIM over time had a higher mean difference than on the FIM (10.6 pts vs 7.5 pts, $p < 0.01$) (Catz, Itzkovich, Agranov, Ring and Tamir 1997).

The SCIM is a standardised rating scale, which is developed to score the person with SCI's ADL objectively (Bluvshtein et al., 2001, Hall 1999). The SCIM measures or scores the people with SCI's functional ability during mobility, be it walking or wheelchair mobility or pressure relief, and self-care such as dressing, bathing and transfers as well as sphincter and respiratory function and control. The SCIM is evaluated to be reliable and valid in the study of functional outcomes in traumatic SCI (Bluvshtein et al., 2001, Itzkovich et al., 2007).

The reliability of the SCIM III is:

- **Adequate to Excellent** interrater reliability for total agreement (Kappa = 0.631 to 0.823)
- **Excellent** interrater reliability for SCIM III subscales (r = 0.902-0.944) and SCIM III total score (r = 0.955)
- **Excellent** interrater reliability within SCIM III subscales (ICC = 0.948-0.971) and SCIM III total score (ICC = 0.977)

(Itzkovich et al., 2007)

A person with a SCI's functional ability depends on the rehabilitation received, motivation of the person, general fitness and other factors such as age, sex, body build, conditions pre-existing the SCI, co-morbidities and social circumstances affecting the individual. The SCIM III rating scale assesses the activity and participation levels in ADL and it has four (4) main sections, which are self-care, respiration, sphincter management and mobility. The total possible SCIM III score is 100 points, while all the sub-sections (e.g. feeding, bathing) are weighted scores between 0 and 15, dependent on their relevance to functionality of the SCI person. The SCIM III measures the following 18 activities associated with:

- Self-care (feeding, bathing, dressing, grooming), maximum total of 20 points.
- Respiration and sphincter management (ventilation, bladder, bowel control, use of toilet) maximum total of 40 points (clinically weighted)
- Mobility (in bed, transfers, indoors and outdoors, wheelchair, walking), maximum total of 40 points.

The SCIM III score allows one to describe the extent of the impairment and the necessary support the patient requires to perform ADL. (Steeves et al., 2007).

The average SCIM III scores for different levels of complete SCI have now been researched and published (Aidinoff, Front, Itzkovich, Bluvshtein, Gelernter, Hart, Beiring-Sorensen, Weeks, Laramee, Craven, Hitzig, Glazer, Zeilig, Aito, Scivoletto, Mecci, Chadwick, El Masry, Osman, Glass, Soni, Gardener, Savic, Bergstrom, Silva and Catz 2011). Aidinoff et al. (2011) performed a multicentre international cohort study to study the discharge SCIM III scores and average change in functional ability as measured by the SCIM III scores during the acute rehabilitation period. Aidinoff et al. studied SCIM III scores of 128 patients and these scores were correlated to the specific SCI level. Aidinoff et al.'s 2011 study was carried out on patients who had sustained complete ASIA A injuries. Another publication also shows the average gain in SCIM III scores for persons with different lesion levels in the post-acute rehabilitation setting (Ackerman, Morrison, Mc Dowell and Vazques 2010). This valuable data can be used to

determine how effective rehabilitation and or experimental therapy has been by observing the outcomes of the person's SCIM III scores in comparison to what is expected for a person with a similar lesion level.

Table 2.1 Discharge SCIM III scores and average gain in SCIM III scores during acute rehabilitation for various levels of SCI (Aidinoff et al., 2011) and post-acute rehab SCIM III gains (*Ackerman et al., 2010)

SCI level	Average SCIM III discharge score	Maximum SCIM III scores on discharge	SCIM III score change during acute rehabilitation	Post-acute SCIM III score changes*
C2+C3	8.0	9	7.0	0
C4	21.3	36.5	12.0	
C5	23.0	32	11.0	3
C6	43.5	66	28.0	9
C7	21.0	38.5	7.0	7
C8+T1	42.0	69	25.0	
T2	60.5	64	19.0	5.5
T3	60.0	75	28.0	
T4	62.5	80.5	27.0	
T5	63.0	69.5	30.5	
T6	57.8	69	32.5	
T7	66.3	70	34.0	6
T8	69.3	70	32.0	
T9	64.5	66	32.0	
T10	63.0	74	31.0	
T11	69.3	71	40.5	
T12	67.5	76	34.0	
L1	72.0	85.5	38.0	
L2	76.3	78	45.0	

New research published by Fekete, Eriks-Hoogland, Baumberger, Catz, Itzkovich, Luthi, Post, von Elm, Wyss and Brinkhof (2013) describes the development and validation of a self-report SCIM III version. The use of a self-report SCIM III (SCIM III SR) questionnaire would allow monitoring of daily activities of community based persons to identify special needs in this population. The results of the study showed criterion validity of the SCIM III SR as compared to the SCIM III. The SCIM SR was developed in English and based on the English SCIM III version. However, only the German version has been validated.

2.6.4. Outcome measures for pain measurement

Steeves et al. (2007) and Alexander et al. (2009) reviewed the outcome measures that can be used on patients with SCI. The following tools were listed by the authors to be useful in assessing pain.

- Visual analogue scale (VAS) rating pain on a scale from 0 (no pain) to 10 (worst imaginable pain);
- 7 point Guy/Farrar patient global impression of pain to measure perceived changes in pain;
- SF-36 quality of life questionnaire;
- Multidimensional pain inventory;
- Brief pain inventory (BPI);
- Neuropathic pain scale;
- Leeds assessment of neuropathic symptoms and signs that distinguishes between neuropathic and nociceptive pain;
- Siddall's classification of pain;
- McGill pain questionnaire; and
- Graded chronic pain questionnaire (GCP).

Not all pain scales distinguish between neuropathic and nociceptive pain. In experimental interventions, which have the potential to stimulate axonal fibre regrowth in central pain pathways within the spinal cord, the pain experienced by the patient could be a possible side effect of the intervention. Alexander et al. (2009) reported the recommendation made by a panel comprising the ASIA, ICORD, ICCP, ISCoS and SCOPE on outcome measures that pain in patients with a SCI be assessed during a face-to-face interview using a VAS.

Dijkers in 2010 compared the VAS, the Visual rating scale (VRS) and The Numeric rating scale (NRS). This study was done specifically in a population consisting of people with SCIs. Dijkers (2010) concluded that of the 3 pain scales that have been recommended for use in people with SCI (the VAS, the NRS and the Visual rating scale (VRS)) there are some reservations concerning the VAS because it requires hand function, which might discriminate against quadriplegic patients with high lesions. Verbal scales may be more appropriate (Dijkers 2010). Dijkers (2010) also wrote the NRS assumes two things: a) that there is such a thing as the worst pain you can imagine; and b) that the anchoring or base level for the worst pain is the same in all individuals. Neither of these assumptions may be true as we each have different experiences of pain. Dijkers (2010) concludes that researchers must be aware of the various limitations of the various instruments.

In 2011 Ferreira-Valente, Pais-Ribeiro and Jensen published a study where the VAS, NRS, VRS, and the Faces Pain Scale-Revised (FPS-R) were compared. These scales were compared because they were considered to be the most commonly used measures of pain intensity. Although all these scales had evidence supporting their validity, the authors compared the relative validity of these 4 scales for detecting differences in painful stimulus intensity. Ferreira-Valente et al. (2011) concluded that the NRS was the most responsive for measuring pain intensity but the VAS showed superiority in ratio-scale qualities. There is also a very small difference in the power analysis for determining the number of subjects required for a study using either the NRS or the VAS. In conclusion Ferreira-Valenti et al. (2011) wrote that the NRS and the VAS should be considered first when assessing sensitivity and responsiveness to pain intensity. The NRS rather than the VAS is recommended for use when there is

a need to distinguish differences between the sexes. The NRS was found to be a slightly more sensitive a pain measure than the VAS, VRS and FPS-R.

Steeves et al. (2007) suggest that over 50% of people living with SCI report experiences of chronic neuropathic pain. As to how to classify pain, be it musculoskeletal, neuropathic, or visceral in a person with SCI has not yet been agreed on. Pain that is described as sharp, stabbing, or burning within the dermatome or just above the level of SCI is often termed ‘at-level neuropathic pain’, and similar types of pain below the level of the lesion have been called ‘below-level neuropathic pain’. If there is restoration of the ability to perceive normal pain sensation from a treatment, a person with an SCI may experience conditions unfamiliar to them such as back pain and other ‘normal visceral pain’. The VAS is a simple tool for measuring a patient’s subjective pain experience. It has been established as valid and reliable in a range of clinical and research applications (McCormack, Horne and Sheather 1988).

The most user-friendly assessment of pain for researchers is patients’ self-report of any changes in pain during a procedure or over a period of time. Pain scales, however, may not always provide an accurate assessment of pain, as pain is a reflection of the person’s perception of pain. A person’s perception is influenced by other factorsemotional health and/or social stressors and interactions (Dijkers 2011). For this study the VAS was used to assess changes in pain and also to measure changes in perceived independence.

In this chapter the literature concerning SCI, its treatment and recovery in terms of optimising functional ability has been discussed. New and possible treatment options were explored and the requirements for determining sample size in clinical trials during research in the medical or pharmaceutical treatment and rehabilitation of patients with SCI have been discussed. Treatment of SCI by using stem cell therapy was discussed in detail as well as the phenomenon of stem cell tourism. Finally the outcome measures recommended for studies in the treatment of SCI were discussed and the motivation for the most appropriate outcome measures selected for this study was given

.

In the following chapter the methodology of this study is discussed.

Chapter 3

Study design and methodology

3.1. Introduction

In this chapter the design of the study, methodology, sampling methods, ethical considerations and compliances are discussed. The research measurement tools and statistical methods are also outlined.

3.2. Study design

This study is a cross-sectional critical analysis of the functional outcome of persons who have sustained traumatic SCIs and who have received some form of stem cell therapy as treatment for their SCI. Data was collated using a questionnaire to collect each patient's biographical data.

The questionnaire was either completed by the participants themselves or during a telephonic with the primary researcher. The neurological level and functional ability were compared to patients' own pre- and post stem cell therapy status. Patients' neurological impairments as well as their level of functional ability pre- and post stem cell therapy were compared to the expected level of functional ability of patients with similar SCIs, as reported in the literature (Aidinoff et al., 2011, Ackerman et al., 2010). For the purpose of this study a biographical questionnaire was compiled and the SCIM III was used to get pre-, post- and current SCIM III scores. ASIA scores were used where available and the SCIM III was used because it is a recommended and effective measure to assess functional ability in the SCI population (Itzkovich et al., 2007). The VAS was incorporated into the questionnaire to measure changes in pain and perceived independence.

3.3. Research setting

This research was conducted amongs people with SCI from across South Africa. They were requested by the researcher personally or via email to fill in the questionnaire, which included a SCIM III outcome measure. When

telephonic interviews were conducted they were performed in the researcher's office. These telephonic interviews were usually used as an additional method to get clarity from participants, where they had filled in the questionnaire and emailed it. When the participants were near enough geographically to the researcher they were seen personally in the unit where the researcher works. In other circumstances communication was via email. Where possible relevant medical records were consulted and requested from other rehabilitation units or therapists.

3.4. Ethical approval (and informed consent)

- Ethical approval for the study was obtained from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria before the study commenced (Protocol number S5/2010). This is attached in Addendum 1 pg 95. Some changes were submitted and proof is displayed on pg 96.

- All participants gave written (or verbal where questionnaire was done telephonically) voluntary informed consent that their personal information could be used in the study. (Informed consent form is in Addendum 2 pg 97).

- Information regarding any participant was kept confidential on the researcher's office computer under a file with a password at the Muelmed Rehabilitation Centre, her laptop or on paper copies in her locked office. Participants' identities were not disclosed to anybody. Participants' information was kept confidential by numbering questionnaires and SCIM III outcome measures completed by participants. The researcher was the only person to keep a record of the participants' identities associated with the number allocated to each participant's documentation.

3.5 Research methodology

3.5.1 Study population

The study population consisted of people with C4-L2 SCI in South Africa who had received stem cell therapy and who could be identified to participate.

3.5.2 Research sample group selection

The participants of the study were recruited through:

a. E mails sent via the data base of Quadpara Association of South Africa (QASA) requesting voluntary participation in research regarding stem cell therapy. The members on the mailing list were requested to contact the researcher if they had undergone any form of stem cell therapy.

b. Participants known to the researcher, who had undergone stem cell therapy, were recruited from the researcher's spinal cord rehabilitation practice, by inviting them to voluntarily participate in this study. These participant's were also asked to refer other people they knew, who had undergone stem cell, to volunteer to participate in the research study. Participants were only included in the study after they have given voluntary informed consent.

c. Participants were also recruited by contacting rehabilitation practices across South Africa, using emails asking the staff to inform people with SCI in their units, who had undergone stem cell therapy of the study. A list of rehabilitation units was obtained from the Southern African Spinal Cord Association's web site that lists the rehabilitation units). If any potential participant was identified in this way they had to give consent to the relevant rehabilitation practice or spinal unit that I as the primary researcher might approach them to participate in the study. When they gave their consent to the rehabilitation practice / spinal unit, I approached the potential participant to obtain their informed consent before they were included in this study.

Number of participants

The population of people with SCI is relatively small and those among the population that can afford stem cell therapy may be limited. The researcher discovered during the recruitment of participants that the number of potential participants was small. Every attempt was made to recruit as large a number as possible from the full population of people

with SCI who had undergone stem cell therapy in South Africa into this study. Because the exact number of persons that have undergone stem cell therapy is not known the researcher reports that a convenience sample was recruited. Because this study included participants who were all but one in the chronic phase of their SCI the sample required would be less, as most natural recovery after the SCI should have already occurred in these patients.

3.5.3. Inclusion and exclusion criteria

3.5.3.1 Inclusion criteria

People with SCI living in South Africa who had received stem cell therapy in South Africa or abroad

People with SCI who had received stem cell therapy and who had received their rehabilitation at a rehabilitation centre or unit or practice in South Africa.

People with SCI who were willing to participate voluntarily in the study and had given their informed consent.

Participants with SCI in good health. This was asked in the questionnaire and specifically as to whether they had diabetes or kidney problems, which are two chronic conditions that may affect people with SCI and may also affect neurology.

The participants were over the age of 18

3.5.3.2 Exclusion criteria:

People living with any other disability and who had received stem cell therapy were excluded.

Stroke

Polio Myelitis

Spina Bifida

Sacral or lumbar plexus injuries

Guillain-Barré syndrome

Transverse Myelitis

Locked-in syndrome and

Traumatic brain injury

Persons with SCI who for any reason were incapable of understanding and completing the questionnaire and SCIM III outcome measure were excluded.

Persons with SCI having any chronic diseases that could negatively affect the outcomes of the study because of neurological effects of the conditions; for example, Diabetes Mellitus or chronic renal failure.

3.5.4. Data collection procedure

People with SCI who met the inclusion and exclusion criteria were approached to participate in the study as per recruitment procedure set out in paragraph 3.5.2.

The aim and objectives of the study were explained to potential participants and they were informed that participation in the trial was voluntary and he / she was free from undue coercion.

Each potential participant had to give his / her written informed consent before they were admitted as participants into the study. When the participants returned the informed consent and completed questionnaire and SCIM III outcome measure, these documents was checked by the researcher to ensure that all questions were answered completely. The informed consent questionnaire and SCIM III are attached as Addenda 2&3. pg. 95 onwards.

3.5.5. Compliance and withdrawal

A participant was able to withdraw their participation in the study at any time during the study without any negative consequences.

Where the questionnaire and SCIM III outcome measure were incompletely filled in or where the participant had not given a clear answer the researcher conducted a follow-up telephonic interview with the participant.

3.5.6. Outcome measures

SCIM III

As described in Chapter 2 the SCIM is a recognised standardised scale for assessing functional independence in SCI (Catz et al., 1997) The SCIM is a sensitive measure of functional ability as it is perceptive enough to display even minor changes of functional ability in people with SCI (Catz et.al, 1997). The SCIM III was recommended at a pre-meeting course at ASIA-ISCOS 2006, Boston, as the primary functional outcome measure for use in people with SCI (Savic & Catz 2009)

The reliability of the Catz-Itzkovich SCIM III assessment by interview was assessed and shows it to be comparable with assessment by observation. The SCIM III is recognised as one of the preferred research instruments in SCI rehabilitation (Savic & Catz 2009). The reliability of a self-report SCIM III version was published in Spinal Cord by Fakete et al. (2013). For this study the SCIM III was used and without changing the content adapted to allow the participant to fill in three (3) separate SCIM III scores for before and after stem cell therapy and their SCIM III score at the time of the study ("current"). (See Addendum 4 pg 107.)

Visual analogue scales

VAS is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured by other means (Wewers 1990). In this study it was used to get an indication of the participants' perception of how they experienced their pain and independence before they went for the stem cell therapy, what they expected the results of the stem cell administration to be and how they experienced pain before and after stem cell therapy. The visual analogue scales used in this study were designed to address two (2) factors that people with SCI face – pain,

expectations of recovery and or helplessness. These factors are not addressed in the SCIM III.

VASs were incorporated into the biographical questionnaire (see questionnaire in Addendum 3 pg 101) to assess the following factors:

- The expected independence as a result of the stem cell therapy on a scale of 1-10 where 0 is total helplessness and 10 is total independence;
- Their present perceived independence, after the stem cell therapy, on a scale of 0-10 where 0 is total helplessness and 10 is total independence;
- Pain experienced before stem cell therapy on a scale of 0-10 where 0 is no pain and 10 is excruciating pain; and
- Pain post stem cell therapy– where 0 is no pain and 10 is excruciating pain.

ASIA assessments

Participants' ASIA assessment scores were collected from their files or from the units where they had received rehabilitation. Not all the participants' ASIA scores were available. To overcome this the researcher asked questions in the questionnaire to determine whether changes in motor strength and innervation occurred post stem cell therapy. This was used to assess change where no actual ASIA scores were available.

The biographical questionnaire was compiled to gather information from participants on age, time post injury, mechanism of injury, stem cell therapy received and costs incurred. It was not a validated questionnaire and had VAS scales incorporated into it. The SCIM III was completed together with the questionnaire but as a separate item at the end of the questionnaire.

3.6. Statistical considerations

Three consultations were held with the statistician. Initially the study was to use a control group of persons with SCI. That would have required a sample size of 30 participants and 30 controls. After consideration it was decided to rather use each person as his own control and then once the articles published by Aidenoff et al., (2011) and Ackerman et al., (2010) came to light it became imperative

that we rather compare each patient to published norms .i.e. the expected outcomes for functionality in SCI as published in these papers.

Statistically in a single arm study e.g. within subject an improvement of 37 points on the SCIM III score from onset to post stem cell therapy would be clinically relevant. Acute phase rehabilitation can be expected to bring about an improvement on average of 22 points on the SCIM and a further improvement of 15 points as a result of the stem cell therapy is regarded as clinically relevant as most improve between zero (0) and nine (9) post rehab without stem cells (average five (5)). A conservative estimate for the standard deviation is expected range of improvement (15-100) divide by 4, i.e. sd = 21.25. A sample of at least 10 participants will have power of at least 90% with the assumption when using a paired t test at the 0.05 level of significance. Note that for this calculation the statistical deviation for difference (pre vs post) is used. i.e.$\sqrt{x}21.25$. Eleven participants were included in the study.

3.7. Data management and analysis

The data from the biographical questionnaire was captured in an Excel spread sheet. The data was stored on computer with a hard copy kept on file at the Muelmed rehabilitation unit in the researcher's private office. The file was secured by password to keep confidentiality. All data was captured personally by the researcher and participants' identities were protected by allocating a unique code number to each participant. No names appeared on the data capturing sheets or spread sheets nor will be reported in any other publication for the purpose of preserving participants' anonymity. The Excel spread sheet and functions were used to analyse the data, namely the biographical data, the costs and type of stem cell therapy received, VAS scores and the pre- and post- and current SCIM III scores. Data was analysed as it was received. Data was then transferred to summary Excel spread sheets.

Data from SCIM III scores and VAS measured were compared before and after the stem cell therapy. Each participant served as his or her own control. The SCIM III scores were also compared to the expected SCIM III scores for the specific lesion level (Aidinoff et al., 2011). The changes in SCIM III scores were

also compared to the expected changes in SCIM III scores in the acute- and post-acute rehabilitation settings (Ackerman et al., 2010).

3.8. Conclusion

This chapter described the methodology, ethical issues and methodology followed during this research project. Results of the data analysis are discussed in Chapter 4.

Chapter 4

Results

4.1. Introduction

In this chapter the summary of data obtained from the biographical questionnaire which included the numeric VAS and the SCIM III outcome measure completed by persons who received stem cell therapy after their SCI is presented.

4.2. Biographical data

Eleven (11) participants could be identified and complied with the inclusion criteria and gave informed consent to participate in the trial. Eight (8) of the eleven (11) participants recruited were treated in a rehabilitation centre where the primary researcher worked. These participants were treated by the researcher or colleagues at the rehabilitation facility. Three (3) participants were unknown to the researcher prior to the study. The biographical data of the participants is presented in Table 4.1 on the following page.

Table 4.1

Biographical data of participants

Subject no.	**Age** (years)	**Gender**	**SCI type**	**Cause**	**Level of injury**	**Time between SCI and stem cell therapy**
1	51	M	Para ASIA A	GSW	T5	5 years
2	36	M	Tetra ASIA A	GSW	C8/T1	8 years
3	39	M	Para ASIA A	GSW	T5	14 days
4	38	F	Tetra ZPP	MBA	C6/7	1 year
5	38	F	Tetra ASIA A	Fall	C4/5	6 years
6	43	M	Tetra ZPP	MVA	C5	7 years
7	42	M	Tetra ASIA A	MVA	C6/7	2 years
8	30	M	Tetra ASIA B	MVA	C6/7	9 months
9	47	M	Para ASIA A	MVA	T12/L1	4 years
10	27	M	Tetra ASIA A	QUAD	C6/7	2.5 years
11	22	F	Para ZPP	QUAD	T5	3 years
	Mean = 36.9	8 M 3 F	4 Para 7 Tetra		4 - C6/7, 2 - T5 1 - C4/5, 1 - C5 1 - C8/T1, 1- T12/L1	Mean = 3.6 years

Key to Table 4.1: Tetra = Tetraplegic, Para = Paraplegic, T = Thoracic, C = Cervical, M = male, F=female, ASIA = American Spinal Injury Association classification for SCI, ZPP = Zone of partial preservation = muscles and skin innervated below the lesion in the complete SCI, MVA = Motor vehicle accident, QUAD = Quad bike accident, GSW = Gunshot wound, MBA = motorbike accident, Fall = fall at same level.

From the biographical questionnaires (a copy is added as Addendum 3 pg 101) the following biographical data was obtained.

- The average age of the eleven (11) patients was 36.9 years ranging from 22-51 years;
- Of the participants eight (8) were male and three (3) female;
- Four (4) participants were paraplegics and seven (7) were tetraplegics;
- The participants' injuries ranged from C4 complete lesion ASIA A to L1 complete ASIA A;
- The causes of their SCI were gunshot wounds (three (3)), motorbike accident (one (1)), falling at the same level (one (1)), motor vehicle accidents (four (4)) and quad bike accidents (two (2));

- Participants indicated on the questionnaire that their expectation of the stem cell therapy was to:
    - Gain any improvement in any function they had lost or that was compromised due to the SCI
    - Improve in hand function
    - Walk and the use of their lower limbs and
    - Improve in bladder and bowel function.
- The main source of information regarding the stem cell therapy prior to the procedure was reported to be from the Internet or by word of mouth from family and friends.

4.3. Nature of the stem cell therapy

Various pre- and post stem cell treatment regimes were recommended to the participants by the doctors who provided the stem cell therapy (Table 4.2). A common recommendation by the physicians at all the centres where stem cell therapy was administered was that participants should undergo at least 3 months of intensive rehabilitation post stem cell therapy. In Table 4.2 the different types of stem cell therapy as well as the route of administration and the country in which the participant received his or her treatment are presented in Table 4.2. Only one (1) participant reported using “Stemenhance” which is an over-the-counter product advertised to enhance the body’s own production of stem cells and assist with healing a variety of conditions. See Table 4.2 overleaf.

Table 4.2

Nature of stem cell treatment, delivery mode and pre- and post stem cell treatment

Patient no.	Nature of stem cells:	Delivery mode	Country of treatment	Pre-stem cell treatment at place of administration	Post-stem cell treatment recommended
1	Autologous stem cells	Lumbar puncture	India	None specific	Rehabilitation
2	Sheep stem cells	Subcutaneous/ intramuscular injection	South Africa	None specific	Rehabilitation, weekly stem cell injection and stem cell tablets
3	Rabbit stem cells	Subdural injection during spinal surgery	South Africa	None specific	Homeopathic tablets rehabilitation
4	Rabbit stem cells	Lumbar puncture. Injections into abdomen	Germany	Detox, ozone therapy	Rehabilitation, multivitamins
5	Rabbit stem cells	Four injections on stomach, one into spinal cord, one on each hip	Germany	One week ozone therapy lipoten drip	Rehabilitation, drips, vit B12
6	Sheep stem cells	Subcutaneous or intramuscular injections into back and neck	South Africa	None specific	Rehabilitation, weekly injections
7	Unknown	Intravenous injection	Holland	None specific	Rehabilitation
8	Foetal stem cells	Intravenously in saline solution. Also injected into subcutaneous tissue around back of neck.	Holland	None specific	Physiotherapy and rehabilitation
9	Rabbit stem cells	Multiple injections	Germany	Detox and preparation medicine	Rehabilitation
10	Foetal stem cells	Lumbar puncture after drainage of syrinx in spinal cord	China	Traditional Chinese medicine, acupuncture, IV drip to boost stem cells.	Physiotherapy 2x/day, stretches more than strengthening exercises arms and legs
11	Foetal stem cells	Lumbar puncture after surgery	China	Traditional Chinese medicine, acupuncture, IV drip to boost stem cells.	Physiotherapy 2x/day, stretches more than strengthening exercises arms and legs, rehabilitation

4.4. Functional outcomes measured by the SCIM III

The participants' functional outcomes were measured on the SCIM III outcome measure. The changes in participants' SCIM III scores are shown in Figure 4.1. The actual SCIM III scores are compared to the expected SCIM III scores in Table 4.3.

The participants' pre- and post stem cell SCIM III scores were compared to their score at the time of filling in the questionnaire.

In Figure 4.1 it can be observed that six (6) of the participants had not reached the expected functional outcome on the SCIM III, as related to their SCI level, before having the stem cell therapy (Aidinoff et al., 2011). The scores of the participants in the author's study were compared to Aidinoff's expected outcomes for a specific injury level.

The maximum score as related to the specific SCI lesion level is also plotted as per Aidinoff et al.'s (2011) research and only one (1) of the eleven (11) participants exceeded this maximum SCIM III score for her lesion level. The reason was that she had zones of partial preservation. Her scores, however, did not change at all post stem cell therapy and remained the same as her pre stem cell treatment SCIM III scores.

This participant (participant no. 11), walked with crutches and ankle-foot-orthosis (AFO) 20% of the time per day pre-stem cell therapy. Post stem cell therapy she uses a full calliper on her more affected leg because of decreased sensation and muscle control post-stem cell therapy. She was told that scar tissue was removed during surgery for the stem cell therapy. This surgery may have caused the decreased sensation and muscle control. Her walking has slowly improved post stem cell therapy but she can only walk with supervision for an hour per day with a calliper AFO and crutches. Her pain on and below the level of the lesion has improved post stem cell therapy procedure.

See Figure 4.1 overleaf.

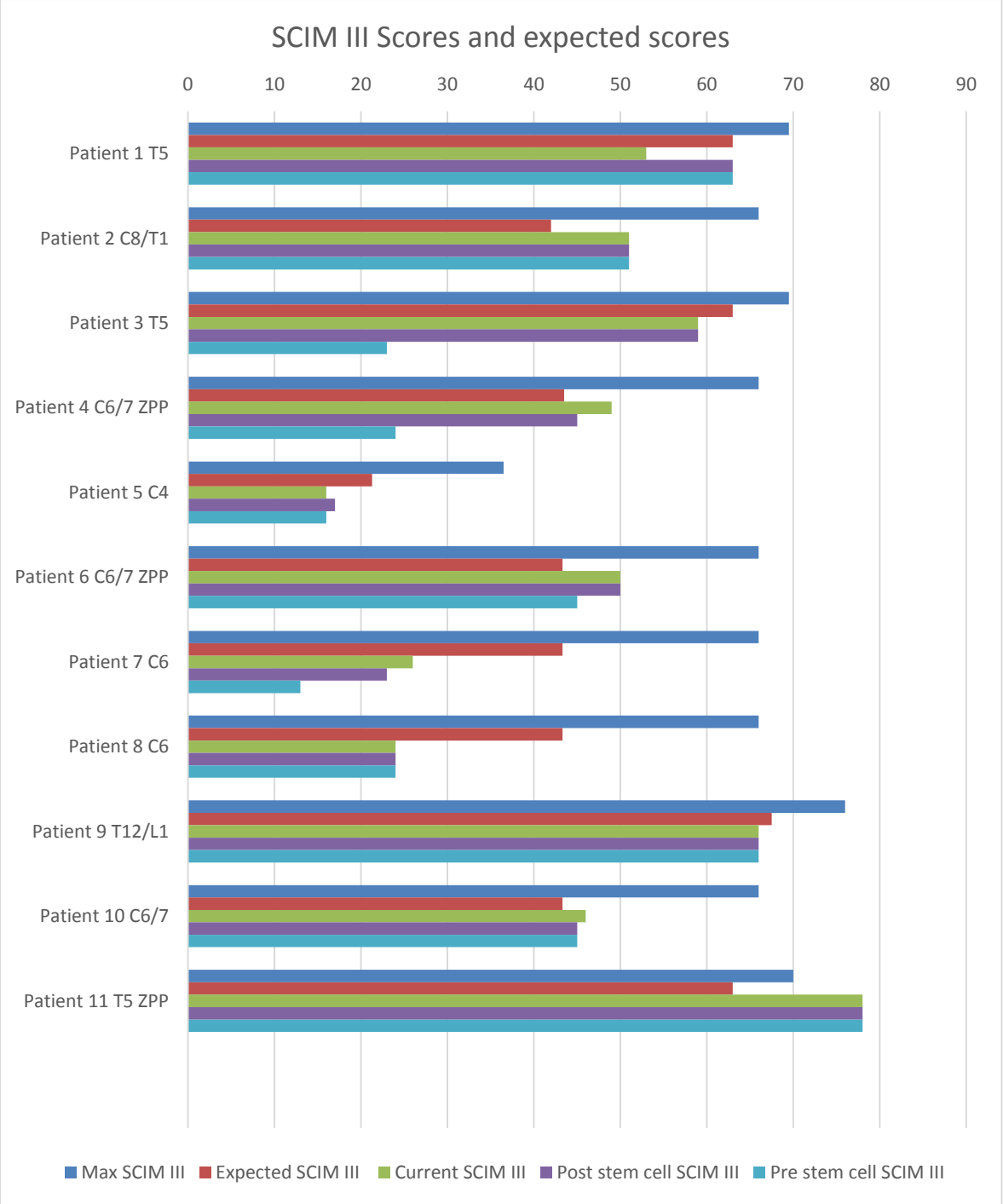

Figure 4.1 Comparison of participants' SCIM III scores pre- and post stem cell therapy, current SCIM III scores and the expected SCIM III score for their level of injury.

Four (4) of the participants' SCIM III scores remained unchanged before and after the stem cell therapy. One (1) participant's (No. 1) score decreased by 10 points after the stem cell therapy because of his change from clean intermittent self-catheterisation to an indwelling catheter.

One (1) participant's (no. 5) SCIM III improved by one (1) point during the post stem cell rehabilitation period and then returned to his pre stem cell SCIM III score and his previous level of dependency once back home again. This participant displayed no long-term benefit from the stem cell therapy.

Participant no. 3 had his stem cell treatment two (2) weeks after his injury and had had no rehabilitation prior to receiving the stem cells. His gain in functional independence on the SCIM III score was 36, which is in line with the gain expected for his level of injury during the acute rehabilitation period according to Aidinoff et al., (2011). He did not, however, reach his expected SCIM III score for the level of his lesion (Aidinoff et al., 2011).

Five (5) participants' SCIM III scores improved post stem cell therapy and rehabilitation, three (3) of the participants had C6/7 lesions, and two (2) achieved better than their expected SCIM III scores but not above the maximum reported SCIM III scores for their level of injury. This improvement could be ascribed to the fact that these two (2) participants both have zones of partial preservation (ZPP).

Of the six (6) participants who reported improved functional independence post stem cell therapy, three (3) achieved their expected SCIM III scores but none exceeded the published maximum SCIM III outcome measure score for their lesion.

Five (5) participants achieved higher than expected published SCIM III scores but two (2) of these (no. 11 and no. 2) had no change in SCIM III score after the stem cell therapy. The remaining three participants (3) all had C6/7 lesions, of whom two (2) had ZPP. None of these three (3) participants exceeded the maximum SCIM III score as reported by Aidinoff et al., (2011).

On average the participant's SCIM III scores improved by 6 points, which is to be expected post-acute rehabilitation (Ackerman et al., 2010).

See Table 4.3 overleaf.

Table 4.3

Summary of SCIM III scores pre- and post stem cell therapy

Subject no:	Level of injury	Pre stem cell therapy SCIM III	Post stem cell therapy SCIM III	Current SCIM III	Expected SCIM III score for injury level (Aidinoff et al., 2011)	Maximum SCIM III score (Aidinoff et al., 2011)	Participant's change in SCIM III scores	Expected change in SCIM III during rehab acute rehab (Aidinoff)	Expected change in SCIM III scores during rehab post-acute rehab (Ackerman)
1	T5	63	63	53	63	69	-10	30.5	5.5
2	C8/T1	51	51	51	42	69	0	25	7
3	T5	23 pre rehab	59	59	63	69	36	30.5	5.5
4	C6/7 ZPP	24	45	49	43.5	66	25	7	7
5	C4/5	16	17	16	19	36.5	1	12	0
6	C6/7 ZPP	45	50	50	43.5	66	5	7	7
7	C6	13	23	26	43.5	66	13	28	9
8	C6	24	24	24	43,5	66	0	28	9
9	T12/L1	66	66	66	67.5	76	0	34	6
10	C6/7	45	45	46	43.5	66	1	7	7
11	T5 ZPP	78	78	78	63	69	0	30.5	5.5
Average							6	22	6

In participants where ASIA scores were available, they were analysed as an adjunct to the participant's functional SCIM III scores.

4.5. Changes in ASIA motor scores and muscle strength

Participants' ASIA motor score changes are shown in Table 4.4. Of the eleven (11) participants, four (4) participants' ASIA motor scores were unchanged pre- and post stem cell therapy. Three (3) participants showed an average improvement of 3.6 points (ranging from 2-5). The improvement in the ASIA scores is ascribed to increased muscle strength in previously innervated muscles, as no new myotomes showed improvement post stem cell therapy. One (1) participant decreased by one (1) point post stem cell therapy and this participant had to use more assistive devices post stem cell therapy. Note that

in the participants where there were no ASIA scores available none of the participants felt stronger or reported that they had new muscles starting to function. Some of the participants in this study did, however, report feeling stronger post rehabilitation. This is where the ASIA motor score did improve but improvement was not due to newly innervated muscles but increased muscle strength in already innervated muscles due to the rehabilitation they received post stem cell therapy.

Table 4.4

Changes in muscle strength and ASIA motor score

Participant	**Pre-stem cell therapy ASIA**	**Post stem cell therapy-ASIA**	**Gain in muscle innervation post stem cell therapy**	**Participants perception of new muscle strength post stem cell therapy**	**Current problems post stem cell therapy**
1	50	50	None	Not stronger	Went from self-catheterization to supra-pubic catheter. Severe neurogenic pain and constipation
2	44	44	None	Not stronger	Spasms
3	50	50	None	Not stronger	None
4	22	27 no new myotomes	None	Yes stronger from rehab	
5	6	8	None	Yes from rehab	Severe neurogenic pain in hands, Spasms
6	None	No better	None	Not stronger	
7	None	No better	None	Not stronger	Lioresal Pump for spasm
8	None	No better	None	Not stronger	
9	50	50	None	Yes stronger from rehab	
10	20	24 no new myotomes	None	Yes stronger from rehab	Spasms and neurogenic pain
11	62	61	none + loss of sensation	Now needs calliper instead of AFO to walk	Unable to walk as well as pre stem cell therapy due to decreased sensation

4.6. Bladder and bowel management

Figure 4.2 shows the outcomes for bowel and bladder management. All eleven (11) participants have neurogenic bowels and make use of a bowel programme and all but one (1) required assistance with their bowel programme. There was no change from before the stem cell therapy. Eight (8) had indwelling catheters and three (3) did clean intermittent self-catheterisation (CISC) so none had normal bladder function. All participants' bladder management stayed the same as before the stem cell therapy, except one (1) participant who regressed from CISC to indwelling catheter.

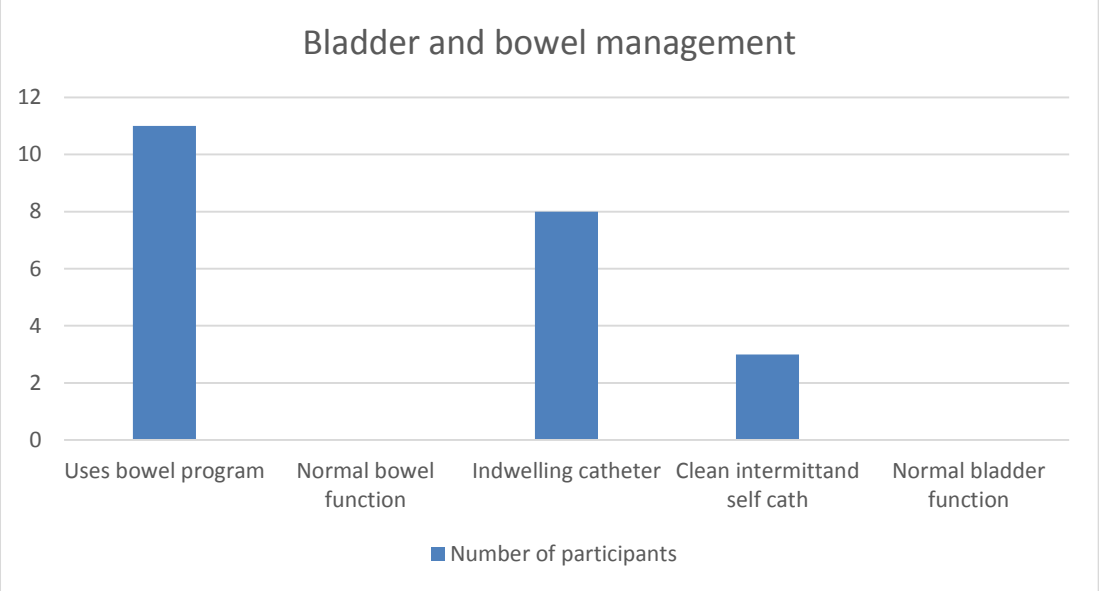

Figure 4.2

Bladder and bowel management post stem cell therapy

4.7. Mobility

Of the eleven (11) participants, post stem cell therapy, two (2) used a power wheelchair for more than 90% of the time. Nine (9) participants used a manual wheelchair for more than 90% of the time. Two (2) of these nine (9) participants did some therapeutic walking, with assistance and assistive devices, and did not walk functionally in their communities.

There was no change in the participant's mobility scores post stem cell therapy compared to the pre-stem cell scores.

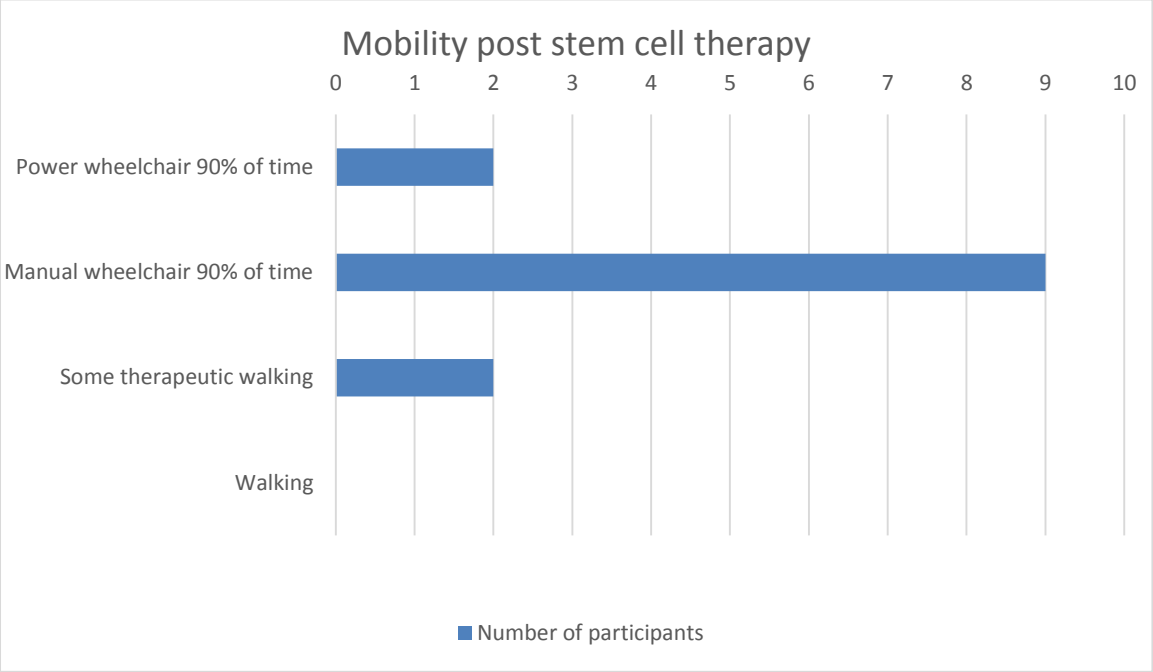

Figure 4.3 Mobility of participants measured on the SCIM III pre- and post stem cell therapy

4.8. Cost of stem cell therapy

A summary of the participants' financial costs for stem cell therapy is given in Table 4.5. According to data filled in by the participants on their questionnaires the costs of the stem cell therapy ranged from zero to R700 000.00 (R 1.00 = USD 0.091 on 23/11/2014). The average cost for the stem cell therapy was R157 927.00. The average costs for extras like travel and accommodation was R56 268.00. The total cost for all 11 participants was R 2 238 520.00 and the average total cost per participant was R 203 501.00. One (1) participant said during the interview that had he been able to reconsider he would rather recommend a person to use the money he himself spent on stem cell therapy to make functional adaptions to his / her home or to buy assistive devices. One (1) participant reported using "Stemenhance". The reported cost was R2000.00 a month for the treatment, which he still uses. His ASIA motor scale score was unchanged. See Table 4.5 overleaf.

Table 4.5

Costs and related costs incurred by patients treated with stem cell therapy for SCI

Patient	Cost of stem cell therapy (ZAR)	Cost of travel/accommodation and other expenses (R)	Treatment cost total (R)
1	R 150 000.00	R 36 000.00	R 186 000.00
2	Free	Not specified	n/a
3	R 150 000.00	R 60 000.00	R 210 000.00
4	R 80 000.00	R 89 000.00	R 169 000.00
5	R 86 200.00	R 93 220.00	R 179 320.00
6	Free	R 11 200.00	R 11 200.00
7	R 76 000.00	R 71 000.00	R 142 000.00
8	R 70 000.00	R 25 000.00	R 95 000.00
9	R 150 000.00	Not sure	R 150 000.00
10	R 650 000.00	R 50 000.00	R 700 000.00
11	R 325 000.00	R 71 000.00	R 396 000.00
Total	R 1 737 200.00	R 506 420.00	R 2 238 520.00
Average	R 157 927.27	R 56 268.88	R 203 501.82

4.9. Participants' pain perception pre- and post stem cell therapy.

Pain is commonly experienced in SCI and in some people it decreases over time and in some becomes unmanageable. Steeves et al. (2007, pg 216) report that: "It has been suggested that over 50% of people living with SCI reported experiences of chronic neuropathic pain." In the biographical questionnaires participants were requested to indicate the intensity of their perceived pain experienced before and after the stem cell therapy on a visual analogue scale. This scale is plotted in Figure 4.4.

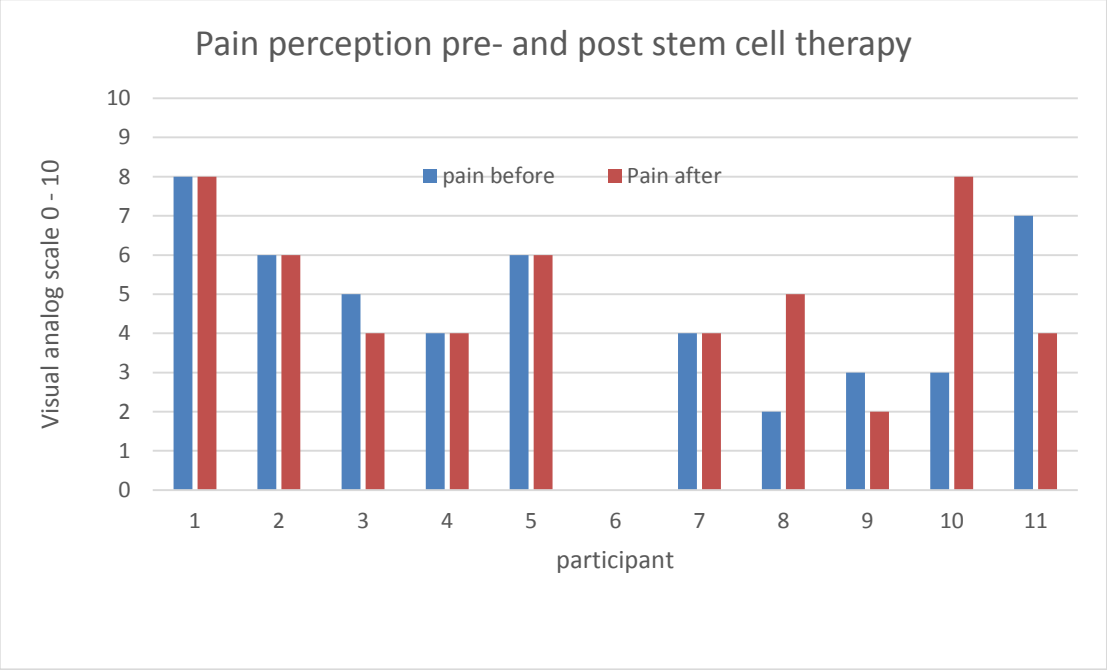

Figure 4.4 Pain perception pre- and post stem cell therapy

Pain was experienced in all but participant number 6. Participants' pain perception ranged from 8 to 0, both before and after stem cell therapy. In six (6) participants there was no change in pain perception before and after the stem cell therapy. Two (2) participants experienced considerably more pain and three (3) participants less pain post stem cell therapy. One (1) of these three (3) participants (no. 11) had a procedure to remove scar tissue in the spinal cord before the stem cells were administered. She reported a decrease in her sensation and also the pain she experienced.

4.10. Perception of functional independence pre- and post stem cell therapy.

The functional independence that participants hoped for before the stem cell therapy and their perceived independence were indicated on a VAS. These perceived independence are presented in Figure 4.5. Much less actual independence was achieved than participants expected. Not one participant reported his or her perceived independence to have improved. Four (4) of the participants had no perceived change in their level of functional independence. Seven (7) participants were less independent than hoped for. Participant number 5 had huge expectations from the stem cell therapy and his hopes were not realised and none of the hoped for new independence was gained post stem cell therapy. These results show that the stem cell therapy did not have the desired functional improvement that the participants had expected.

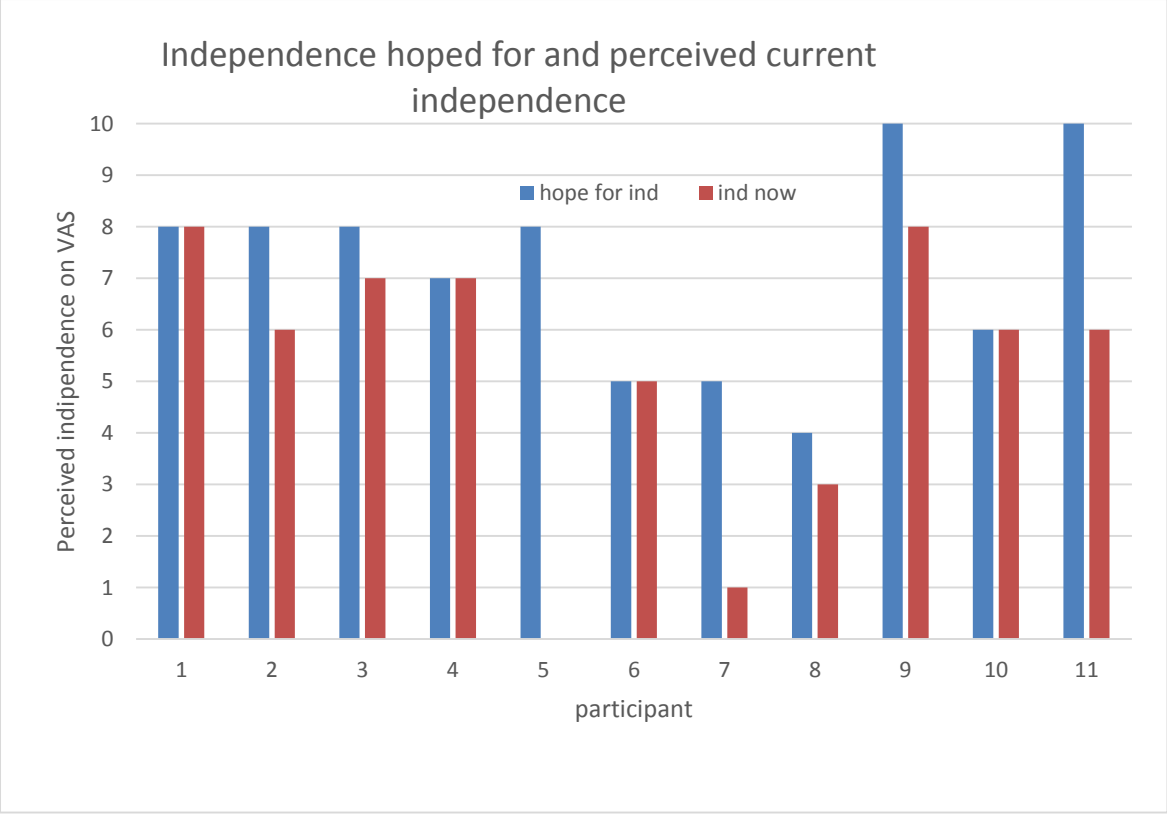

Figure 4.5 Independence hoped for and perceived current independence post stem cell therapy.

4.11. Clinical signs that participants experienced post stem cell therapy.

The clinical signs that participants reported in the biographical questionnaire that were experienced after the stem cell therapy are listed as follows:

- Constipation;
- I have permanent pain in my legs and especially my feet. I also have quite strong spasms from time to time;
- Back pain at times, headaches with any infection;
- Headaches, stress, spasms in neck;
- Occasional pains, constipation and spasms;
- Neck pain, pins & needles all over body; and
- Bladder spasticity and spasms.

Six (6) participants reported pain, seven (7) participants reported spasm and three (3) participants reported headaches. Many of these conditions are common complaints for people with SCI. Some reported increased symptoms but these cannot necessarily be said to be a result of the stem cell therapy.

Medication being used included Lioresal or Baclophen for spasticity, Dutrisitol or Ditropan for bladder spasticity, Lyrica, Neurontin and Lentogesic for pain, and Dulcolax and other laxatives as required for a bowel management programme. These are commonly used by people with SCI and were not prescribed by the stem cell therapy clinics.

4.12. Summary of Chapter 4

In Chapter 4 the results of the biographical questionnaire and SCIM III outcome measure were summarised. The results of the pre- and post SCIM III scores were listed, as well as a comparison to the expected outcomes for similar SCI levels. The ASIA motor score results were tabulated, as well as the pain and perceived functional outcomes as measured on the VAS.

Chapter 5 presents a discussion of the results in Chapter 4. A conclusion and recommendations are drawn from the results of this study and recommendations for further research are given.

Chapter 5

Discussion, conclusion and recommendations

5.1. Introduction

In Chapter 5 the outcomes of a critical analysis of the survey amongst participants who received stem cell therapy for post traumatic SCI are discussed. The study was performed to determine whether the stem cell therapy that participants received had any influence on their level of functional ability, as measured on the SCIM III. The results of the study are discussed and concluded. The outcome and conclusions based on this study were also used to compile a brochure, to enable people with SCI who may consider stem cell therapy to make an informed decision on whether to undergo stem cell therapy or not.

Limitations of the study are also discussed. Recommendations for further research are made based on the discussion, conclusions and limitations in this study.

5.2. Discussion of results

- The average age of the 11 patients was 36.9 years ranging from 22-51 years which falls into the economically active age group and which is the most common age group within which people sustain SCI (Wyndaele and Wyndaele 2006).
- Of the participants eight (8) were male and three (3) female; this gender ratio is to be expected in relation to the general incidence of SCI (Wyndaele and Wyndaele 2006).
- Four (4) participants were paraplegics and seven (7) were tetraplegics, almost double the number of participants were tetraplegics. This ratio between paraplegic and tetraplegic lesions can be ascribed to the fact that the severity of the tetraplegics' physical impairments were greater than those of a paraplegic, which may result in the tetraplegics'

increased need for a cure so as to be less dependent on other people for their daily care.

- The participants' injuries ranged from C4 complete lesion ASIA A to L1 complete ASIA A.
- The causes of their SCI were gunshot wounds (three (3)), motorbike accident (one (1)), falling at the same level while at a foam party(one (1)), motor vehicle accidents (four (4)) and quad bike accidents (two (2)). These are all part of the group of common causes of SCI in South Africa.
- Four (4) participants had paraplegic SCI lesions while seven (7) participants in this study had tetraplegic SCI lesions. Three (3) participants had ZPP while one (1) participant has an ASIA B lesion.

Each participant's pre-stem cell therapy ASIA motor scores (where available) and SCIM III scores served as his or her control with which their post stem cell scores were compared. These SCIM III scores were also compared to the expected SCIM III scores for their respective SCI lesion level (Aidinoff et al., 2011).

The participants received stem cell therapy in South Africa, India, Germany, Holland and China. The type of stem cells that were administered to the participants as well as the mode of delivery and the pre- and post stem cell therapy and rehabilitation differed for each participant.

Although the pre-stem cell therapy SCIM III scores were lower than the post stem cell scores in five (5) participants, only three (3) of the participants' post stem cell therapy SCIM III scores were higher than their expected SCIM III score for their level of injury. Not one participant achieved the maximum reported SCIM III score for their lesion and two (2) of these participants had ZPP which also influenced their level of functional ability positively. In the five (5) participants whose pre-stem cell therapy SCIM III scores were lower than their post stem cell therapy scores, the difference in SCIM III scores cannot be ascribed to the success of the stem cell therapy, because the post stem cell therapy SCIM III scores did not exceed the expected or the maximum scores for the type of lesion the participants presented with. The improvement in post

stem cell therapy SCIM III scores in these participants can be ascribed to the intensive rehabilitation that all the participants received post stem cell therapy. The additional vitamins, injections, intravenous drips or tablets might have had an effect on participants' perception of general well-being but, as already mentioned, none of the participants' SCIM III scores exceeded their maximum scores, which could be ascribed to improved neurological innervation which would result in improved level of function above that expected for the level of injury.

Three (3) patients reported a slight improvement (decrease) in pain perception post stem cell therapy, while none of the participants indicated that their perceived independence post stem cell therapy on a numeric VAS scale had improved. Three (3) participants indicated that their perceived functional ability on the VAS scale has decreased. Six (6) of the participants mentioned objective symptoms that they experienced post stem cell therapy such as spasm, decreased bladder control, neurogenic pain and constipation. These symptoms are, however, also symptoms that patients with an SCI often experience post injury. It is therefore not possible to ascribe these symptoms to a negative result of the stem cell therapy except in the case of two (2) patients who reported (1) a decrease in functional walking and sensation and (2) a decrease in bladder control.

Effective stem cell treatment for SCI would show an improvement in both muscle innervation due to the newly formed neural pathways, which would be translated into improved functional ability. Effective stem cell therapy would have shown an improvement in SCIM scores beyond the expected outcomes for the level of injury and improved ASIA motor scores below the level of injury.

None of the eleven (11) participants in this study gained significant functional improvement beyond the expected outcomes for their level of injury as measured by the SCIM III, and no new muscle innervation was observed as shown by the available ASIA motor scores or was reported by any of the participants.

The functional improvements in six (6) participants (one (1) of whom reverted back after discharge home to his pre-stem cell SCIM III level) are ascribed most

likely to the rehabilitation given post stem cell therapy and not to nerve regeneration, as none of them improved significantly more than the expected outcomes for their lesion level. The improvement is probably due to the rehabilitation and plasticity and new skills that were learnt (Blesch and Tusynski 2009). Six (6) of the eleven (11) participants have not reached expected functional outcomes to date. Five (5) participants exceeded their expected SCIM III scores, two (2) of whom has sparing of muscles and sensation below the level of lesion but only one (1) exceeded the maximum SCIM III score. The expected SCIM III scores are reported for complete SCIs and do not include accurate scoring for persons with ZPP (Aidinoff et al., 2011). The participant no 11 who exceeded the maximum SCIM III score for the lesion level, scores didn't change at all after the stem cell treatment. Of these five (5) participants, whose SCIM III scores improved, two (2) didn't change at all in SCIM III score post stem cell therapy. Four (4) of the total eleven (11) participants showed no improvement in SCIM III scores after the stem cell therapy.

It was noted that the participants that achieved or exceeded their SCIM III scores were all tetraplegics except one (1). The principal researcher did not consider them to be more functional than expected for their lesion type. Could it be that the demographics of our SCI population was different from those covered in Aidinoff et al.'s (2011) study.

According to Curt et al.'s (2007) research where subjects' ASIA scores were measured in a period up to 48 weeks after injury, the average improvement in ASIA scores for an ASIA A patient was 14 points for tetraplegics and 7 points increase in ASIA motor score for paraplegics. For ASIA B patients, the ASIA motor score increased by 24 points in tetraplegics and by 30 points in paraplegics. These improvements are ascribed to neural plasticity that underlies the post-injury recovery together with mechanisms of compensation and strengthening in persons that sustained SCI. In this study where there were improvements in ASIA motor scores it occurred in already innervated myotomes which showed improvement as a result of rehabilitation.

Some of the results post stem cell treatment – loss of sensation, increased pain, decreased function, the need for more assistive devices and even no change

are not indicative of effective therapy for patients with SCI. In fact in the case of these participants the results reflect that stem cell treatment may have detrimental effects for patients with SCI (as a result, for example, to the site of injection)(Lukovic et al 2014). This outcome was shown in six (6) of the eleven (11) participants in this study who reported negative effects of the treatment (Table 4.4).

There is strong evidence that therapy from stem cells will impact on the future treatment of SCI (Garbossa et al., 2012) but that further research is required to translate the laboratory research into clinical therapy so that people with SCI can benefit from it. Snyder and Teng (2012) explain that an SCI is not a single entity but a series of simultaneous and interacting pathological processes and that multimodal actions are required to find a cure, one possible facet of treatment being stem cell therapy.

A trend that has been noticed amongst people living with a SCI is that they engage in “stem cell tourism” (Meissner-Roloff and Pepper, 2013) because they are desperately seeking for a cure for their condition. The fact that the websites promise a cure for SCI using stem cell therapy, without research evidence exploits the emotional vulnerability of people living with SCI to seek for a cure. After unsuccessful stem cell treatment these people often experience hopelessness and depression.

These people are willing to spend large amounts of money to find an instant cure and do not consider the lack of evidence demonstrating clinical efficacy. The large sums of money participants in this study spent to undergo stem cell therapy are reflected in Table 4.5. The outcome of this study enables the researcher to compile a pamphlet that will enable patients who have sustained an SCI and who are considering stem cell therapy to make an informed decision based on research evidence. The international campaign for cure (ICCP) has published guidelines to guide and enable people with SCI who consider participation in clinical trials to make informed decisions before they join clinical trials (Steeves et al., 2007). The ICCP also warns that people who have undergone stem cell therapy will most probably be excluded from or disqualified

from future ethically approved trials owing to the stem cell therapy that they have already received.

In contrast to the participants in this study who paid large sums of money, people with SCI who would like to participate in clinical trials should not be required to do this at their own cost but should be funded to participate in the trials.

The ICCP position statement on unproven cellular therapies warns of the risks of partaking in unproven therapies both for the participant but also for the future of research in the field of SCI. This warning is given due to the fact that these participants may sustain loss of function, strength or sensation and experience pain or worsening spasticity or infections or tumours and rejection of the stem cells and then even have no change of condition at all and suffer depression as a result of loss of hope. They then will be excluded from future ethical trials because they have already received stem cell therapy and then there is a risk that useful medical evidence will not be generated through a lack of numbers of participants for ethical trials (Blight et al., 2009). This trend underlines the need for effective legislation and means of enforcement in all countries to guard against consumer exploitation by providers of unproven therapies.

5.3. Conclusion

The stem cell therapy administered to people living with SCI in the five (5) centres that participants in this study visited do not seem to be beneficial to these people. It is clear from the literature that the basic research in laboratories is not ready to be translated into clinical treatment for SCI (Illes, Remier and Kwon 2011). In comparing the type stem cell therapy that the participants received, it is evident that not all the procedures were done according to researched delivery methods that are being performed currently. The fact that some participants received stem cells from rabbits and lambs and one (1) didn't even know the source of the stem cells warrants the question: Was this effective stem cell therapy?

These participants were misled into going for unproven therapy believing this would cure their SCI and now have no cure to show for all the money spent.

There is, however, strong evidence that therapy from stem cells will impact on the future treatment of SCI (Garbossa et al., 2012) but that further research is required to translate the laboratory research into clinical therapy so that people with SCI can benefit from it. Snyder and Teng (2012) explain that an SCI is not a single entity but a series of simultaneous and interacting pathological processes and that multimodal actions will be required to find a cure, one possible element of this cure being stem cell therapy. Until such time that the efficacy of stem cell therapy has been proved by ethically approved studies, people living with SCI should be discouraged from going for stem cell therapy. Furthermore, people living with SCI should be discouraged to seek stem cell treatment from clinics that are advertised on the Internet and be advised to rather keep themselves in good health, supple and strong with no complications, so that when successful stem cell treatment has been ethically approved, they will be in the best possible position to benefit from it.

Rehabilitation aiming to achieve the best functional outcome is still the most important part of the treatment of SCI. Effective goal-directed client-centred and outcome-based rehabilitation should be available to all persons with SCI to allow them to achieve the best outcomes and to be effective role players participating in their communities.

There is no evidence that current ‘stem cell’ therapies administered outside of registered clinical trials for people living with spinal cord injuries are beneficial.

A pamphlet that can be used to advise people with SCI, their families as well as rehabilitation professionals on the current outcome of stem cell therapy, according to the findings from this research, is compiled and added as an Addendum 5 pg 121.

5.4. Limitations of the study

The fact that the study was not a prospective clinical trial is a limitation. Because it was more retrospective in nature the researcher had to rely on telephonic interviews and or self-reported SCIM III scores. The primary researcher had to rely on participants’ memory and truthfulness in reporting on the bibliographical questionnaire and SCIM III. Such a situation leaves room for biased opinion.

The self-reporting by participants was also a limitation because it was not possible for the researcher to prompt participants (as in during a face-to face-interview) to remember important subjective detail or to guide them to remember objective data. Owing to the fact that randomised clinical trials do not receive ethical approval until further research has been done to ensure the safety and a potential positive functional outcome to participants, a survey of this nature is the only option to obtain reasonable evidence.

A further limitation is the use of a non validated questionnaire. A pilot testing phase would have been preferable but would have further reduced sample size.

The small number of participants was definitely a limitation in this study. Although the primary researcher did everything possible to recruit as many as possible participants for this study, people were not willing to come forward if they had undergone stem cell therapy that was not successful or that did not meet their expectations.

Because this study was based on a retrospective analysis of data of people with SCI who had undergone stem cell therapy, ASIA scores could not be obtained for some of the participants. Not all participants received their rehabilitation at the same centre, so pre-stem cell records could not be retrieved from the archives.

The time between the participants' SCI and the time they received stem cell therapy varied between 14 days post injury to 8 years post injury with a mean of 3.6 years. This should not have had an effect on the outcome of this study because each participant served as his or her own control. However, the time post injury could have affected the outcome of the effect of the stem cell treatment.

The patients received stem cell therapy from different centres or clinics. There is therefore not enough evidence to compare the outcome of paticipants who received stem cell therapy from the different clinics nor to compare the difference between the different forms of stem cells that were administered to the participants. As written in the previous paragraph it would not have had any effect on this study because participants served as their own control group and

it was not the purpose of this study to investigate the differences in delivery or effectiveness of different types of stem therapy.

5.5. Conflicts of interest

The researchers have no conflict of interest in the outcome of the study.

5.6. Recommendations for further research

Before stem cell therapy is to become a recognised form of treatment for patients with an SCI, well-controlled clinical trials (randomised clinical trials) need to be undertaken. At present, ethically approved and recognised trials are being conducted but most are phase I and II trials aimed at determining safety in humans (Chhabra et al., 2009, Mothe and Tator 2012). Although the translation process of basic research into clinical application in clinical trials is long and frustrating for people with SCI and their families and rehabilitation specialists, thorough research is required to ensure safety and produce meaningful reproducible functional improvement in people living with SCI.

Once pre-clinical research has progressed to the extent that ethically approved clinical trials can be conducted on humans with SCI, it would be essential to perform accurate and regularly spaced full ASIA scores as well as standardised outcomes measures such as the SCIM III. These scores together with sophisticated nerve and spinal cord conduction tests could determine the physiological and clinical outcomes of stem cell therapy.

The outcome levels and especially the SCIM III functional outcome measure scores of specifically tetraplegics should be compared with those in the rest of the world so as to add to the data base compiled by Aidinoff (2011).

The effectiveness of current acute treatment regimes and rehabilitation management of patients with SCI should be investigated to standardise and optimise effective rehabilitation of patients with SCI.

There is an urgent need for the drafting, formalising and implementation of comprehensive stem cell legislation in South Africa to avoid emotional exploitation of patients living with SCI. This may not stop people with SCIs from going overseas for treatment but may encourage ethical research and treatment within our own borders.

References:

Ackerman P, Morrison SA, Mc Dowell S and Vazques L., 2010. Using the SCIM III to measure functional recovery in a post-acute spinal cord injury program. *Spinal Cord*, 48, 380-387.

Aidinoff E, Front L, Itzkovich M, Bluvshtein V, Gelernter I, Hart J, Beiring-Sorensen F, Weeks C, Laramee MT, Craven C, Hitzig SL, Glazer E, Zeilig G, Aito S, Scivoletto G, Mecci M, Chadwick RJ, El Masry WS, Osman A, Glass CA, Soni BM, Gardener BP, Savic G, Bergstrom EM, Silva P a.nd Catz A., 2011. Expected SCIM III scores for various levels after complete SCl lesions. *Spinal Cord*, 49, 893-896.

Alexander MS, Anderson KD, Biering-Sorensen F, Blight AR,Brannon R, BryceTN, Creasey G, Catz A, Curt A, Donovan W, Ditunno J, Ellaway P, Finnerup NB, Graves DE, Haynes BA, Heinerman AW, Jackson AB, Johnston MV, Kalpakjian CZ, Kleitman N. Krassioukov A, Krogh K, Lammertse D, Magasi S, Mulcahey MJ, Schurch B, Sherwood A, Steeves JD, Stiens S, Tulsky DS, van Hedel HJA and Whiteneck G., 2009. Outcome measures in spinal cord injury: recent assessments and recommendations for future directions. *Spinal Cord*, 47, 582-591.

Amadour MJ and Guest JD., 2005. An appraisal of ongoing experimental procedures in human spinal cord injury. *Journal of Neurological Physical*, 29 (2), 70-86.

Anderson KD., 2004. Targeting recovery: Priorities of the spinal cord- injured population. *J Neurotrauma*, 21, 1371-1383.

Barclay E., 2009. Stem cell experts raise concerns about medical tourism. www.theLancet.com March14 2009, 373, 883-884.

Barnabe-Heider F and Frisen J., 2008. Stem cells for Spinal cord repair. *Cell stem cell Review*. March, 16-24.

Beijing Puhua International Hospital website. Viewed May 2012 and Nov 2014 http://www.puhuachina.com/stem-cell-center/stem-cell-cente.

Blesch A and Tuszynski., 2009. Spinal cord injury: Plasticity, regeneration and the challenge of translational drug development. *Trends in Neurosciences*, 32(1), 41-47.

Blight A, Curt A, Ditunno JF, Dobkin B, Ellaway P, Fawcett J, Fehlings M, Gossman RG, Lammertse DP, Privat A, Steeves J, Tuszynski M, Kalichman M and Guest JD., 2009. Position statement on the sale of unproven cellular therapies for spinal cord injury. *Spinal Cord*, 47, 713-714.

Bluvshtein V, Front L, Itzkovich M, Aidinoff E, |Gelernter I, Hart J, Biering-Sorensen F, Weeks C, Laramee MT , Craven BC, Hitzig SL, Glaser E, Zeilig G, Aito S, Scivoletto G, Mecci M , Chadwick RJ, El Masry WS, Osman A, Glass CA, Silva P, Soni BM, Gardner BP, Savic G, Bergstrom EM and Catz A., 2011. SCIM III is reliable and valid in a separate analysis for traumatic spinal cord lesions. *Spinal cord*, 49, 292-296.

Bregman BS, Kunkel-Bagden E, Reier PJ, Dai HN, McAtee M and Gao D., 1993. Recovery of function after spinal cord injury: mechanisms underlying transplant-mediated recovery of function differ after spinal cord injury in new-born and adult rats. *Exp Neurology*, 123, 3-16.

Brown JM, Deriso DM and Tansey KE., 2012. From contemporary rehabilitation to restorative neurology. *Clinical Neurology and neurosurgery*, 114, 471-474.

Burns AS and Ditunno JF., 2001, Establishing prognosis and maximizing functional outcomes after spinal cord injury a review of current and future directions in rehabilitation management. *Spine*, 26 No 24S, S137-S145.

Burns AS, Lee BS, Ditunno JF Jr and Tessler A., 2003. Patient selection for clinical trials: the reliability of the early spinal cord Injury examination. *J Neurotrauma*, 20, 477-82.

Catz A, Itzkovich M, Agranov E, Ring H and Tamir A., 1997. SCIM spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord*, 35, 850-856.

Catz A, Itzkovich M, Tesi L, Biering-Sorensen F, Weeks C, Laramee MT , Craven BC, Tonack M, Hitzig SL, Glaser E, Zeilig G, Aito S, Scivoletto G, Mecci M , Chadwick RJ, El Masry WS, Osman A, Glass CA, Silva P, Soni BM, Gardner BP, Savic G, Bergstrom EM, Bluvshtein V and Ronen J,. 2007. A multicentre international study of the spinal cord independence measure, version III: rasch psychometric validation. *Spinal cord*, 29, 275-291.

Caulfield T, Ogbogu U, Murdoch C and Einsiedel E., 2008. Patent, Commercialization and the Canadian Stem Cell Community. *Regenerative Medicine*, 3, 483-496.

Chhabra HS, Lima C, Sachdeva S, Mittal A, Nigam V, Chaturvedi D, Arora M, Aggarwai A, Kapur R and Khan TAH., 2009. Autologous mucosal transplant in chronic spinal cord injury: an Indian pilot study. *Spinal cord*, 47, 887-895.

Creasy G and Scott CT., 2009. Stem cell transplants: the power of peer-to-peer. *Nat Biotechnol,* Jan, 27(1), 21-22.

Curt A, JA Van Hedel H, Klaus D and Dietz V., 2008. Recovery from a Spinal cord injury: significance of compensation, neural plasticity and repair. *Journal of Neurotrauma*, 25, 667-685.

Curt A, Schwab ME and Dietz V., 2004. Providing the clinical basis for new interventional therapies: refined diagnosis and assessment of recovery after SCI. *Spinal cord*, 42, 1-6.

Cushing H., 1927. Organization and activities of the neurological service American expeditionary forces. In: Ireland MW, ed. The medical department of the United States Army in the world war. Washington, DC: Government Printing Office, 749-758.

Cyranoski D., 2006. Patients' warned about unproven spinal surgery. *Nature*, 440, 850-851.

Dawson J, Shamley D and Jamous MA., 2008. A structured review of outcome measures used for the assessment of rehabilitation interventions for spinal cord injury. *Spinal Cord*, 46, 768-780.

Ditunno JF and Burns AS., 2005. Neurological and functional capacity outcome measures: essential to spinal cord injury clinical trials. *JRRD* May/June, 4(3), 35-42.

Dobkin BH Curt A and Guest J., 2006. Cellular transplants in China: Observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabil and neural repair*, 20(1), 5-13.

Donnelly EM, Lamanna J and Boulis NM., 2012. Stem cell therapy for the spinal cord. *Stem Cell Research & Therapy*, 3, 24.

Ellaway PH, Anand P, Bergstrom EMK, Catley M, Davey NJ, Frankel HL, Jamous A, Mathias C, Nicotra A, Savic G, Short DD and Theodorou S., 2004. Towards improved clinical and physiological assessments of recovery in spinal cord injury: a clinical initiative. *Spinal Cord,* 42, 325-337.

Elsberg C., 1931. The Edwin Smith Surgical Papyrus: The diagnosis and treatment of injuries to the skull and spine 5000 years ago. *Annals of med history*, March 5: 271-279.

Eltorai IM., 2003. Ch 1 History of spinal cord medicine. In Spinal cord medicine: Principles and practice Vernon W Lin Editor in chief. New York: Demos medical publishing, 3-13.

Ertelt S., 2008. FDA Delays Geron's Human Embryonic Stem Cell Research Trials, www.LifeNews.com Editor, *August 18.*

Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, Bartlett PF, Blight AR, Dietz V, Ditunno J, Dobkin BH, Havton LA, Ellaway PH, Fehlings MG, Privat A, Grossman R, Guest JD, Klietman N, Nakamura M, Gaviria M and Short D., 2007. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*, 45, 190-205.

Fekete C, Eriks-Hoogland I, Baumberger M, Catz A, Itzkovich M, Luthi H, Post MWM, von Elm E, Wyss A, and Brinkhof MWG., 2013. Development and validation of a self-report version of the spinal cord independence measure (SCIM III). *Spinal Cord*, 51, 40-47.

Ferreira-Valente MA, Pais-Ribeiro JL and Jensen MP., 2011. Validity of four pain rating scales. *Pain*, 152, 2399-2404.

Fitzgerald K**.,** 2012**.** Revolutionary Stem Cell Treatment Repairs Spinal Cord Injuries In Paralyzed Dogs. Viewed April 2013. www.medicalnewstoday.com/articles/252982.php.

Formal CS, Cawley MFC and Stiens SA., 1997. Spinal cord injury rehabilitation. 3 Functional outcomes. *Arch Phys Med Rehabil*, 78, S59-S64.

Garbossa D, Boido M, Fontanella M, Fronda C, Ducati A and Vercelli A., 2012. Recent therapeutic strategies for spinal cord injury treatment: possible role of stem cells. *Neurosurg rev*, 35, 293-311.

Godlwana L, Gounden P, Ngubo P, Nsibande T, Nyawo K and PuckreeT., 2008. The Incidence and profile of spinal tuberculosis in patients at the only public hospital admitting such patients in KwaZulu-Natal. *Spinal Cord,* 46, 372-374.

Grossman R, Short D, Nakamura M, Coleman WP, Gaviria M and Privat A., 2007. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. *Spinal Cord*, 45, 206-221.

Hall KM, Cohen ME, Wright J, Call M and Werner P., 1999. Characteristics of the functional independence measure in traumatic spinal cord injury. *Arch Phys Med Rehabil,* 80, 1471-1476.

Hawryluk GWJ, Rowland J, Kwon BK and Fehlings MG., 2008. Protection and repair of the injured spinal cord: a review of completed, ongoing, and planned clinical trials for acute spinal cord injury. *Neurosurgery focus*, 25(5), 1-16.

Heineman AW, Yarkony GM, Roth EJ, Lovell L, Hamilton B, Ginsburg K, Brown JT and Meyer PR Jr., 1989. Functional outcome following spinal cord injury. A comparison of specialized spinal cord injury center vs general hospital short-term care. *Arch Neurol*, 46(10), 1098-1102.

Illes J, Remier JC and Kwon BK., 2011. Stem cell clinical trials for spinal cord injury: rediness, reluctance, redefinition. *Stem cell Rev*, 7(4), 997-1005.

Itzkovich M, Gelernter I, Biering-Sorensen F, Weeks C, Laramee MT, Craven BC, Tonack M, Hitzig SL, Glaser E, Zeilig G, Aito S, Scivoletto G, Mecci M, Chadwic RJ, El Masry WS, Osman A, Glass CA, Silva P, Soni BM, Gardiner BP, Savic G, Bergstrom EM, Bluvshtein V, Ronen J and Catz A., 2007. The spinal cord independence measure (SCIM) version III reliability and validity in a multi-centre international study. *Disabil and Rehabil*, 29, 1926-1933.

Jensen GS, Hart AN, Zaske LAM, Drapeau C, Gupta N, Schaeffer DJ and Cruickshank JA., 2007. Mobilization of human CD34+CD133+ and CD34+CD133 stem cells invivo by consumption of an extract from Aphanizomenon flos-aquae—related to modulation

of CXCR4 expression by an L-selectin ligand. *Cardiovascular Revasculisation Med*, 8, 189-202.

Kawada H., 2006. Administration of Haematopoietic cytokines in the sub acute phase after cerebral infarction is effective for functional recovery facilitating proliferation of intrinsic neural stem /progenitor cells and transition of bone marrow derived neuronal cells. *Circulation*, 113(5), 701-710.

Kiatpongsan S and Sipp D., 2008. Offshore stem cell treatments. *Nature reports stem cells* 3 Dec published online.

Krause JS, Carter R, Pickelsimer EE and Wilson D., 2008. A prospective study of health and risk of mortality after spinal cord injury. *Arch Phys Med Reha*bil, 89 (8), 1482-1491.

Kwon BK, Okon EB, Plunet W, Baptiste D, Fouad K, Hillyer J, Weaver LC, Fehlings MG and Tetzlaff W., 2011. A systematic review of directly applied biologic therapies for acute SCI. *Journal of Neurotrauma*, 28, 1589-1610.

Lau D, Ogbogu U, Taylor B, Stafinski T, Menon D and Caulfield T., 2008. Stem cell clinics online: The direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell*, 3, 591-594.

Lim PAC and Tow AM., 2007. Recovery and regeneration after spinal cord injury: A review and summary of recent literature*. Ann Acad Med Singapore*, 36, 49-57.

Lukovic D, Stojkovic M, Moreno-Manzano V, Bhattacharya S and Erceg S., 2014. Perspectives and Future Directions of Human Pluripotent Stem Cell-Based Therapies: Lessons from Geron's Clinical Trial for Spinal Cord Injury. *Stem cells and development*, 23(1), 1-4.

Marino RJ, Jones L, Kirshblum S, Tal J and Dasgupta A., 2008. Reliability and repeatability of the motor and Sensory examination of the International Standards for Neurological Classification of spinal cord injury. *J spinal cord Med*, 31(2), 166-170.

Maynard FM jr, Bracken MB, Creasey G, Ditunno JF jr, Donovan WH, Ducker TB, Garber SL, Marino RJ, Stover SL, Tator CH, Waters RL, Wilberger JE and Young W.,

1997. International standards for neurological and functional classification of spinal cord injury. American Spinal Injury Association. *Spinal Cord*, 35, 266-274.

McCormack HM, Horne D J de L and Sheather S., 1988. Clinical applications of visual analogue scales: a critical review. *Psychological Medicine,* 18, 1007-1019.

Meissner-Roloff M and Pepper MS., 2013. Curbing stem cell tourism in South Africa. *Applied and Translational Genomics*, 2, 22-27.

Mills C., 2009. The Truth about Wheels. Published by the author.

Mothe AJ and Tator CH., 2012. Advances in stem cell therapy for spinal cord injury. *The journal of clinical investigation*, 122, 3824-3831.

Munce SE, Wodchis WP, Guilcher SJ, Couris CM, Verrier M, Funq K, Craven BC and Jaqlal SB., 2013. Direct costs of adult traumatic spinal cord injury in Ontario. *Spinal cord*, 51(1), 64-69.

Nandoe Tewarie Rishi DS, Hurtado A, Bartels RHMA, Grotenhuis JA and Oudega M., 2010. A clinical perspective of spinal cord injury. *NeuroRehabilitation*, 27, 129-139.

Nandoe Tewarie Rishi DS, Oudega M, Gaby JR., 2012. Ch22 Bone marrow stromal cells for repair of the injured spinal cord. New Advances in Stem Cell Transplantation Edited by Demirer T. Published by In tech, 471-494.

Nelson B., 2008. Stem cell researchers face down stem cell tourism. *Nature Reports Stem cells* published online 5 June 2008.

Price DD, Staud R and Robinson ME., 2012. How should we use the visual analogue scale (vas) In rehabilitation outcomes? Ii: visual analogue scales as ratio scales: an alternative to the view of Kersten et al*.,. J Rehabil Med*, 44(9), 800-804

Ronsyn MW, Berneman ZN, Van Tendeloo VFI, Jorens PG and Ponsaerts P., 2008. Can cell therapy heal a spinal cord injury? *Spinal cord*, 46, 532-539.

Rosenfeld J and Gillett GR., 2004. Ethics, stem cells and spinal cord repair. *MJA*, 180 (12), 637-639.

Savic G, Bergstrom EM, Frankel HL, Jamous MA and Jones PW., 2007. Inter-rater reliability of motor and sensory examinations performed according to the American Spinal Injury Association standards. *Spinal Cord,* 45(6), 444-451.

Savic G and Catz A., 2009 Update on functional independence measures. ISCOS congress 2009.

Scivoletto G, Morganti B, Ditunno P, Ditunno JF and Molinari M., 2003. Effects of age on spinal cord lesion patients' rehabilitation. *Spinal cord*, 41(8), 457-464.

Snyder EY and Teng YD., 2012. Stem cells and spinal cord repair. *The New England Journal of Medicine*, 366(20), 1940-1942.

Stats SA census 2011 www.statssa.gov.za/census2011

Steeves JD, Fawcett JW, Tuszynski MH, Lammertse D, Curt AEP, Ditunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, Havton LA, Grossman R, Short DJ, Nakamura M, Katoh H, Coleman WP, Gaviria M, Privat A, Kalichman MW and Rask C., 2007. Experimental treatment for SCI: what you should know if you are considering participation in a clinical trial. ICCP 2007, Prepared for publication by ICORD Vancouver Canada. (www.icord.org)

Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MW, Ditunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, Grossman R, Short D, Nakamura M, Coleman WP, Gaviria M and Privat A., 2007. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. *Spinal Cord*, 45, 206-221.

Tator CH., 2006. Review of trials in Human spinal cord injuries: Issues, difficulties, and recommendations*. Neurosurgery*, 59, 957-987.

Theron dV F and Burger M., 2003. Evaluation of spinal cord afflictions in Gauteng Health. In proceedings of the SASCA congress 2003 Gauteng South Africa.

Thuret S, Moon LDF and Gage FH., 2006. Therapeutic interventions after spinal cord injury. *Nature reviews Neuroscience*, 7, 268-243.

Waring WP 3rd, Biering-Sorensen F, Burns S, Donovan W, Graves D, Jha A, Jones L, Kirshblum S, Marino R, Mulcahey MJ, Reeves R, Scelza WM, Schmidt-Read M and

Stein A., 2010. 2009 review and revisions of the international standards for the neurological classification of spinal cord injury. *J Spinal Cord Med*., 33(4), 346-352.

Wilcox JT, Cadotte D and Fehlings MG., 2012. Spinal cord trials and the role of bioengineering. Neuroscience Letters, in press. doi:10.1016/j.neulet.2012.02.028. 1-10.

Wewers M.E and Lowe N.K., 1990. A critical review of visual analogue scales in the measurement of clinical phenomena. *Research in Nursing and Health*, 13, 227-236.

Wirth B. van Hedel HJ. Kometer B. Dietz V and Curt A., 2008. Changes in activity after a complete spinal cord injury as measured by the Spinal Cord Independence Measure II (SCIMII). *Neurorehabilitation & Neural Repair*, 22(3), 279-87.

Wyndaele M and Wyndaele JJ., 2006. Incidence, prevalence and epidemiology of Spinal cord injury: what learns a worldwide literature survey? *Spinal Cord*, 44, 523-529.

Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz- Bourget J Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, SlukvinII and Thomson JA., 2007. Induces pluripotent stem cell lines derived from human somatic cells. *Science*, 318, 1917-1920.

Addendums

Addendum 1. Ethical clearance:

22-FEB-2010 12:10 From: To:Susan Groenewald P.1/1

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

4/02/2010

Number	:	**S5/2010**
Title	:	A retrospective analysis of the perceived outcome of stem cell therapy for persons living with a spinal cord injury
Investigator	:	Melanie Skeen, Department of Physiotherapy, University of Pretoria (SUPERVISORS: Dr C A Eksteen / Prof M Pepper)
Sponsor	:	**None**
Study Degree:		**MPhysT (Research)**

This Student Protocol has been considered by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria on 4/02/2010 and found to be acceptable.

Prof AG Nienaber	(female) BA (Hons) (Wits); LLB (Pretoria); LLM (Pretoria); LLD (Pretoria); Diploma in Datametrics (UNISA)
Prof V.O.L. Karusseit	MBChB; MFGP (SA); M.Med (Chir); FCS (SA)
Prof J A Ker	Deputy Dean: MBChB (Pretoria); MMed (Int) (Pretoria); MD (Pretoria)
Dr N K Likibi	MBChB.; Med.Adviser (Gauteng Dept. of Health)
Dr MP Mathebula	(female) Deputy CEO: Steve Biko Academic Hospital
Dr T S Marcus	(female) BSc (LSE), PhD (University of Lodz, Poland)
Mrs M C Nzeku	(female) BSc (NUL); MSc Biochem (UCL,UK)
Snr Sr J. Phatoli	(female) BCur (Et.Al); BTech Oncology
Mr Y M Sikweyiya	MPH (Umea University Umea, Sweden); Master Level Fellowship (Research Ethics) (Pretoria and UKZN); Post Grad. Diploma in Health Promotion (Unitra); BSc in Health Promotion (Unitra)
Dr L Schoeman	(female) BPharm (North West); BAHons (Psychology)(Pretoria); PhD (KwaZulu-Natal); International Diploma in Research Ethics (UCT)
Dr R Sommers	Deputy Chairperson: (female) MBChB; M.Med (Int); MPhar.Med
Prof C W van Staden	CHAIRPERSON: MBChB (Pretoria); MMed(Psych) (Pretoria); MD (Warwick,UK); FCPsych (SA); FTCL (London); UPLM (UNISA)
Prof TJP Swart	BChD, MSc (Odont), MChD (Oral Path)

Student Ethics Sub-Committee

Prof R S K Apatu	MBChB (Legon,UG); PhD (Cantab); PGDip International Research Ethics (UCT)
Dr A M Bergh	(female) BA (RAU); BA (Hons) (Linguistics) (Stell); BA (Hons) (German) (UNISA); BEd (Pretoria); PhD (Pretoria); SED (Stell)
Mrs N Briers	(female) BSc (Stell), BSc Hons (Pretoria), MSc (Pretoria); DHETP (Pretoria)
Dr S I Cronje	BA (Pretoria); BD (Pretoria); DD (Pretoria)
Prof D Millard	(female) B.Iur (Pretoria); LLB (Pretoria); LLM (Pretoria), AIPSA Diploma in Insolvency Law (Pretoria); LLD (UJ)
Dr S A S Olorunju	BSc (Hons). Stats (Ahmadu Bello University –Nigeria); MSc (Applied Statistics (UKC United Kingdom); PhD (Ahmadu Bello University – Nigeria)
Dr L Schoeman	CHAIRPERSON: (female) BPharm (North West); BAHons (Psychology)(Pretoria); PhD (KwaZulu-Natal); International Diploma in Research Ethics (UCT)
Dr R Sommers	Deputy Chairperson (female) MBChB; M Med (Int); MPhar.Med

DR L SCHOEMAN; BPharm, BA Hons (Psy), PhD; Dip. International Research Ethics
CHAIRPERSON of the Faculty of Health Sciences Student Research Ethics Committee, University of Pretoria

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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
UNIVERSITY OF PRETORIA
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Faculty of Health Sciences Research Ethics Committee

29/01/2015

Approval Certificate
Amendment
(to be read in conjunction with the main approval certificate)

Ethics Reference No.: S5/2010

Title: A critical analysis of the functional outcome of people with spinal cord injuries who have received stem cell therapy.

Dear Mev M Skeen

The **Amendment** as described in the documents received on 28/11/2014 was approved by the Faculty of Health Sciences Research Ethics Committee on the 28/01/2015.

Please note the following about your ethics amendment:
- Please remember to use your protocol number (**S5/2010**) 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

Professor Werdie (CW) Van Staden
MBChB MMed(Psych) MD FCPsych FTCL UPLM
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).

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♦ Web: http://www.up.ac.za/healthethics ♦ H W Snyman Bld (South) Level 2-34 ♦ Private Bag x 323, Arcadia, Pta, S.A., 0007

*** 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.*

Addendum 2: Informed consent

Participant's information leaflet &informed consent form for non-intervention study

1. **Title of study:** A retrospective analysis of the perceived outcome of stem cell therapy for persons living with a spinal cord injury

2. **Introduction:** Dear Mr/Mrs…… Date:……..……

3. 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 the 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.

4. **Nature and purpose of this study**

   You are invited to take part in a research study. The aim of this study is to evaluate effect on functional activity of stem cells in persons living with spinal cord injuries. This is to assess if there are any positive or negative effects of stem cell therapy. This is to help other persons with spinal cord injuries in the future by drawing up a document with recommendations for people living with spinal cord injuries and professionals treating these injuries.

5. **Explanation of procedures to follow:**

   This study involves answering some questions about your spinal cord injury, about the stem cell therapy you received if you did receive stem cell therapy and about how active you are, about your bladder and bowel function, pain, spasms and mobility and transfers. All this information you will fill in on a questionnaire and email back to the investigator. Should you not understand a question or need clarity you are free to email me or call me.

6. Risk and discomfort involved:

The only discomfort involved may be sitting at your computer to fill in the questionnaire. No procedures are to take place. You can also request to fill in the questionnaire over the phone.

7. Possible benefits of the study:

The benefits of this study could be to all spinal injured persons as we understand the treatment of their condition better.

8. I understand that I may at any time withdraw from the study.

9. I may at any time withdraw from the study with the understanding that no consequences will flow from my refusal to participate in this study.

10. The study has been approved by the academic committee of the University of Pretoria.

11. This protocol has been submitted to the Faculty of Health Sciences Research Ethics committee, University of Pretoria and written approval has been granted by that committee. The study has been structured in accordance to the Declaration of Helsinki (Oct 2000), 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.

12. **Information:**

If I have any questions concerning this study, I should contact Melanie Skeen at melanie@jamrehab.co.za or 012 4400800 or 0825653745

13. **Confidentiality**:

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

14. Consent to participate in the study:

I have read or have had read to me in a language that I understand the above information before signing this consent form. The content and meaning of this information has been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I understand that if I do not participate in this study it will not alter my management in any way. I hereby volunteer to take part in this study.

I have received a signed copy of this informed consent agreement.

……	…….
Name of person with Spinal injury	Date
……	……..
Person obtaining informed consent	Date
……..……	…….
Witness	Date

Verbal personal informed consent (applicable when person cannot read or write)

I, the undersigned, Melanie Skeen , have read and have explained fully to the person living with spinal cord injury, named……and /or his/her relative, the patient information leaflet which has indicated the nature and purpose of the study in which I have asked the person to participate. The explanation I have given has mentioned both the risks and benefits of the study. The person indicated that he or she understands that he/she will be free to withdraw from the study at any time for any reason and without jeopardizing his or her treatment.

I hereby certify that the person has agreed to participate in this study.

Person's Name: (please print)……

Investigator name: (Please print)……..

Investigators signature:……Date…….……

Witness's name: (please print)…….

Witness's signature:……..Date:……

(Witness -sign that he /she has witnessed the proves of informed consent)

Addendum 3. Biographical questionnaire

Stem cell questionnaire: (Please fill in as much detail as possible and contact me should you have any questions)

1. Name:_____(this will remain confidential throughout study)
2. Age:_____
3. Sex: Male / Female (please mark one)
4. Are you in good Health? Yes/No (please mark one)
5. Do you have diabetes? Yes/No (please mark one)
6. Do you have kidney problems? Yes/No if yes explain

   _____
7. Date of your spinal cord injury:_____
   Level of injury:_____(C/T/L)
8. Are you complete or incomplete:_____
   _____(explain)
9. Where did you receive rehabilitation and for how long? _____
   _____
10. Have you received any kind of stem cell therapy? Yes/No **If No proceed to question no.35**
11. Have you used “Stem enhance” tablets? Yes/No **If No proceed to question no.15**
12. What dosage have you used and from when (date) to when?_____
    _____
13. Are you currently using “Stem enhance” Yes/No if No why did you stop? Explain please_____
    _____
    _____
14. Would you recommend the use of “Stem enhance”? Yes/No if Yes why:_____
    _____
    _____

If no stem cell procedure was done please proceed to question no. 25

15. Date/(s) of Stem cell procedure?_____
16. Time of procedure after spinal cord injury?_____
17. Where was procedure performed? SA/ overseas Please state where_____

_____

_____

18. How was the procedure done? (Please give as much detail as possible)___

_____

_____

_____

_____

_____

_____

_____

_____

19. How long did the procedure take? _____

_____

20. Was it repeated? Yes /No If Yes why? _____

_____

21. Did you receiver any special treatment before the stem cells? Please describe_____

_____

_____

_____

22. Did you receive any treatment afterwards e.g. Physiotherapy or medication? Please describe_____

_____

_____

_____

_____

_____

23. Do you have a website or contact details of the institution, place or practitioner who performed the Stem cell procedure? _____

_____

_____

_____

24. What was the total cost of the Stem cell procedure:_____

_____ Please specify currency)

25. Cost of Stem enhance per month R _____

_____**If this is the only cost proceed to no. 28**

26. Breakdown of costs: Please specify currency

    a. Travel: _____
    b. Accommodation: _____
    c. Pre and post procedures: _____
    d. Actual stem cell procedure: _____
    e. Hospitalization &/rehabilitation afterwards:_____

27. Other costs: Please specify_____

_____

28. Please describe any other treatment received after stem cell therapy

_____

_____

_____

_____

_____

_____

29. For what period:_____

_____

30. What did you hope to gain from stem cell therapy_____

_____

_____

_____

_____

_____

_____

31. What did you expect the result from your stem cell therapy to be on a scale of 1-10 where 0 is total helplessness and 10 is total independence? Please mark this on the line below:
    0----------10
32. Score your pain before stem cell therapy on the line below where 0 is no pain and 10 is excruciating constant pain:
    0----------10
33. Has your muscle strength improved Yes/No
34. Are new muscles working which were not working before the stem cell therapy: Yes/No If Yes please describe this:_____
    _____
    _____
    _____
    _____
    _____
35. How do you see yourself currently on a scale of 0-10 where 0 is total helplessness and 10 is total independence? Please mark this on the line below:
    0----------10
36. Score your present experience of pain on the line below where 0 is no pain and 10 is excruciating constant pain:
    0----------10
37. Please describe your spasm :a/b/c/d/e
    a. No Spasm
    b. Light spasm limbs bend easily
    c. Marked Spasm but part moved easily
    d. Fairly bad spasm difficult to move limb
    e. Very bad spasm limb fixed straight or bent

38. Describe your bowel function

presently:

_____

_____

_____

_____

_____

39. Describe your bladder function

currently:

_____

_____

_____

_____

_____

40. Mobility : the % time spent using the following:

a. Electric wheelchair: _____%

b. Wheelchair(Manual): _____%

c. Walking with assistive devices: _____%

d. Walking independently: _____%

41. Do you experience any of the following presently? If yes please describe

a. Pain?

_____

b. Spasm?

_____

c. Headaches?

_____

d. Other such as nausea, constipation or dizziness?_____

_____

_____

_____

42. Could these changes be because of anything else besides the stem cells? If so please explain:

_____

_____

_____

_____

_____

43. What therapy, medication or treatment are you currently receiving?

_____

_____

44. SCIM questionnaire: Please fill in the SCIM questionnaire below:

a. In the first block please put your pre-stem cell of after initial rehabilitation score in the second block please fill in your post stem cell score (if applicable)

b. In the third block please fill in your current score(what you are like presently)

Thank you for participating in this research project. Please proceed to the SCIM on page 11

Addendum 4: SCIM III

SCIM-SPINAL CORD INDEPENDENCE MEASURE

(Enter the score for each function in the adjacent square, below the description.

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
Self-Care	**SCORES:**		
1. Feeding (cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid) 0. Needs parenteral, gastrostomy, or fully assisted oral feeding 1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices 2. Eats independently; needs adaptive devices or assistance only for cutting food and/or pouring and/or opening containers	**Feeding scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
3. Eats and drinks independently; does not require assistance or adaptive devices			
2. Bathing upper body (soaping, washing, drying body and head, manipulating water tap). **A-upper body;** **A.** 0. Requires total assistance	**Bathing upper body scores:**		
1. Requires partial assistance 2. Washes independently with adaptive devices or in a specific setting (e.g., bars, chair) 3. Washes independently; does not require **a**daptive **d**evices or **s**pecific **s**etting (not customary for healthy people) (adss)			
B Bathing lower body **B.** 0. Requires total assistance 1. Requires partial assistance	**Bathing lower body scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
2. Washes independently with **a**daptive **d**evices or in a **s**pecific **s**etting (adss) 3. Washes independently; does not require **a**daptive **d**evices (adss) or **s**pecific **s**etting			
3. Dressing (clothes, permanent orthoses: dressing, wearing, undressing) **A-upper body;** **A.** 0. Requires total assistance 1. Requires partial assistance with **c**lothes **w**ith**o**ut **b**uttons, **z**ippers or **l**aces (cwobzl) 2. Independent with cwobzl; requires **a**daptive **d**evices and/or **s**pecific **s**ettings (adss) 3. Independent with cwobzl; does not require adss; needs assistance or adss only for bzl 4. Dresses (any cloth) independently; does not require adaptive devices or specific setting	**Dressing upper body score:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
3B-Dressing lower body (clothes, shoes, permanent orthoses: dressing, wearing, undressing) **B.** 0. Requires total assistance 1. Requires partial assistance with **c**lothes **w**ith**o**ut **b**uttons, **z**ips or **l**aces (cwobzl) 2. Independent with cwobzl; requires adaptive devices and/or specific settings (adss) 3. Independent with cwobzl without adss; needs assistance or adss only for bzl 4. Dresses (any cloth) independently; does not require adaptive devices or specific setting	**Dressing lower body scores:**		
4. Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup) 0. Requires total assistance 1. Requires partial assistance 2. Grooms independently with adaptive devices	**Grooming scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
3. Grooms independently without adaptive devices			
SUBTOTALS (0-20)			
Respiration and Sphincter Management			
5. Respiration 0. Requires tracheal tube (TT) and permanent or intermittent assisted ventilation (IAV) 2. Breathes independently with TT; requires oxygen, much assistance in coughing or TT management 4. Breathes independently with TT; requires little assistance in coughing or TT management 6. Breathes independently without TT; requires oxygen, much assistance in coughing, a mask (e.g., peep) or IAV (bipap) 8. Breathes independently without TT; requires little assistance or stimulation for coughing 10. Breathes independently without assistance or device	**Respiration scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
6. Sphincter Management - Bladder 0. Indwelling catheter 3. Residual urine volume (RUV) > 100cc; regular catheterization or assisted intermittent catheterization 6. RUV < 100cc or intermittent self-catheterization; needs assistance for applying drainage instrument 9. Intermittent self-catheterization; uses external drainage instrument; does not need assistance for applying 11. Intermittent self-catheterization; continent between catheterizations; does not use external drainage instrument 13. RUV <100cc; needs only external urine drainage; no assistance is required for drainage 15. RUV <100cc; continent; does not use external drainage instrument	**Sphincter Management – Bladder scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
7. Sphincter Management - Bowel 0. Irregular timing or very low frequency (less than once in 3 days) of bowel movements 5. Regular timing, but requires assistance (e.g., for applying suppository); rare accidents (less than twice a month) 8. Regular bowel movements, without assistance; rare accidents (less than twice a month) 10. Regular bowel movements, without assistance; no accidents	**Sphincter Management – Bowel scores:**		
8. Use of Toilet (perineal hygiene, adjustment of clothes before/after, use of napkins or diapers). 0. Requires total assistance 1. Requires partial assistance; does not clean self 2. Requires partial assistance; cleans self independently	**Use of Toilet scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
4. Uses toilet independently in all tasks but needs adaptive devices or special setting (e.g., bars) 5. Uses toilet independently; does not require adaptive devices or special setting**)**			
SUBTOTALS(0-40)			
Mobility			
9. Mobility in Bed and Action to Prevent Pressure Sores 0. Needs assistance in all activities: turning upper body in bed, turning lower body in bed, sitting up in bed, doing push-ups in wheelchair, with or without adaptive devices, but not with electric aids 2. Performs one of the activities without assistance 4. Performs two or three of the activities without assistance	**Mobility in Bed and Action to Prevent Pressure Sores scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
6. Performs all the bed mobility and pressure release activities independently			
10. Transfers: bed-wheelchair (Locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet). 0. Requires total assistance 1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., sliding board) 2. Independent (or does not require wheelchair)	**Transfers: bed-wheelchair scores:**		
11. Transfers: wheelchair-toilet-tub (if uses toilet wheelchair: transfers to and from; if uses regular wheelchair: locking wheelchair, lifting footrests, removing and adjusting armrests, transferring, lifting feet) 0. Requires total assistance 1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., grab-bars)	**Transfers: wheelchair-toilet-bathtub scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
2. Independent (or does not require wheelchair)			
Mobility (indoors and outdoors, on even surface)			
12. Mobility Indoors 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair	**Mobility Indoors scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
3. Requires supervision while walking (with or without devices) 4. Walks with a walking frame or crutches (swing) 5. Walks with crutches or two canes (reciprocal walking) 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without walking aids			
13. Mobility for Moderate Distances (10-100 meters) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Requires supervision while walking (with or without devices) 4. Walks with a walking frame or crutches (swing) 5. Walks with crutches or two canes (reciprocal walking) 6. Walks with one cane	**Mobility for Moderate Distances (10-100 meters) scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
7. Needs leg orthosis only 8. Walks without walking aids			
14. Mobility Outdoors (more than 100 meters) 0. Requires total assistance 1. Needs electric wheelchair or partial assistance to operate manual wheelchair 2. Moves independently in manual wheelchair 3. Requires supervision while walking (with or without devices) 4. Walks with a walking frame or crutches (swing) 5. Walks with crutches or two canes (reciprocal waking) 6. Walks with one cane 7. Needs leg orthosis only 8. Walks without walking aids	**Mobility Outdoors (more than 100 meters) scores:**		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
15. Stair Management 0. Unable to ascend or descend stairs 1. Ascends and descends at least 3 steps with support or supervision of another person 2. Ascends and descends at least 3 steps with support of handrail and/or crutch or cane 3. Ascends and descends at least 3 steps without any support or supervision	**Stair Management scores:**		
16. Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm and footrests, transferring to and from car, bringing wheelchair into and out of car) 0. Requires total assistance 1. Needs partial assistance and/or supervision and/or adaptive devices 2. Transfers independent; does not require adaptive devices (or does not require wheelchair)	**Wheelchair-car transfer scores:**		
	Ground-wheelchair transfer scores:		

FUNCTION	Pre stem Cell / after Rehab score	Post stem Cell(if applicable)	Current Score
17. Transfers: ground-wheelchair 0. Requires assistance 1. Transfers independent with or without adaptive devices (or does not require wheelchair)			
SUBTOTAL (0-40			
TOTAL SCIM SCORE (0-100)			

Addendum 5. Pamphlet designed about stem cell therapy