

Glossary

A

ACE	Angiotensin converting enzyme
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
ANS	Autonomic nervous system
Anti-CCP	Anti-cyclic citrullinated peptide antibodies
ARA	American Rheumatism Association

B

BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute

C

CAD	Cardiac autonomic dysfunction
CG	Control Group
CL	Constriction latency
cm	Centimetres
CRP	C-reactive protein
CRT	Cardiovascular reflex tests
CT	Computed tomography
CTD	Cardiac thoracic disease
CV	Cardiovascular
CVD	Cardiovascular disease

D

D	Deterioration
DAS	Disease activity score
deg	Degree
dif	Post-value minus Pre-value
DL	Dilation latency
DM	Diabetes mellitus
DMARDs	Disease modifying drugs

E

ECG	Electrocardiogram
EG	Experimental group
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism

H

HAQ	Health assessment questionnaire
HCG	Healthy control group
HF	High frequency

HF(nu)	High frequency normalised units
HIV	Human immune-deficiency virus
HMGB ₁	High mobility group box-1
HR	Heart rate
HRT	Heart rate turbulence
HRV	Heart rate variability
HT	Hypertension

I

I	Improvement
IL	Interleukin
IQR	Interquartile range

K

kg	Kilogram
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L

L	Left
LDH	Lactate dehydrogenase
LF	Low frequency
LF/HF	Low frequency/high frequency ratio
LF(nu)	Low frequency normalised units
Ln	Natural logarithm

M

MANOVA	Multivariate analyses of variance
MCP	Metacarpophalangeal
MCV	Maximum constriction velocity
MI	Myocardial infarction
min	Minutes
mmHG	Millimetres of mercury
MS	Multiple sclerosis
MTP	Metatarsophalangeal
MWU	Mann Whitney U test

N

NE	Norepinephrine
NPY	Neuropeptide Y
NSAIDs	Non-steroidal anti-inflammatory drugs

O

OA	Osteo-arthritis
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P

P	Parasympathetic
PAD	Pupillary autonomic dysfunction
PADI	Peptidyl arginase deaminase
PaGA	Patient global assessment
PhGA	Physician global assessment
PIP	Proximal interphalangeal
PMR	Polymyalgia rheumatica

pNN50 The percentage of successive RR-interval differences larger than 50ms computed over the entire recording, indicator of vagal influence on HRV

PP Pancreatic polypeptide

PsA Psoriatic arthritis

R

r Right

RA Rheumatoid arthritis

RAC Rheumatoid arthritis control group

RAE Rheumatoid arthritis exercise group

RAG Rheumatoid arthritis group

RCT Randomised controlled trial

RF Rheumatoid factor

RM Repetition maximum

RMSSD Root mean square of the standard deviation between RR-intervals, indicator of vagal influence

ROM Range of motion

RR The mean of the intervals between successive QRS complexes, result of vagal and sympathetic influence on HRV

RRIV RR-interval variation

RRSD Standard deviation of intervals between successive QRS complexes, indicator of vagal and sympathetic influence on HRV (Overall HRV)

S

s Seconds

S Sympathetic

SD Standard deviation

SD1 Indicator of the standard deviation of the immediate, or short-term, RR variability due to parasympathetic efferent (vagal) influence on the sino-atrial node

SD2 Indicator of the standard deviation of the long-term or slow variability of the heart rate. It is accepted that this value is representative of the global variation in HRV

SJ Swollen joint

Sjö Sjögrens

SLE Systemic lupus erythemathosus

sqrt Square root

SSc Systemic sclerosis

SSR Sympathetic skin response

T

TJ Tender joint

TNF Tumour necrosis factor

TO Turbulence onset

TS Turbulence slope

V

VAS Visual analogue scale

VLF Very low frequency

W

WHO World Health Organisation

My husband, Hans



My dog, Remi



APPENDICES

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Appendix 1

WHO definition of Health

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

The correct bibliographic citation for the definition is:

Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.

The Definition has not been amended since 1948



Appendix 2

Medical History Questionnaire

Demographic Information

Last name First name Date of Birth

Home phone Work phone General

Address

Section A

1. When was the last time you had a physical examination?
2. If you are allergic to any medications, foods, or other substances, please name them.
3. If you have been told that you have any chronic or serious illnesses, please list them.
4. Give the following information pertaining to the last 3 times you have been hospitalized. *Note: Women, do not list normal pregnancies.*

	Hospitalisation 1	Hospitalisation 2	Hospitalisation 3
Reason for hospitalisation			
Month and year of hospitalisation			
Hospital			

Section B

During the past 12 months

- | | | |
|------------------------------------------------------------------------------------------------------------|-----|----|
| 1. Has a physician prescribed any form of medication for you? | Yes | No |
| 2. Has your weight fluctuated more than a few kilograms? | Yes | No |
| 3. Did you attempt to bring about this weight change through diet or exercise? | Yes | No |
| 4. Have you experienced any faintness, light-headedness, or blackouts? | Yes | No |
| 5. Have you occasionally had trouble sleeping? | Yes | No |
| 6. Have you experienced any blurred vision? | Yes | No |
| 7. Have you had any severe headaches? | Yes | No |
| 8. Have you experienced chronic morning cough? | Yes | No |
| 9. Have you experienced any temporary change in your speech pattern, such as slurring or loss of speech? | Yes | No |
| 10. Have you felt unusually nervous or anxious for no apparent reason? | Yes | No |
| 11. Have you experienced unusual heartbeats such as skipped beats or palpitations? | Yes | No |
| 12. Have you experienced periods in which your heart felt as though it were racing for no apparent reason? | Yes | No |



At present

- | | | |
|--------------------------------------------------------------------------------------------------------------|-----|----|
| 1. Do you experience shortness or loss of breath while walking with others your own age? | Yes | No |
| 2. Do you experience sudden tingling, numbness, or loss of feeling in your arms, hands, legs, feet, or face? | Yes | No |
| 3. Have you ever noticed that your hands or feet sometimes feel cooler than other parts of your body? | Yes | No |
| 4. Do you experience swelling of your feet and ankles? | Yes | No |
| 5. Do you get pains or cramps in your legs? | Yes | No |
| 6. Do you experience any pain or discomfort in your chest? | Yes | No |
| 7. Do you experience any pressure or heaviness in your chest? | Yes | No |
| 8. Have you ever been told that your blood pressure was abnormal? | Yes | No |
| 9. Have you ever been told that your serum cholesterol or triglyceride level was high? | Yes | No |

10. Do you have diabetes? Yes No

If yes, how is it controlled?

- | | |
|------------------------------------------|--------------------------------------------|
| <input type="checkbox"/> Dietary means | <input type="checkbox"/> Insulin injection |
| <input type="checkbox"/> Oral medication | <input type="checkbox"/> Uncontrolled |

11. How often would you characterize your stress level as being high?

- | | | |
|---------------------------------------|-------------------------------------|-------------------------------------|
| <input type="checkbox"/> Occasionally | <input type="checkbox"/> Frequently | <input type="checkbox"/> Constantly |
|---------------------------------------|-------------------------------------|-------------------------------------|

12. Have you ever been told that you have any of the following illnesses?

- | | | |
|------------------------------------------------------|-------------------------------------------|----------------------------------------|
| <input type="checkbox"/> Myocardial infarction | <input type="checkbox"/> Arteriosclerosis | <input type="checkbox"/> Heart disease |
| <input type="checkbox"/> Coronary thrombosis disease | <input type="checkbox"/> Rheumatic heart | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Coronary occlusion | <input type="checkbox"/> Heart failure | <input type="checkbox"/> Heart valve |
| <input type="checkbox"/> Heart block | <input type="checkbox"/> Aneurysm | <input type="checkbox"/> Heart murmur |
| <input type="checkbox"/> Thyroid disease | <input type="checkbox"/> Angina | |

13. Have you ever had any of the following medical procedures?

- | | |
|--------------------------------------------------|------------------------------------------------|
| <input type="checkbox"/> Heart surgery | <input type="checkbox"/> Pacemaker implant |
| <input type="checkbox"/> Cardiac catheterization | <input type="checkbox"/> Defibrillator |
| <input type="checkbox"/> Coronary angioplasty | <input type="checkbox"/> Heart transplantation |

Section C

Has any member of your immediate family been treated for or suspected to have had any of these conditions? Please identify their relationship to you (father, mother, sister, brother, etc.).

- | | |
|------------------|------------------------|
| A. Diabetes | C. Stroke |
| B. Heart disease | D. High Blood Pressure |

Section D

How long have you had arthritis (in years)? _____

Did you do any training/exercising one year ago? If so, what did you do?

Are you currently involved in training/exercising? If so, what do you do?

Appendix 3

The 1987 revised criteria for the classification of rheumatoid arthritis (traditional format)*	
Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

*For classification purposes, a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is *not* to be made.

PIP proximal interphalangeal joint

MCP metacarpophalangeal joint

MTP metatarsophalangeal joint

Arnett FC, et al. Arthritis and Rheumatism. The American Rheumatism Association 1987 revised criteria for the classification of Rheumatoid Arthritis. Vol. 31, No 3 (March 1988), 315-324

Appendix 4

Classification of Global Functional Status in Rheumatoid Arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.



This questionnaire identifies information from you to provide a record of your health status

SCORING

- Score each item within the 8 categories.
- Select and add the highest score within each category
- Divide the sum of the category scores by the number of answered categories.
- If the item score is zero but an assistive device is used: score 1.
Help from another person is required: score 2.
Both a special device and help is required: score 3.

$$(\text{Subtotal 1} + \text{Subtotal 2}) \div \text{No. of answered categories} = \text{HAQ}$$

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Circle the one best answer for your usual abilities DURING THE PAST WEEK

	Without ANY Difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
1 DRESSING AND GROOMING					
Were you able to:					
1. Dress yourself, including tying your shoelaces and doing buttons?	0	1	2	3	
2. Shampoo your hair?	0	1	2	3	
2 GETTING UP					
Were you able to:					
1. Stand up from a chair without armrests?	0	1	2	3	
2. Get in and out of bed?	0	1	2	3	
3 EATING					
Were you able to:					
1. Cut up your meat?	0	1	2	3	
2. Lift a full cup or glass to your mouth?	0	1	2	3	
3. Open a new milk carton?	0	1	2	3	
4 WALKING					
Were you able to:					
1. Walk outdoors on flat ground?	0	1	2	3	
2. Climb up five steps?	0	1	2	3	
					Subtotal 1
Please tick (✓) any of the following AIDS or EQUIPMENT that you usually use for any of these activities mentioned above:					
<input type="checkbox"/>	Walking stick	<input type="checkbox"/>	Wheelchair	<input type="checkbox"/>	Specially adapted chair
<input type="checkbox"/>	Walking frame	<input type="checkbox"/>	Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc.)	<input type="checkbox"/>	Other (Please Specify)
<input type="checkbox"/>	Crutches	<input type="checkbox"/>	Specially adapted utensils (such as for eating and cooking)	<input type="checkbox"/>	
Please tick (✓) any of the following categories for which you usually need HELP FROM ANOTHER PERSON:					
<input type="checkbox"/>	Dressing and Grooming	<input type="checkbox"/>	Walking	<input type="checkbox"/>	
<input type="checkbox"/>	Getting up	<input type="checkbox"/>	Eating	<input type="checkbox"/>	

Circle the one best answer for your abilities OVER THE PAST WEEK

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
5 HYGIENE					
Were you able to:					
1. Wash and dry your body?	0	1	2	3	
2. Have a bath?	0	1	2	3	
3. Get on and off the toilet?	0	1	2	3	
6 REACHING					
Were you able to:					
1. Reach up for and take down a 2.5 kg object (e.g. a bag of sugar) from just above your head?	0	1	2	3	
2. Bend down to pick up clothing from the floor?	0	1	2	3	
7 GRIPPING					
Were you able to:					
1. Open car doors?	0	1	2	3	
2. Open jars that have been previously opened?	0	1	2	3	
3. Turn taps on and off?	0	1	2	3	
8 ACTIVITIES					
Were you able to:					
1. Go shopping (supermarket, post office, bank etc.)?	0	1	2	3	
2. Get in and out of a car?	0	1	2	3	
3. Do domestic tasks such as vacuuming or gardening?	0	1	2	3	
					Subtotal 2
Please tick (✓) any of the following AIDS or EQUIPMENT that you usually use for any of the activities mentioned above:					
<input type="checkbox"/>	Raised toilet seat	<input type="checkbox"/>	Bath rail	<input type="checkbox"/>	
<input type="checkbox"/>	Bathtub seat	<input type="checkbox"/>	Long-handled aids for reaching things	<input type="checkbox"/>	
<input type="checkbox"/>	Jar opener (for jars previously opened)	<input type="checkbox"/>	Long-handled aids in bathroom (e.g. a long handled brush for the body)	<input type="checkbox"/>	
<input type="checkbox"/>		<input type="checkbox"/>	Other (Please specify)	<input type="checkbox"/>	
Please tick (✓) any of the following categories for which you usually need HELP FROM ANOTHER PERSON:					
<input type="checkbox"/>	Hygiene	<input type="checkbox"/>	Gripping and opening things	<input type="checkbox"/>	
<input type="checkbox"/>	Reaching	<input type="checkbox"/>	Shopping and domestic tasks	<input type="checkbox"/>	

Appendices on CD

Appendix 6 T08165 HRV Normality Tests.docx

Appendix 7 T08165 HRV MANOVA using $\ln(\text{HRV})$.docx

Appendix 8 T08165 HRV analysis 24 March.docx p69-71 and p74-76

Appendix 11 T08165 Confidence intervals

Appendix 12 T08165 Phase II HAQ Analysis p1-6

Appendix 9

Participant Informed Consent form: Rheumatoid Arthritis Group

AUTHORISATION TO PARTICIPATE IN A RESEARCH PROJECT.

TITLE OF STUDY: Influence of water and land based exercise on the autonomic function, disease activity and functional capacity in females suffering from Rheumatoid Arthritis: Randomised Control Trial.

1. THE NATURE AND PURPOSE OF THIS STUDY

You are invited to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.

Motivation

Rheumatoid Arthritis is an inflammatory disease affecting the joints and other organs. Patients experience difficulty in performing activities of daily living and have a risk of heart related problems. Exercise is known to increase functional capacity and decrease heart related problems.

Further studies are needed to proof that this is true in Rheumatoid Arthritis patients.

2. EXPLANATION

- A Rheumatologist will confirm the diagnosis of Rheumatoid Arthritis.
- Information regarding the study will be given. Questions will be answered and then you will sign the Informed Consent.
- Certain measurements that will be done, will be explained to you, including:
 - Heart Rate Variability:
 - You will lie down in a supine position in a low noise area, at a comfortable temperature (± 22 degrees Celsius) for 5 minutes.
 - A 10-minute ECG will follow. The first 5 minutes in a supine position and the next in an upright position. Evaluation of the autonomic control of your heart will be done on the sampled

RR intervals. The blood pressure will be monitored during both phases.

- CRP (inflammatory marker):
 - o Blood test. Blood will be drawn from a vein in the arm.
- Biokinetic measurements:
 - o Height/Body mass/Leg strength/Heart rate/Blood pressure/Walking test/Handgrip strength/Flexibility
- You will be asked to complete a questionnaire (Health Assessment Questionnaire). It will take about 10 minutes to complete.
- You will also be asked to complete a questionnaire on your medical history. This will take 20-30 minutes.
- You will be involved in an exercise programme. The exercise programme will consist of
 - Warm up
 - Walking or aerobic water exercise program, depending on the group you are in
 - Stretching
 - Cool down

The exercise will be done at a level at which you will still be comfortably able to talk (60-80% of your maximum heart rate)

- The exercise programme will last for 3 months. Patients who wish to continue with their exercise programme after the 3-month period, will be allowed to do so. All procedures will be explained and a biokineticist will oversee the programme.
- Depending on what group you are in, you will either do water exercises, land exercises or no exercises. This allocation will be random and you will be asked to accept your allocated position.

3. RISK AND DISCOMFORT INVOLVED

The only possible risk and discomfort involved is the taking of blood from a vein and the performance testing. There might be some muscle stiffness at the start of the exercise programme, but this will diminish.

4. POSSIBLE BENEFITS OF THIS STUDY

It is expected that the quality of life will improve, and that the risk for heart related problems would decrease.

In case of any medical emergency arising, medical treatment will be provided on the premises. Should any referrals be required, costs incurred by private patients will be referred to their medical aids. Patients who do not have medical aids will be referred to an approved state hospital.

5. 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.

PARTICIPANT

- I understand that I am being asked to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.
- I understand that if I do not want to participate in this study, I will still receive standard treatment.
- I may at any time withdraw from this study.
- I give my approval that results obtained may be published anonymously.

- **INFORMATION**

If I have any questions concerning this study, I should contact:

Dr DC Janse van Rensburg (Section Sports Medicine, University of Pretoria)

(Tel: 012-420 6057. After hours: 083 305 6036)

- **CONSENT TO PARTICIPATE IN THIS STUDY**

I have read or 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 have been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I hereby volunteer to take part in this study.

Participant.....

2008/.....Date

Witness.....

Participant Informed Consent form: Healthy Control Group

AUTHORISATION TO PARTICIPATE IN A RESEARCH PROJECT.

TITLE OF STUDY: Influence of water and land based exercise on the autonomic function, disease activity and functional capacity in females suffering from Rheumatoid Arthritis: Randomised Control Trial.

6. THE NATURE AND PURPOSE OF THIS STUDY

You are invited to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis. We want to compare normal healthy controls such as yourself to people suffering from Rheumatoid Arthritis.

Motivation

Rheumatoid Arthritis is an inflammatory disease affecting the joints and other organs. Patients experience difficulty in performing activities of daily living and have a risk of heart related problems. Exercise is known to increase functional capacity and decrease heart related problems.

Further studies are needed to proof that this is true in Rheumatoid Arthritis patients.

7. EXPLANATION

- Information regarding the study will be given. Questions will be answered and then you will sign the Informed Consent.
- Certain measurements that will be done, will be explained to you, including:
 - Heart Rate Variability:
 - You will lie down in a supine position in a low noise area, at a comfortable temperature (± 22 degrees Celsius) for 5 minutes.
 - A 10-minute ECG will follow. The first 5 minutes in a supine position and the next in an upright position. Evaluation of the autonomic control of your heart will be done on the sampled RR intervals. The blood pressure will be monitored during both phases.
 - Height measurement with a tape measure
 - Weight measurement with a standardised scale.
- You will also be asked to complete a questionnaire on your medical history. This will take 20-30 minutes.

8. RISK AND DISCOMFORT INVOLVED

None.

9. POSSIBLE BENEFITS OF THIS STUDY

Although you will not directly benefit by the study, your willingness to participate by having your Heart Rate Variability measured, might make it possible for us to improve the quality of life and increased health risks of patients with Rheumatoid Arthritis.

In case of any medical emergency arising, medical treatment will be provided on the premises. Should any referrals be required, costs incurred by private patients will be referred to their medical aids. Patients who do not have medical aids will be referred to an approved state hospital.

10. 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.

PARTICIPANT

- I understand that I am being asked to take part in a research study. The aim of this study is to determine if exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.
- I understand that if I do not want to participate in this study, I will still receive standard treatment.
- I may at any time withdraw from this study.
- I give my approval that results obtained may be published anonymously.

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If I have any questions concerning this study, I should contact:

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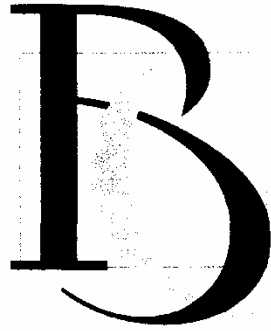
Participant.....

2010/.....Date

Witness.....



Appendix 10



BCOMPLIANT cc

CERTIFICATE OF PARTICIPATION

THIS SERVES TO CERTIFY THAT

Dr. D.C. Janse van Rensburg

HAS ATTENDED AND SUCCESSFULLY COMPLETED A

GCP REFRESHER COURSE

IN PRETORIA

TRAINER SIGNATURE: RETHA BRITZ

DATE:

CPD Accreditation Number: MDB015/002/01/2010 – 6 Ethics & 6 Clinical CPD Points

Materials Received at Training:

- ICH GCP Booklet
- SA GCP Booklet (2006)
- Presentations printed as hand-outs
- ABPI Guidelines
- World Medical Association: Declaration of Helsinki (Oct 2008)