Assessment of functional capacity in Low-resource settings – Adapted six-minute walk tests

By

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Summary

Background: Measuring functional capacity is an important assessment tool that aids researchers and clinicians in determining the diagnosis, prognosis, and management of patients in various populations. The gold standard for functional capacity testing is cardiopulmonary exercise testing. However, this test requires specialised equipment and trained staff, and is therefore not readily available in many clinical settings. The 6-minute walk test (6MWT) is used as a validated alternative, requiring minimal resources or training. In 2002 the American Thoracic Society (ATS) published guidelines to standardise the implementation of the test. However, considering several constraints, especially within the context of ow-resource settings (LRS) researchers and clinicians alike have had to adapt the methods used when implementing the test. Using different methods for the same test may limit the interpretation and clinical applications of the test. The aim of this theses is to evaluate the application and protocols used for the 6-minute walk test within LRS.

Methods: A scoping review was undertaken to identify published studies that implement adapted protocols when conducting the 6MWT. Additionally, the rationale for these adaptations were investigated. Five electronic databases were accessed and searched from inception to October 2019. Data concerning the study source, participants, reported 6MWT purpose, variations (e.g. course length), 6MWT outcome, and rationale for making protocol adaptations were extracted. The findings in this study were used to inform the development of a cross-sectional study with the aim to determine the agreement between the ATS standard 30m 6MWT pathway, a 10m straight and a 10m figure-of-eight pathway, in patients with non-communicable disease.

Results: The search returned 564 records of which 22 studies were included. Studies were predominantly conducted in lower-middle income countries. The most common adaptation made to ATS guidelines was course length, being either shorter or longer than the standard 30 meters. Few studies (n = 8, 36%) provided a rationale for adapting the 6MWT. However, based on these eight studies, space limitations was the most common argument for making adaptations. Subsequently, we recruited 27 patients with one or more non-communicable disease to perform two 6MWTs. Fifteen participants performed both a 30 meter straight and a 10m straight 6MWT and twelve participants performed a 30m straight and a 10m figure-of-eight 6MWT. Regardless of chosen configuration (10m figure-of-eight versus 10m straight), a shortened 6MWT pathway resulted in a significantly smaller 6-minute walk distance. Moreover, the difference was larger than the reported minimal clinically important difference thereby highlighting the clinical implications of adapting the 6MWT.

Conclusion: Strict adherence to the ATS guidelines for conducting the 6MWT is challenging. Common adaptations included a change in course length and/or course configuration (chapter 2), with such adaptations having clinically relevant implications to the outcome of the 6WMT (chapter 3). This provides limitations to the application and interpretation of the test. Researchers and clinicians need to take this into consideration when adapting the protocol used for the 6MWT. Reference equations that take into account the adaptations should be considered. However, accounting for every variation of the test may not be feasible. Alternative tests for functional capacity testing within the context of LRS may be a more practical solution.

Opsomming

Agtergrond: Die evaluering van funksionele kapasiteit is 'n belangrike assesseringsinstrument wat navorsers en gesondheidswerkers help om die diagnose, prognose en behandeling van pasiënte in verskillende populasies te bepaal. Die goue standaard vir funksionele kapasiteitstoetse is kardiopulmonale oefentoetsing. Hierdie toets benodig egter gespesialiseerde toerusting en opgeleide personeel, en is nie altyd toeganklik in alle kliniese omgewings nie. Die 6-minute staptoets (6MWT) word as 'n geldige alternatief gebruik, wat minimale hulpbronne of opleiding benodig. In 2002 het die Amerikaanse Torakale Assosiase (ATS) riglyne gepubliseer om die implementering van die toets te standaardiseer. In die lig van verskeie beperkings, veral binne die konteks van instellings met lae hulpbronne (LRS), moes navorsers en gesondheidswerkers egter die tegniek wat gebruik is tydens die implementering van die toets, aanpas. Die gebruik van verskillende tegnieke vir dieselfde toets kan die interpretasie en kliniese toepassings van die toets beperk. Die doel van hierdie riglyne is om die toepassing en tegniek van die ses minute staptoets binne LRS te evalueer.

Metode: 'n Omvattende literatuur studie is onderneem om gepubliseerde studies te identifiseer wat aangepaste protokolle implementeer tydens die uitvoering van die 6MWT. Die rasionaal van hierdie aanpassings was ook ondersoek. Vyf elektroniese databasisse was identifiseer en ondersoek vanaf insepsie tot Oktober 2019. Data rakende die studiepopulasie, deelnemers, gerapporteerde 6MWT-doel, variasies (bv. lengte), 6MWT-uitkoms en rasionaal vir die aanpassing van protokol was identifiseer. Die bevindings in hierdie studie is gebruik om die ontwikkeling van 'n dwarsdeursnee-studie in te lig met die doel om die ooreenstemming tussen die ATS-standaard 30m 6MWT-bane en 'n 10m-reguit- en 'n 10m-syfer-van-agt-roete te bepaal, by pasiënte met nie -oordraagbare siektes.

Resultate: Die soektog het 564 studies identifiseer waarvan 22 studies ingesluit is. Die studies was hoofsaaklik in laer- tot middelinkomste lande gedoen. Die algemeenste aanpassing aan die Amerikaanse Torakale Assosiasie (ATS) -riglyne was die lengte van die baan, of dit was korter of langer as die standaard 30 meter. Minimale studies (n = 8, 36%) verskaf 'n rede vir hierdie aanpassing van die 6MWT. Van die agt studies was ruimtebeperkings egter die algemeenste probleem om aanpassings te maak. Dus het ons 27 pasiënte met een of meer nie-oordraagbare siektes ingesluit om twee 6MWT's uit te voer. Vyftien deelnemers het beide 'n 30 meter reguit en 'n 10 m reguit 6MWT uitgevoer en twaalf deelnemers het 'n 30 m reguit en 'n agt figuur van agt 6 MWT uitgevoer. Ongeag die aanbeveelde struktuur (10m figuur van agt versus 10m reguit), 'n verkorte 6MWT-baan het gelei tot 'n aansienlik kleiner loopafstand van 6 minute. Die verskil was boonop groter as die gerapporteerde minimale klinies belangrike verskil. Hierdie bevindinge beklemtoon die kliniese implikasies van die aanpassing van die 6MWT.

Gevolgtrekking: Streng toepassing van die ATS-riglyne vir die uitvoering van die 6MWT is uitdagend. Algemene aanpassings het 'n verandering in lengte en/of konfigurasie ingesluit (Hoofstuk 2), met sodanige aanpassings wat klinies relevante implikasies het vir die uitkoms van die 6WMT (Hoofstuk 3). Dit beperk die toepassing en interpretasie van die toets. Navorsers en gesondheidswerkers moet dit in ag neem wanneer hulle die tegniek van die 6MWT aanpas. Verwysingsvergelykings wat die aanpassings in ag neem, moet oorweeg word. Om elke variasie van die toets te bereken, is egter nie moontlik nie. Alternatiewe toetse vir funksionele kapasiteitstoetse binne die konteks van LRS kan 'n meer praktiese oplossing wees.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
ATS	American Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Testing
GPS	Global Positioning System
HIC	High Income Country
LIC	Low Income Country
LMIC	Lower-Middle Income Country
LRS	Low-Resource Setting
MCID	Minimum Clinical Important Difference
UMIC	Upper-Middle Income Country

Chapter: 1 Introduction

Functional capacity, exercise tolerance and cardiorespiratory fitness are considered synonymous terms used to describe an individual's ability to perform activities at both a maximal and submaximal intensity. Functional capacity, traditionally, is quantified by measuring the amount of oxygen consumed by an individual using maximum effort in a maximal effort test.(1,2) Additionally, functional capacity is also used to describe an individual's ability to perform everyday activities at a sub-maximal level. Functional capacity reflects the health and combined functioning of the cardiovascular, pulmonary, and skeletal muscle systems. The assessment of functional capacity provides essential diagnostic and prognostic information in various diseases as well as in developing appropriate exercise plans for patients in various pathologies.

Cardiopulmonary Exercise Testing (CPET) is upheld as the gold standard for maximal exercise testing. CPET provides information on an integrative response, of the cardiopulmonary system, to exercise.(1,3) However, the test requires an advance laboratory setting with specific equipment (e.g., ergometer, metabolic cart) and specially trained staff. Additionally, the application of this test is limited in patient's whose performance may be affected by pain, fatigue, impaired balance and/or abnormal gait patterns.(4) Ultimately these facets of CPET result in the test not being readily available and/or accessible, especially in primary care settings or applicable in all populations. For these reasons, the need for an alternative and more accessible field test arose.(1,5)

The six-minute walk test (6MWT), a sub-maximal field test, was first used in 1982 by researchers looking for an alternative to the first time-limited field test. The 12-minute walk test was introduced to test the fitness of highly conditioned individuals. Subsequently, they found excellent correlation between the distances walked in the 12 and 6 minutes minute limited tests.(1,5,6) In 1984, further research of the 6MWT found that using different encouragement strategies during the 6MWT resulted in a significant effect on the distances achieved and emphasised a need to standardise the field test.(1,7,8) However, it wasn't until 2002 that the American Thoracic Society (ATS), by way of a consensus conference, developed and published guidelines for the standardisation of the 6MWT. The aim of these guidelines was to homogenise the clinical application and allow for comparisons internationally and across studies.(9,10)

The ATS guidelines explain details on the practicality of the test, indications for using it, as well as factors that may affect the test, amongst others. Moreover, a step by step protocol provides clinicians and researchers with safety measures, patient preparation, and guidelines on interpretation. According to the ATS guidelines, the 6MWT is performed on a hard-flat straight walkway. Depending on the

weather, the test can be conducted either indoors or outdoors. The walkway must measure 30m in length and be marked at every 3m point. Turnaround points should be marked with a cone, where patients are expected to make sharp 180˚ turns.(10) Patients should rest for at least 10 minutes before the test, during which safety measures and patient vitals are checked. Furthermore, standardised instructions and phrases of encouragement at set intervals are provided.(9)

The 6MWT is a self-paced, walking test aimed at objectively quantifying functional capacity by evaluating the distance a participant is able to walk in 6 minutes.(11–14) Participant performance is interpreted by using this distance (6MWD) as an absolute value comparing different attempts, for instance pre- and post-intervention, and as a "percentage of predicted" through the use of previously established reference equation.(12) In healthy participants, the 6MWD generally ranges between 400-700m; with a walking distance less than 82% of predicted considered abnormal.(15,16) Additionally, the minimal clinical important difference assists in the interpretation of change in 6MWD between several 6MWT attempts. A systematic review by Bohannon et al. established an MCID of 30.5 based on six articles in adults with various pathologies.(17) Additional information is obtained from the participants rating of dyspnoea and fatigue using the Modified BORG Scale as well as the participants' cardiorespiratory response which is assessed by measuring heart rate and oxygen saturation pre- and post- test.(18). The 6MWD thus has several applications: 1) as a once off measure to determine functional status, 2) determining the need for and prescription of ambulatory oxygen in patients with cardiorespiratory disease and 3) predicting hospitalisation and mortality in patients with chronic disease.(19) The 6MWD has several clinical applications, for instance in determining the need for and prescription of ambulatory oxygen in patients with cardiorespiratory disease as well as predicting hospitalisation or mortality in patients with chronic disease.(19) Within the field of rehabilitation science the 6MWT is also used as a measure of efficacy to report on interventions and to determine the appropriate exercise prescription in patients with a decreased exercise tolerance. An example of such application is the prescription of walking intensity for cardiac rehabilitation at "65%-75% of the mean speed achieved during a 6MWT".(11,12)

Since the development of the ATS guidelines, reference equations for interpreting the 6MWT have been established across geographical locations, including various low- and middle-income countries. The development of these normative values illustrates the widespread use of the 6MWT as a measure of functional capacity and its continued integration in clinical practice. However, despite the apparent ease in conducting the test, studies report the use of 6MWT protocols that divert from the widely adopted ATS guidelines.(20) Adaptations to the protocols may include changes to the walkway layout and distance and/or changes in test instructions and encouragement.(14,21) To our knowledge, two

studies investigated the effect of changing the walkway distance of the 6MWT on the 6MWD in patients with COPD. A study by Beekman et al compared the 6MWD achieved on a 30m and 10m distance walkway, while a study by Klein et al. compared the 6MWD on a 30m and 20m walkway. Both studies conclude that the shorter walkway resulted in participants achieving a clinically relevant shorter 6MWD than on the 30m walkway.(22,23) Furthermore, evidence suggests that circular or continuous pathways result in longer distances than straight pathways.(24) A systematic review of the 6MWT in stroke population reported that of the 127 studies included in their review, the use of adapted protocols was more common than ATS guideline compliance. Additionally, they noted that both the adherence to the ATS guidelines and reporting of adaptations made to protocols were poor.(10) While Brooks et al. reported no significant effect between conducting the 6MWT indoors vs outdoors, both settings may have their own limitations. (8,25) While finding a 30m walkway indoors may prove difficult, unfavourable weather conditions in may impede outdoor testing. However, also in favourable weather conditions and outdoor testing environment may have limitations. For instance, a study into the reproducibility and validity of the use of an outdoor 6MWT reported that participants refused to complete the outdoor test; arguably owing to the possibility of encountering their neighbours and feeling embarrassed.(26) Moreover, the use of a treadmill 6-minute walk test has been studied. While the treadmill eliminates the need for a 30m corridor, the study reports that the distance achieved can be 15% lower than the standard test. This method may impact the "self-paced" nature of the test.(5) Conducting the 6MWT within the confines of the ATS guidelines, although challenging, is important for the standardisation and interpretation of the test. These studies highlight the impact of adapting the methods.

When reviewing the adaptations described in the literature, originating mostly from high-income countries, one notices that they pertain mostly to the lay-out (length and configuration) of the 6MWT pathway. One can argue that in settings of low resource, where the gold standard (CPET) is unavailable (particularly in primary care settings) standardisation of testing is even more crucial. Yet, there is reason to believe that there may be additional constraints that (SUPPORT) adaptations to the standard protocol. These may include both the access to health care facilities and transport, the lack of human resources, (health) illiteracy and others.

The aim of this thesis is to evaluate the application and methods of the 6MWT in LRS. To that extent, in Chapter 2, we conducted a comprehensive scoping review and report on the adaptations which have been made to the 6MWT ATS guidelines in LRS as well as the rationale for making these adaptations. This scoping review is submitted to the South African Journal of Physiotherapy for their consideration. The aim of this review was to determine the adaptations made when conducting the

6MWT in LRS, the purpose of the adapted test as well as the rationale for the adaptations. The results of this review facilitate a platform for discussion around the feasibility of the ATS standardised 6MWT in these settings. Subsequently, in Chapter 3 we report on a cross-sectional study in 27 patients with non-communicable disease, in which we investigate the agreement of two modified 6MWT with a standardised 6MWT in a LRS. In Chapter 4 the results of the scoping review and cross-sectional study, the clinical implications as well as the potential for future research are discussed.

Chapter: 2 Scoping Review

Six-minute walk test (6MWT) protocol variations in low-resource settings – A scoping review

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Abstract

Introduction: The six-minute walk test (6MWT) is a validated tool, of submaximal intensity, used to objectively measure functional exercise capacity across numerous pathologies. Individualized exercise is a key component of any comprehensive rehabilitation program, in particular for those with non-communicable disease associated with poor exercise tolerance. Adequate and individualised exercise prescription is linked to improvements in physical function and improvements in quality of life. In 2002 the American Thoracic Society (ATS) developed and published guidelines on how to implement the 6MWT in a standardised manner. Despite the relative ease of conducting the 6MWT as per the ATS guidelines, adaptations such as a change in course length and configuration are being implemented, with potential clinical implications Therefore, the objective of this scoping review is to identify i) what 6MWT adaptations to the ATS guidelines have been described in low-resource settings, ii) the purpose of the adapted 6MWT and iii) the reported argumentation for making these adaptations in relation to the specific context.

Methods: Cochrane Library, EBSCOhost (Africa Wide, CINAHL, Medline), PubMed, Scopus and Web of Science were searched from inception until October 2019. Studies that adapted the 6MWT and were conducted in low-resource settings (LRS) were included. Data concerning: the study source, participants, reported 6MWT purpose, variations (e.g. course length), 6MWT outcome and rationale were extracted.

Results: The search returned 564 records of which 22 studies were included. Studies were predominantly conducted in lower-middle income countries (n=18; 82%). The most common adaptation made to the ATS guidelines was course length (n=19; 86%). Eight studies provided a rationale for adapting the 6MWT, of which space constraints was the most common.

Conclusion: Space constraints is the most common reported reason for diverting from the ATS guidelines when using the 6MWT in low-resource settings. Heterogeneous adaptations were made to the course length, or configuration to address these space limitations. Interestingly, few other adaptations were reported (e.g. change of instructions, or alternative safety protocols). The results of this review confirm that we need to rethink the value of the ATS guided 6MWT in low-resource settings (and beyond).

2.1 Introduction

The six-minute walk test (6MWT) is a validated tool, of submaximal intensity, used to objectively measure functional exercise capacity across numerous pathologies including patients with multiple co-morbidities.(15,27) This field test is conducted by having a participant walk a fixed lap length over a set time period of six minutes (15). In 2002 the American Thoracic Society (ATS) developed and published guidelines on how to implement the test in a standardised manner.(9) These guidelines aim to promote consistent clinical application of the test thereby allowing comparison, globally, across studies.(1)

The ATS guidelines stipulate that the test is conducted indoors, on a hard-flat surface, using a 30m (100ft) straight path (i.e. walkway or lap length); marked with cones on each end. Participants are subsequently instructed to walk as far as you can in 6 minutes, and standard phrases of encouragement are used at every minute mark. The 6 minute walk distance (6MWD), the primary outcome derived from the 6MWT, is calculated by adding the number of completed laps with the distance of the unfinished lap the participant was able to achieve by the end of the six minutes.(12) The 6MWD can be interpreted by comparing it to a predicted normative value, using previously established reference equations or by using it as an absolute value for comparison to a previously completed test by the same participant.(28) Subsequently, there are many ways one can use the 6MWD in clinical practice or research.

Individualized exercise is the evidence-based cornerstone of any comprehensive rehabilitation program for those with non-communicable disease; in particular those related to lifestyle (e.g. diabetes, cardiovascular disease). Improvements in physical function, through exercise, have been linked to a reductions in premature mortality and morbidity(29) and clinical risk markers as well as improvements in quality of life,(30) amongst others. For instance, patients with COPD have shown improvement in quality of life (QOL) and a reduction in their symptoms when following a low to mild intensity exercise programme. However, greater physiological responses like increased exercise capacity and decreased ventilatory demand are noted when exercise programmes are higher intensity. This emphasises the need for patient assessment to help guide clinicians in developing patient specific, yet appropriate, exercise programmes.

While the gold standard for the objective measurement of maximal functional capacity is Cardiopulmonary Exercise Testing (CPET),(1) one can argue that this resource-heavy (i.e. equipment, training) test is often not feasible or necessary. Conversely, the six-minute walk test (6MWT) is often recommended as the field test of choice in day to day clinical practice. Reasons for this include its applicability in various populations, physiological systems and settings. Additionally,

the test is easy to perform, not time consuming, does not require additional equipment or special skills and is also more representative of the exertion of everyday activities.(1,12,15)

However, despite the relative ease of conducting the 6MWT in a standardised way, particularly in comparison to CPET, adaptations to "ATS guided 6MWT" are being implemented.(20) Typically, these adaptations may include changes to walkway distance and configuration, a practise run or test instructions and encouragement etc. The 6MWD may be influenced by these adaptations,(14,21) for instance due to changes in gait speed and/or strategy adopted and number of turns made to complete the test.(21,31)

For example, Beekman et al. showed that reducing pathway distance from 30 to 10m, resulted in the patients with COPD achieving an average 49.5m shorter distance.(32) The difference in 6MWD between the two pathway distances was attributed to the increased number of turns and less time spent at optimal walking pace.(32) This discrepancy in 6MWD, in this case due to a difference in pathway length, may have clinical impactions. Firstly, if one would compare the 10m results to established references equations developed using ATS guidelines, it is likely that the patient's functional abilities will be markedly underestimated. Secondly, the 49.5m is larger than the minimum clinically important difference (MCID) reported for the 6MWT in COPD patients of 35m by Puhan et al.(33) and 30m by Polkey et al.(34) Thirdly, using data based on different 6MWT protocols interchangeably could lead to premature or delayed discharge of patients or inappropriate exercise prescription.

In case of misinformed discharge, this may have a compounding effect, specifically in already resource-constrained or overburdened health care environments. Collectively, these examples highlight the importance of using standardized testing protocols, particularly in settings of low resources, where the gold standard for cardiopulmonary exercise testing is often unavailable and physical resources (e.g. space) may be limited.

The objective of this scoping review is therefore to identify: i) what 6MWT adaptations to the ATS guidelines have been described in low-resource settings, ii) the purpose of the adapted 6MWT and iii) the reported argumentation for making these adaptations in relation to the specific context.

2.2 Methods

This scoping review was conducted in accordance with the framework provided by Arksey and O'Malley (35) and reported according to the PRISMA guidelines including scoping review extensions.(36)

2.2.1 Data sources and Search Strategy

Five bibliographical databases were accessed through the Stellenbosch University Library: Cochrane Library, EBSCOhost (AfricaWide, CINAHL, Medline), PubMed, Scopus and Web of Science. Searches were conducted (BF) from inception to 31 October 2019. Search Terms included variations of the following main search terms: six-minute walk test, low-resource setting and developing countries (see Addendum A).

2.2.2 Study Selection

After the completion of the searches and removing duplicates, titles and abstracts were independently screened by two reviewers (BF and MH). Any disagreements were discussed by the reviewers and a third reviewer was consulted (SH) in the case of irreconcilable disagreements. An identical procedure was followed for full text screening to determine final full text inclusions. All original research study designs that were available in English were considered. Included studies must have reported on and used an adapted/modified version of the 6MWT and conducted the test within the context of low-resource setting.(37) In the absence of a clear definition for LRS, within the context of an UM or HIC, studies were included based on the language (e.g. rural) used by the study in conjunction with online resources (detail on the location or context of a specific clinic) and purposeful discussion amongst the authors. After becoming familiar with the sources, decisions were made to exclude case studies and case series and any studies that performed the 6MWT according to ATS guidelines or did not report on the methods used. Despite searching online resources from inception, articles published before 2002 (year of published ATS guidelines) were excluded.

2.2.3 Data Extraction and Synthesis

A data extraction form was developed, and revised as necessary, to extract relevant data from the included full-text articles and captured under the following headings: source, participants, reported 6MWT purpose, variations, outcomes and rationale. In case the rationale for making adaptations was unclear, corresponding authors were contacted. Data was extracted by the primary reviewer BF and verified independently by a second reviewer (MH). In the event of group data (e.g. male and female, or intervention/control group) being reported separately, an aggregated 6MWD mean and standard deviation were calculated for each study, using the formula provided in the Cochrane handbook;

excluding data reported separately for diseased groups with healthy controls.(38) In case of longitudinal studies only baseline data were extracted.

2.2.4 Concepts and context

2.2.4.1 Low-resource setting

In line with previous research, a low-resource setting was defined as a low-income country (LIC) or lower-middle income country (LM) as per the World Bank Criteria,(39) or in the event of an upper middle income country (UM) or high income country (HIC) an explicit statement indicating a LRS (e.g. rural, minority populations, poverty) was required.(37)

2.2.4.2 6MWT variations

The test was considered adapted when it deviated from the 2002 ATS guidelines for the 6MWT, (40) and grouped in the following categories:

- Distance; shorter or longer than 30m (100ft)
- Configuration i.e. not a straight pathway
- Venue; not indoors
- Instructions or encouragement were not as provided by the ATS guidelines
- “Other”

2.3 Results

See figure 2.1 for the PRISMA flow chart. Of the 564 records identified across the five databases, 428 remained after removing duplicates. After the initial title and abstract screening 342 articles were identified for full text screening. Available full texts were screened for eligibility resulting in the exclusion of 320 articles. Reasons for exclusion are provided in figure. A total of 22 studies were included in this review.

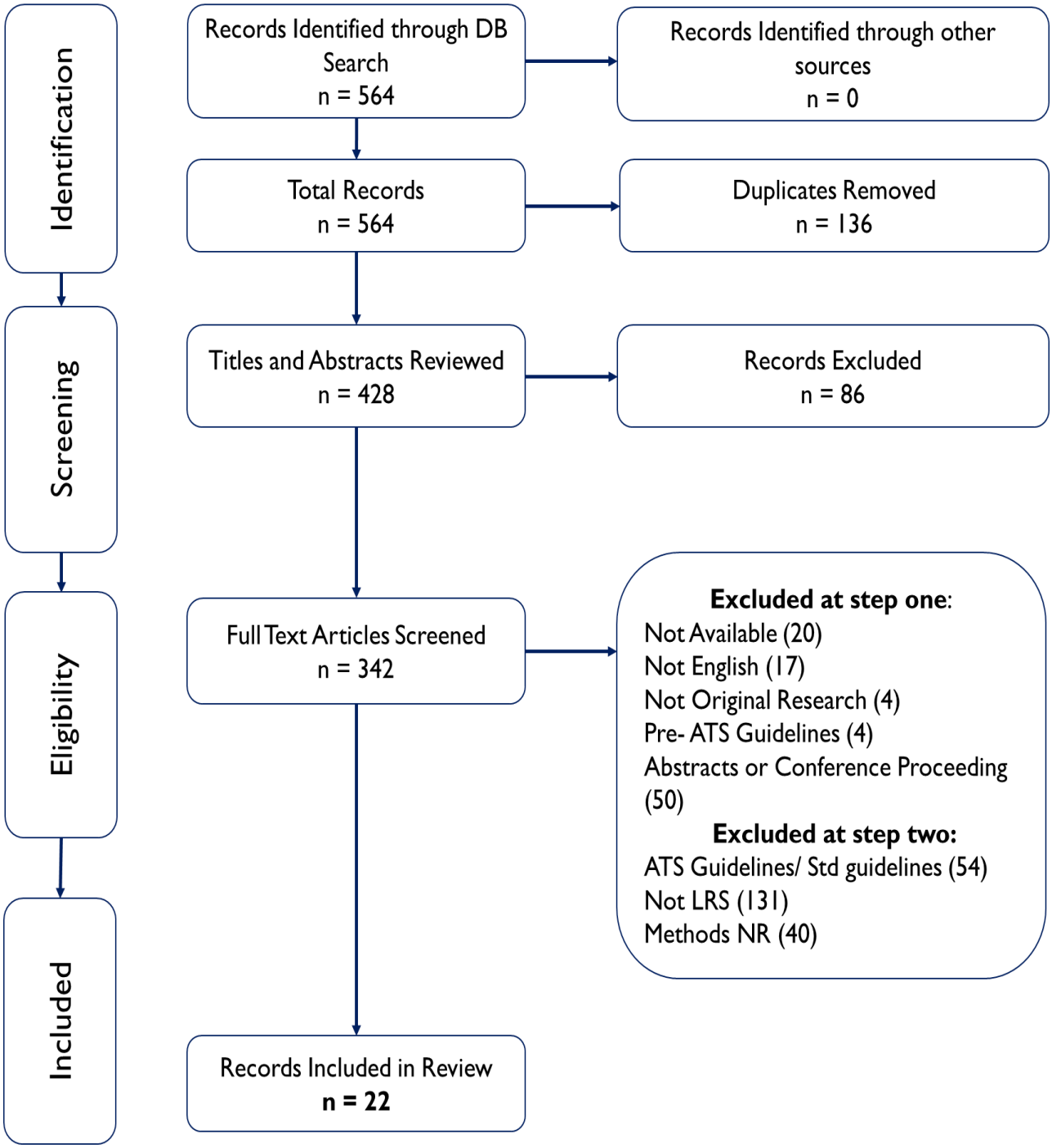

Figure 2.1: PRISMA flow chart of data synthesis

Table 2.1 provides an overview of all included studies (n=22). The earliest study included in this review was published in 2011 while remaining studies were between 2012 – 2019. Various study designs were included with randomised controlled trials (45%) being the most frequent. The most common diagnoses in which an adapted 6MWT was reported include respiratory disease (36%) and cardiovascular disease (18%). Studies were conducted predominantly in LMICs (n=18; 82%), followed by two studies (9%) conducted in LIC (Benin and Malawi), while two (9%) studies were conducted in a low-resource context of either an UM (Brazil) or HIC (Australia).

2.3.1 6MWT Purpose

The majority of included studies (64%) reported using the 6MWT as a measure of submaximal exercise or functional capacity to determine the effect or effectiveness of an intervention in various pathologies. Other purposes of the 6MWT included validation of the 6MWT against other measures,(16,41) developing normative values,(16,42) or as a descriptive variable in association with lung spirometry or QOL.

2.3.2 6MWT Adaptations

Figure 2 provides an overview of the adaptations made by the included studies. The most common adaptation made to the ATS guidelines was that of course length (n=19; 86%) ranging between 10 to 85 meters per lap. Of studies that adapted the course length, 10 (53%) reported a shorter pathway and 9 (47%) reported a pathway distance longer than 30m. Twelve studies reported using a different configuration than straight, including using a rectangular (43–46) or square (41) layout. One study reported using a 6MWT protocol developed by the study's investigator.(16) Four studies (18%) specifically reported conducting the 6MWT outdoors, 11 (50%) studies conducted the test indoors, as per ATS guidelines, while the remaining studies did not report detail on the test venue.

Instructions as per the ATS Guidelines were used in 7 (32%) of the studies, while 13 (59%) studies reported instructions that were modified to include effort (e.g. walk briskly) or objective (e.g. cover as much distance as possible).(42)

The use of encouragement was generally not well reported, standardized phrases were used (n=3; 14%), while adapted (n=2; 9%) encouragements included giving time at non-standardized time intervals.(41) Some studies refrained from using any encouragement during the test. Three studies included in this review reported "other" adaptations which could all be linked to the use of technology. Nusdwinuringtyas et al.(16) compared a conventional 6MWT (though 15m course length) with one performed on a Biodex® gait trainer, reporting a non-significant mean difference of 2.73 meters.(16) Similarly, Mohamed et al.(47) used a treadmill (controlled by the patient) to perform

their test. Finally, Worringham et al. reported using Global Positioning System (GPS) monitoring to remotely track the distances walked by patients in a natural environment over the course of 6 minutes. (48)

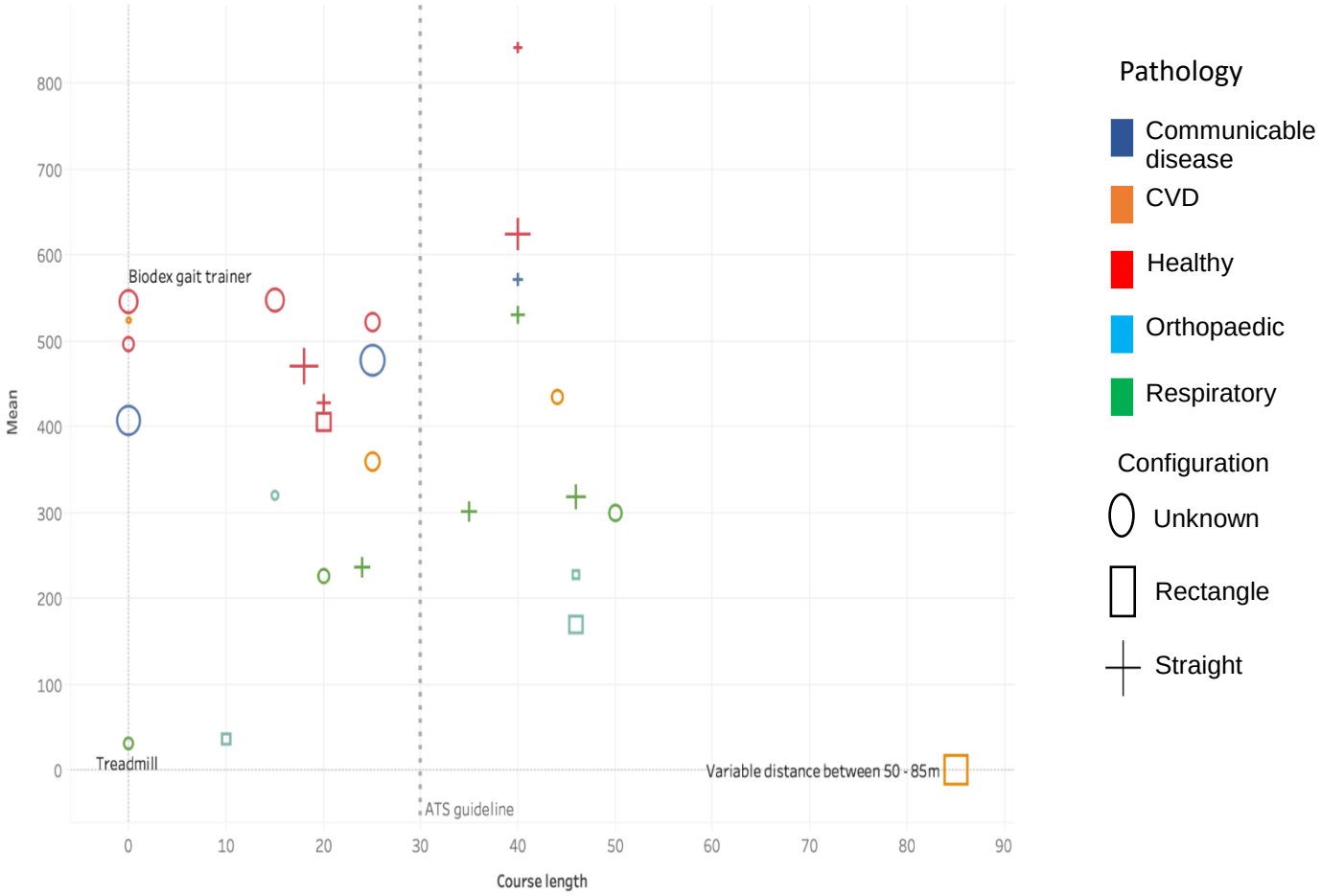

Figure 2.2: A graphical summary of the 6MWT Variations for included studies (n=22).

2.3.3 Rationale for making adaptations

Eight of the included studies, five of which through author correspondence, provided a specific rationale for using an adapted 6MWT relative to a conventional ATS guideline version. Space constraints, as a result of environmental conditions, was the most common rationale for adapting the 6MWT.(16,41,43,44,49,50) Worringham et al. reported conducting the test off-site for participants unable to attend standard rehabilitation sessions while, Mohammed et al. reported using a treadmill (stationary test) allows for continuous monitoring of patient parameters.

Table 2.1: Overview of included studies

Source		Participants n; age (Range) Diagnosis	6MWT Reported Purpose	ATS Guideline Variation						6MWD Baseline Mean (SD)	Rationale
Study Design	Location Setting			Length	Configuration	Venue	Instructions	Encouragement	Other		
Worringham et al.[48] 2011 Pre-Post	Australia‡ Metropolitan Tertiary Hospital & Rural Community Health Centre	6 Adults (42-67) Recent cardiac event or surgery	Evaluate pre-post impact of intervention on walking distance	NA	NA	Out door	NR	NR	Monitored by GPS to track distance walked	524 (NR)	Unable to attend conventional rehabilitation
Locks et al.[43] 2012 RCT	Brazil‡ Physiotherapy School Clinic	83 Adults (>60) Healthy	Assess impact of intervention on cardiorespiratory fitness	20m	Rectangle (9x1m)	NR	Continuously at a comfortable pace. Cover as much ground as possible in 6 min	NR		405 (62)	NR The space that we had available to conduct the 6MWT §
Sen et al.[51] 2012 Cross-Sectional	Kolkata India† Department of Paediatric cardiology	81 Children (5-18) Congenital Cardiac disease	Evaluation of submaximal exercise capacity following surgical intervention	25m	NR	In door	Walk briskly	NR		360 (82)	NR
Ralph et al.[49] 2013 Case Control	Papau Indonesia† Outpatient Clinic	200 Adults Pulmonary Tuberculosis	Evaluate residual disability positive pulmonary TB results	NR	NR	Out door	ATS	NR		C: 497(63) I: 408	NR Did not have a long walking track available§
Rao et al.[42] 2013 Cross-Sectional	Pakistan† Medical institute of Karachi	296 Adults (15-65) Healthy	Develop gender-specific predictive equations for healthy Pakistanis	18m	Straight Flat	In door	Cover as much distance as possible	Standard Protocol		470 (10)	NR

Source		Participants	6MWT	ATS Guideline Variation						6MWD	Rationale
Study Design	Location Setting	n; age (Range) Diagnosis	Reported Purpose	Length	Configuration	Venue	Instructions	Encouragement	Other	Baseline Mean (SD)	
Zaky et al.[44] 2013 RCT	Cairo Egypt† Hospital	30 Children (8-12) Haemophilic Knee Arthritis	Determine effect intervention on functional ability	10m	Rectangle	In door	ATS	NR		36 (11)	Available Space
Mohamed et al. [47] 2014 RCT	Egypt† Outpatient Chest Clinic	31 Adults (19-70) Chronic Respiratory Illnesses	Determine efficacy of intervention on 6MWD	NA	NA	NR	ATS	ATS	Electrical treadmill	32 (11)	Allows for constant monitoring
Nusdwinuringtyas et al.[16] 2014 Cross-Sectional	Indonesia† Department of Medical Rehabilitation Cipto Mangunkusumo Hospital	123 Adults (18-50) Healthy	Develop protocol-specific normative reference values	15m	1st 6MWT protocol investigator developed	NR	NR	NR	2nd 6MWT on Biodex gait trainer	547 (54) 545 (54)	NR No 30m distance§
Sogbossi et al.[41] 2014 Prospective Cohort	Benin* Rehabilitation Centre	230 Adults Stroke	Validate against ABILOCO Benin scale	50-85m	Square	NR	As Quickly as Possible	Informed of time at 2,4,5 Minutes		NR	NR Contextual/ environmental restrictions across different testing centres
Agrawal et al.[52] 2015 Prospective Cohort	India† Rural based teaching hospital	129 Adults >50 Chronic Respiratory Disease	Determine the association of different factors and functional exercise capacity	46m	Straight	In door	ATS	ATS		318 (89)	NR

Source		Participants	6MWT	ATS Guideline Variation						6MWD	Rationale
Study Design	Location Setting	n; age (Range)Diagnosis	Reported Purpose	Length	Configuration	Venue	Instructions	Encouragement	Other	Baseline Mean (SD)	
Ben Saad et al.[53] 2015 Case Control	Tunisia† Farhat Hached Hospital	290 Adults (>/40) Obstructive sleep-apnoea-hypopnea-syndrome	To compare 6MWD between severe OSAHS patients (under CPAP treatment) with healthy controls	40m	Straight	Out door	ATS	None		C: 624 (109) I: 531 (115)	NR
Guessogo et al.[54] 2016 Prospective Cohort	Cameroon† Jamot Hospital	28 Adults Pulmonary TB	Evaluate change in functional capacity during intervention	40m	Straight Long	NR	ATS	Time given every minute		C: 842 (53) I: 572 (121)	NR
Khan et al.[55] 2016 RCT	New Delhi† Medical College and Associated Hospital	60 Adults COPD	Evaluate impact of intervention on physical function	50m	NR	In door	Standard	Standard		299 (18)	NR
Mahmoud et al.[56] 2016 RCT	Egypt Cairo†	40 Adult Men (50-60) Ischemic Heart Disease	Determine effect of intervention	44m	NR	NR	Walk continuously covering as much ground as you can	NR		434 (3)	NR
Ben Saad et al.[53] 2015 Case Control	Tunisia† Farhat Hached Hospital	290 Adults (>/40) Obstructive sleep-apnoea-hypopnea-syndrome	To compare 6MWD between severe OSAHS patients (under CPAP treatment) with healthy controls	40m	Straight	Out door	ATS	None		C: 624 (109) I: 531 (115)	NR
Guessogo et al.[54] 2016 Prospective Cohort	Cameroon† Jamot Hospital	28 Adults Pulmonary TB	Evaluate change in functional capacity during intervention	40m	Straight Long	NR	ATS	Time given every minute		C: 842 (53) I: 572 (121)	NR

Source		Participants	6MWT	ATS Guideline Variation						6MWD	Rationale
Study Design	Location Setting	n; age (Range)Diagnosis	Reported Purpose	Length	Configuration	Venue	Instructions	Encouragement	Other	Baseline Mean (SD)	
Ranjita et al. [57] 2016 RCT	India†	81 Adults (30-60) COPD	Determine effect of intervention on EC	35m	Straight Flat	In door	As much distance as possible	Standard phrases		302 (66)	NR
Agrawal et al. [58] 2017 Pre-post	Mumbai India† Tertiary Health Care Centre	80 Adults Interstitial Lung Disease	Determination association of 6MWD (%predicted) with spirometry	24m	Straight Long	In door	ATS	NR		236	NR
Daabis et al.[59] 2017 RCT	Egypt† Hospital Department of Chest Disease	45 Adults COPD	Evaluate if intervention is a useful addition in pulmonary rehabilitation	20m	NR	NR	Standard protocol	NR		226 (107)	NR
Harikesavan et al.[45] 2017 RCT	India† College of Physical Therapy Hospital	18 Adults (>50) Total Knee Replacement	Impact of intervention on long-term functional performance	46m	Rectangle	In door	As quickly as feels safe	NR		228 (71)	NR
Laing et al.[50] 2017 RCT (cross-over)	Vietnam† Training Centre of Orthopaedic Technologies	17 Adults Unilateral Transtibial Amputation	Impact of intervention on functional mobility	15m	NR	In door	Walk at a normal comfortable speed	NR		320 (53)	NR Limited space available inside of the clinic §
Sims Sanyahumbi et al.[60] 2017 Cross-Sectional	Malawi* Outpatient clinic of Children's Centre	222 Children (4-18) HIV+	Compare exercise performance between HIV positive and healthy children	25m	NR	Out door	Walk between cones for 6 minutes	NR		C: 521 (82) I: 478 (75)	NR
Harikesavan et al.[46] 2019 Prospective Cohort	India† Manipal Hospital	78 Adults >50 Knee Osteo-arthritis	Evaluate influence of intervention	46m	Rectangular Circuit	In door	As much distance as possible	NR		169 (70)	NR

Source		Participants	6MWT	ATS Guideline Variation						6MWD	Rationale
Study Design	Location Setting	n; age (Range)Diagnosis	Reported Purpose	Length	Configuration	Venue	Instructions	Encouragement	Other	Baseline Mean (SD)	
Tripathi et al.[61] 2019 RCT	India†	60 Adults (18-45) Healthy	Evaluate efficacy of intervention on physical performance	20m	Straight	In door	At normal Speed	NR		427 (42)	NR

Key: m= meters, NA= Not Applicable, NR= Not Reported, * = Low Income Country, † = Low to Middle Income Country, ‡ = Conducted in a Low-resource context of either High/Upper-Middle income country = Control, I = Intervention, COPD = Chronic Obstructive Pulmonary Disease, § = Additional information obtained through author correspondence

2.4 Discussion

To the best of our knowledge this is the first study to explore adaptations to the ATS guidelines for conducting a 6MWT, in conjunction with the rationale for making these changes, specifically in low-resource settings. Twenty-two studies were identified that predominantly reported variations in course length, and configuration. In general, the methods used for conducting the 6MWT were poorly reported.

The 6MWT is recommended as the field test for assessing functional exercise capacity across populations. Globally, LRS are seeing a significant, albeit slow, shift in disease burden from communicable disease towards non-communicable diseases. Due to the nature of the test its applicability to assist in clinical decision making and its' association with important outcomes like hospitalisation and mortality there are compelling arguments for including the 6MWT as a key measure across the continuum of care.

Standardisation in conducting the test is paramount from several perspectives including: the construct validity of the test as a measure of functional capacity, the within-patient homogeneity moving through various tiers of the health care system, and ability to synthesize research outputs across settings for guideline development. This review assists in understanding the adaptations to the 6MWT ATS guidelines, drafted in 2002, made in low-resource settings to inform the academic and clinical landscape and potentially consider the need for reconsidering these guidelines in the light of space constraints or other resource limitations (e.g. rurality).

There is a large body of evidence to show that the 6MWD is sensitive to the methods in conducting the 6MWT. In this review, space limitations specifically, were most commonly reported as a reason for shortening the course length. Interestingly, almost half of studies included in this review reported using a longer course length, though often in combination with a course reconfiguration (e.g. 80m, square). While this review demonstrated the adaptations made in LRS, it must be noted that high resource settings are challenged with the same obstacles when conducting the 6MWT. For instance, Thaweewannakij et al. reported using a 6x4m rectangular walkway due to absence of a large enough walkway in the communities where the tests were conducted.(62) It is also worth noting one specific adaptation to the 6MWT that we did not consider in the scope of this review. The 2-minute walk test or other adaptations to the duration of the test and its potential practical implications (e.g. time savings) were not studied. The notion of "low-resource settings" is more encompassing than a lack of

space. Barriers in service delivery, such as the logistics in accessing care, also need to be considered.(63) In this light, the GPS based 6MWT to be used in a real-life environment (48) is a particularly interesting technological advancement when moving towards telehealth and access to rural populations. A study by Brooks et al. found, within reasonable weather conditions, no significant difference in 6MWD between indoor and outdoor 6MWT test settings.(25)

In an academic context, diverting from ATS guidelines might be less problematic in the context of pre to post testing when evaluating within patient or sample changes over time. However, in clinical settings this may lead to the lack of continuity as referred to earlier.

2.4.1 Limitations

This review had some limitations. First, the methods used for conducting the 6MWT, if reported, could often only be derived at full-text review stage. For many studies at full-text review, it was unclear as to the exact methods used. Given that some of the included studies in this review referred to the ATS guidelines as the 6MWT protocol yet still reported adaptations thereof, may indicate that adaptations were missed in those studies referring to the ATS guidelines with no further detail reported. In addition, the need for many articles to be considered at full-text review, led to the selection process being substantially time consuming. Second, additional adaptations could have been derived from studies conducted in high-resource settings not included in this review. Finally, the impact of the adaptations on the primary outcome (6MWD) could not be derived from the data due to the underlying heterogeneity. Surprisingly, few studies reported validating their adapted 6MWT protocols against the gold standard.

2.4.2 Conclusion

Space constraints is the most common reported reason for diverting from the ATS guidelines when using the 6MWT in low-resource settings. Adaptations were made to the course length, or configuration to address these space limitations, often in conjunction. The ATS guidelines may need to be revisited, or context-specific norm values need to be developed, in order for the 6MWT to be more conducive to low-resource settings (or other settings with space limitations).

Chapter: 3 Manuscript

A modified six-minute walk test (6MWT) for low-resource settings - A cross sectional study

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Abstract

Introduction: The 6-minute walk test is a validated tool used to assess functional capacity in a range of patient populations. In 2002 the ATS developed a protocol to standardise the implementation of the test. However, as a result of space restrictions, adaptations are made to the ATS guided protocol in LRS. There is evidence to suggest that adapting the 6MWT methods affects the outcome of the test. Affecting the interpretation and clinical application of the test. Therefore, the aim of this study was to determine the agreement between the 6MWD achieved on the standard 30m, a straight 10m and a figure-of-eight 6MWT.

Methods: A cross-sectional study was conducted in Bishop Lavis, a socio-economically challenged community. Twenty-seven adults with non-communicable disease were randomised into performing one of the adapted (straight 10m or figure-of-eight) 6MWT pathways in addition to the ATS standard 6MWT on the same day. The order of testing was determined randomly. The concordance correlation coefficient was used to assess agreement, classified as poor <0.2 as poor, 0.4 - 0.6 as moderate, 0.6 - 0.8 as good and >0.8-1.0 as very good.

Results: Fifteen participants were randomised to Group A, and performed the 10m Straight 6MWT in addition to the ATS standard 6MWT. The mean (SD) 6MWD30 was 437 (42) meters, while the mean 6MWD10 was 371 (57) meters. The mean difference (SE; p-value) between the 6MWD was 67 meters (8.6; $p < .01$) Poor concordance was found between the 6MWT30 and 6MWT10. Twelve participants were randomised to Group B, and performed a 6MWTF8 in addition to the 6MWT30. The mean 6MWD30 was 424 (67) meters while the mean 6MWDF8 was and 347(58) meters. The mean difference (SE; p-value) between the 6MWD was 77m (6.0; $p < .01$) (see figure 3.1). Moderate concordance was found between the 6MWT30 and 6MWTF8.

Conclusion: The present data demonstrates that independent of configuration, hard or soft turns, using a shorter pathway reduces the 6MWD. Establishing context specific reference values or developing alternative measures of functional capacity in LRS should be considered.

3.1 Introduction

The six-minute walk test (6MWT) is a validated field test used to determine functional exercise capacity in various population groups, including patients with chronic disease.(11,13) The 6MWT measures the distance the participant is able to walk, on a hard flat surface, at their own pace in six minutes with the ultimate goal being to walk as far as possible. As per the American Thoracic Society (ATS) Guidelines, published in 2002, the participant is allowed to self-pace and stop or rest as necessary, walking back and forth, on a 30 meter walkway while standard phrases of encouragement are used to motivate the patient.(9)

In comparison to the 6MWT, exercise capacity can also be measured using other field tests such as the incremental shuttle walk test and through cardiopulmonary exercise testing (CPET). The latter is still upheld as the gold standard for testing peak exercise tolerance, in particular due to the ability of CPET to discern underlying physiological mechanisms leading to exercise intolerance in patient populations.(14,64) However, due to the costliness of equipment and specialised training needed to perform CPETs, they are less frequently available and used.(14) Additionally, in diseased populations, the application of this test may be limited by factors such as pain and fatigue.(4) In contrast, the 6MWT is of submaximal intensity and therefore better tolerated, in particular by the elderly and specific patient populations.(62,65) Owing to its simplicity, not requiring specific exercise equipment or skills, and it's resemblance to activities of daily living, the 6MWT is therefore a widely used field test and proxy of functional exercise capacity.(11,15)

The primary outcome of the 6MWT is the distance that the participant is able to walk in the six minute time frame.(11) The six minute walk distance (6MWD) achieved at the end of the test is of value in both clinical and research settings for instance through its association with peak oxygen uptake.(13,31) The 6MWT can be interpreted by comparing the 6MWD with a predicted distance through the use of relevant reference equations or as an absolute value. The comparison between actual and predicted 6MWD informs a clinical interpretation of exercise capacity and facilitates prescription of exercise intensity, evaluation of the effectiveness of treatment interventions in cardiopulmonary and neurological rehabilitation, and readiness for community reintegration.(11,13) In healthy participants a 6MWD ranging between 400 - 700m is considered normal while a distance less than 350m is associated with increased mortality risk or viewed as abnormal.(15,28)

Even with the apparent ease in conducting the test according to the ATS guidelines, and the minimal resources required, a scoping review (chapter 2) highlighted that adaptations are made to ATS guided protocol for conducting the 6MWTs in low-resource settings. Most prominently, these adaptations were attributed to space restrictions (i.e. lack of 30m, quiet, hallway) and resulted in changes to

different components of the test, most commonly walkway length and configuration.(66) However, adaptations to the ATS guidelines are not necessarily unique to low-resource settings. A systematic review conducted in 2014 comparing time- and distance- limited walking tests reporting on the reference values and methods for conducting the 6MWT and found that only 48% of 25 studies used a 30m walkway as recommended by the ATS. Again, space limitations was the main reason for using a shorter than recommended walkway.(13) While these adaptations may make sense from a pragmatic point of view, there are potential clinical implications of doing so.

Multiple studies have attempted to validate a shorter than 30m course length for the 6MWT, showing that using a course length shorter than the ATS recommended 30m, results in a significantly smaller 6MWD,(31,32) which also exceeds the minimally clinical important difference. Additional research emphasises that using a shorter distance has clinical implications for patients, in particular when used in conjunction with reference values that are developed based on the ATS standard 30m 6MWT.(32) Using the 6MWD achieved on varied pathway lengths can either underestimate or overestimate the patient's abilities affecting patient treatment plans and may lead to unrealistic goals from patient interventions.(31–33,67).

There is reason to believe that the 6MWD achieved, is in part related to the number of turns made during the 6MWT as well as the distance walked at an optimal pace. A shorter pathway increases the number of turns during the test. Additionally, the minimum distance required, in healthy older adults, for acceleration ranges from 2.17 to 3.23m and for deceleration is 1.80 to 1.85m.(23) Consequently, a shorter pathway increases the number of turns and the distance available to maintain a steady-state phase of walking. This effect may be exacerbated, for instance in those with neurological conditions that affect balance and gait patterns and/or strategies.(10) Conversely, studies found that when altering the course layout of the 6MWT to continuous pathways (e.g. an oval), resulted in an increased or overestimation of 6MWD. Highlighting once more, the effects of modifying pathway configuration. As the development of normative values and clinical decision cut-off values for each distance is timely and costly, ideally one would try to develop a 6MWT that optimizes space needs while retaining the time spent at optimal speed. One such configuration is the figure-of-eight 6MWT, which eliminates a "hard turn" and "loss of speed" through the use of a figure-of-eight shaped pathway.(20,21) Such a pathway configuration has not been studied in a patient population, and specifically in a pragmatic (i.e. non-laboratory) low-resource setting.(66)

Therefore, the aim of this study was to determine the agreement between the 6MWD achieved on i) the 30m straight and a 10 meter straight 6MWT as well as ii) a 10 meter figure-of-eight configuration

and 30m straight 6MWT as per ATS guidelines, in an adult population with one or multiple non-communicable diseases.

3.2 Methodology

This cross-sectional study is a sub-analysis of a randomised feasibility trial conducted in Bishop Lavis, Cape Town.(17) The protocol for the study has previously been published (trial registration: PACTR201807847711940) (Addendum B).(17) Ethical approval for the study was obtained from the Stellenbosch University Health Research and Ethics Council (M17/09/031) (Addendum C) as well as the Western Cape Department of Health (Addendum D). Data for this study was collected between 21st January 2019 and 20th December 2019. All data was collected by the same assessor (BF) and digitally stored using an online platform (Castor EDC) (Addendum E). All participants were assigned a unique identifier when entering the study and data was anonymised prior to the transfer from the data collection form to analysis software. Informed consent was obtained at the beginning of the larger study in either English or Afrikaans (Addendum F). Additional consent was not required as the 6MWT was included as part of physical assessment in the protocol for the larger study.

3.2.1 Study setting

Bishop Lavis is a predominantly Afrikaans speaking community,(68) and socio-economic challenged community, with ~47% of households living off a monthly income of R3200 or less. The general education level in Bishop Lavis can be considered relatively low with only 28% of the population older than 20 years having completed grade 12 or higher.(69) The community also battles several social issues including drug and alcohol abuse, domestic violence, gangsterism and unemployment.(70) Participants for this study were recruited from the Bishop Lavis Community Health Centre (BLCHC) a primary health care institution found in the Tygerberg East District of this region of the Cape Metropole. Services offered include child health, family planning, the care of patients with chronic disease, rehabilitative and dental services.(68)

3.2.2 Study Population and Sampling

A convenience sample was drawn from the second follow up phase of the primary study. Adults of the Bishop Lavis community who received medical care at the BLCHC with one or more of the following NCDs namely cancer, cardiovascular disease, chronic respiratory disease and diabetes mellitus were recruited. The inclusion and exclusion criteria for this study were:

3.2.2.1 Inclusion criteria

- Adults – 18 years of age or older
- Independently ambulant with or without walking aid

- Confirmed (stable) one or more of the following NCDs – Cardiovascular Disease, chronic respiratory disease, cancer, Diabetes mellitus
- Participant in larger study at final follow-up

3.2.2.2 Exclusion criteria

- Pregnant Individual
- Wheelchair bound
- General or disease-specific contra-indications for exercise or exercise testing in line with the American College of Sports Medicine guidelines

3.2.3 Sample Size

The definitive sample size for this study was dependent on the inclusion rate for the larger study, and retention of participants at the time of the third and final visit (16 weeks). The adapted 6MWT were conducted as part of the physical assessment in the larger study. The sample size of the study was limited as a result of COVID-19 countermeasures which required the early termination of the overarching study. A sample of 27 participants were included in this study.

3.2.4 Outcome Measures

Patient demographic information – age, gender and NCD burden – was recorded at baseline assessment. At the 2nd follow up (16 weeks post baseline assessment) physical measures including: height (cm), weight (kg) were documented. These measures represent a subset of all measures included in the overarching study and were selected due to their reported effect on the 6MWD.(15)(28)(62)

3.2.5 6MWT

Participants, on the same day, performed two different 6MWT configurations. A minimum of 30 minutes rest between the two 6MWT was implemented. All participants (n = 27) performed a standard straight 30m 6MWT (6MWT30) and in addition one of the two adapted pathways. Participants were randomised into either Group A or Group B. Group A (n = 15) performed a straight 10m 6MWT (6MWT10) and Group B (n = 12) performed a 10m figure-of-8 6MWT (6MWTF8) (See figure 1). The order in which the two tests were performed as well as group allocation was determined randomly using a 1:1 randomization scheme (https://www.randomizer.org/). All participants were familiar with the 6MWT having completed 6MWTs at a previous assessment.

All ATS guidelines, apart from course length and/or configuration, for adapted tests, were adhered to. The tests were performed inside or outside, decided on a case-by-case basis, depending on the

weather and the availability of physical space as well as how full/busy the indoor passages were. Based on previous literature, no impact on the indoor/outdoor settings was expected.(25) Participants were instructed to "walk as far as you can" in six minutes and were allowed to stop and rest as needed. Assistive devices were used if necessary. Participants were seated for 10 minutes prior to testing in which baseline measurements: blood pressure, heart rate, oxygen saturation and fatigue and dyspnoea (Modified Borg Scale) were recorded. One lap was demonstrated by the assessor prior to the patient starting the test. During testing standardised phrases of encouragement, at one-minute intervals, were used. The assessor and a chair were positioned in the middle of the course, with the assessor remaining stationary. Laps were counted using a stopwatch. All test measurements (e.g. heart rate) were repeated within a minute of completion. Additionally, any other symptoms post testing was recorded. When a participant stopped or was unable to continue the test, the distance achieved at that time was accepted as the 6MWD and reasons for stopping were documented. All cardiorespiratory variables were recorded at that time. As per the ATS guidelines, participants were monitored throughout the assessment for the following: chest pain, ashen appearance, dyspnoea, leg cramps, staggering and diaphoresis. No adverse events occurred during testing. All test instructions, encouragement and measurement were performed in language of the patient's choice (English or Afrikaans) (Addendum G).

3.2.6 Statistical Analysis

Data analysis was performed using statistical software IBM® SPSS® version 26. Data were presented as mean (SD) for normally distributed variables and medians for those with non-normal distribution. Non-parametric testing was used to test the null hypothesis of no significant difference in the 6MWD between: i) a 6MWT30 and 6MWT10 pathway, ii) a 6MWT30 and 6MWTF8 pathway and iii) a 6MWT10 and 6MWTF8 pathway. To test the agreement between each of the layouts Concordance Correlation Coefficients (CCC) was used. According to McBride and Barnhart et al. Lin's CCC has emerged as the most popular method for measuring agreement between multiple methods, on the same subject, measuring the same continuous variable.(71,72) CCC's measurement ranges from 0-1. When all data lie on the 1:1-line perfect agreement is indicated. Altman interprets this similarly to Pearson's correlation coefficient. Agreement was interpreted as follows: <0.2 as poor, 0.4 - 0.6 as moderate, 0.6 - 0.8 as good and >0.8-1.0 as very good.(73,74)

3.3 Results

Patient characteristics are summarised in Table 3.1. Twenty-seven adults with one or more non-communicable disease were included in this analysis. Participants were between the ages of 31-73 years old, mostly female (66%), and 17 (63%) patients presenting with more than one co-morbidity. All demographic variables were normally distributed, and there were no significant differences between these variables across groups. Cardiorespiratory variables measured at baseline and change in the measures post 6MWT are reported in Table 3.2.

Table 3.1: Patient Characteristics

Characteristics	Group A $6MWT_{10}$ n=15	Group B $6MWT_{F8}$ n=12	p Value
Diagnosis, n			
Cardiovascular Disease	13	11	p= 0.681
Cancer	1	0	p= 0.362
Chronic Respiratory Disease	4	4	p= 0.706
Diabetes	9	7	p= 0.930
More than one co-morbidity, n (%)	9 (60)	8 (66)	p= 0.722
Sex, n male (%)	5 (33)	4 (33)	p= 0.573
Age (yrs.), mean (SD)	59.0 (8.9)	58.8 (10.4)	p= 0.896
Height (cm), mean (SD)	160 (9.3)	163 (6.4)	p= 0.148
Weight (kg), mean (SD)	80.8 (14.8)	84.8 (23.9)	p= 0.121

$6MWT_{30}$= as per the ATS guidelines, a straight walkway measuring 30m in length; $6MWT_{10}$= straight, shortened walkway measuring 10m in length; $6MWT_{F8}$= modified walkway measuring 10m in length,%= percentage, yrs.= years, SD = standard deviation, cm= centimetres, kg= kilograms

3.3.1 6MWT30 vs 6MWT10

Fifteen participants who were randomised to Group A, performed the 6MWT10 in addition to the 6MWT30. The 6MWD was normally distributed for the 6MWT30. The mean (SD) 6MWD30 was 437 (42) meters, while the mean 6MWD10 was 371 (57) meters. All but one participant achieved a shorter distance on the 6MWT10. The mean difference (SE; p-value) between the 6MWD was 67 meters (8.6; $p < .01$) (see figure 3.1). Poor concordance was found between the 6MWT30 and 6MWT10 with a r_conc=.40 (95%CI 0.15 to 0.60). (See figure 3.2). There was no significant difference between the pre-test cardiorespiratory variables. In addition, no significant difference was found in the change between pre-test and post-test cardiorespiratory variables.

Table 3.2: Cardiorespiratory variables

	Group A (n = 15)		Group B (n = 12)		$6MWT_{10}$ vs $6MWT_{F8}$
Variables	**$6MWT_{30}$**	**$6MWT_{10}$**	**$6MWT_{30}$**	**$6MWT_{F8}$**	**MD (SE)**
Distance, m Mean (SD)	437 (42)	371 (57)	424 (67)	347 (58)	**23(22)**
MD(SE)	**67(8.6)**		**77(6.0)**		
Baseline Heart Rate, bpm Mean (SD)	79 (19)	75 (18)	78 (10)	80 (8)	**4.6(5.6)**
MD(SE)	**3.3(5.6)**		**0.6(2.0)**		
Δ Heart Rate, bpm Mean (SD)	11(16)	15 (14)	9 (16)	8 (13)	**7.0(5.1)**
MD(SE)	**3.7(5.3)**		**0.5(4.4)**		
Baseline Dyspnea, Borg (0-10) Mean (SD)	0.1 (0.3)	0.3 (1.3)	0.6 (1.6)	0.2 (0.4)	**0.2(0.4)**
MD(SE)	**0.3(0.3)**		**0.4(0.5)**		
Δ Dyspnea, Borg (0-10) Mean (SD)	1.3 (1.2)	0.7 (1.6)	0.6 (1.6)	1.3 (1.3)	**0.7(0.6)**
MD(SE)	**0.7(0.4)**		**0.8(0.5)**		
Baseline Fatigue, Borg (0-10) Mean (SD)	0.1 (0.5)	0.3 (0.7)	0.2 (0.6)	0 (0)	**NA**
MD(SE)	**0.2 (0.2)**		**NA**		
Δ Fatigue, Borg (0-10) Mean (SD)	1.3 (1.5)	1.5 (1.6)	1.7 (1.7)	1 (1.2)	**0.3(0.6)**
MD(SE)	**0.1(0.4)**		**0.4(0.6)**		
Baseline SpO_2, % Mean (SD)	94 (3)	95 (3)	94 (3.5)	95 (3)	**0.1(1.2)**
MD(SE)	**0.9(1.2)**		**1.7(1.4)**		
Δ SpO_2, % Mean (SD)	1 (2.4)	0.5 (1.6)	-1 (3.2)	-1 (3.7)	**1.3(1.0)**
MD(SE)	**0.5(0.7)**		**0.2(1.4)**		

6MWT= six-minute walk test, MD(SE) = Mean Difference (Standard Error), (SD)= Standard Deviation, bpm= beats per minute, SpO2= Transcutaneous Oxygen Saturation, Δ= Change in, NA= Analysis not applicable as mean (SD) is = 0

3.3.2 6MWT30 vs 6MWTF8

Twelve participants who were randomised to Group B, performed a 6MWTF8 in addition to the 6MWT30. 6MWD data was normally distributed for 6MWTF8. The mean 6MWD30 was 424 (67) meters while the mean 6MWDF8 was and 347(58) meters. The mean difference (SE; p-value) between the 6MWD was 77m (6.0; $p < .01$) (see figure 3.1). All participants achieved a shorter distance on the 6MWTF8. Moderate concordance was found between the 6MWT30 and 6MWTF8

with a r_conc=.52 with (95% CI -.25 to .0.71. (See figure 3.2) There was no significant difference between the pre-test cardiorespiratory variables. In addition, no significant difference was found in the change between pre-test and post-test cardiorespiratory variables.

3.3.3 6MWT10 vs 6MWTF8

Two groups independently performed a modified 6MWT in addition to the 6MWT30. Fifteen participants were randomised to the performing the 6MWT10 vs 12 participants in the group performing the 6MWTF8. The mean (SD) 6MWD10 was 371 (57) meters and the mean (SD) 6MWDF8 was 347(58) meters. The mean difference (SE) between the 6MWD was 23m (22) (see figure 3.1) There was a significant difference between the 6MWD of the two modified pathways $p<0.05$. There was no significant difference between the pre-test cardiorespiratory variables between groups for the 6MWT10 and 6MWTF8. In addition, no significant difference was found in the change between pre-test and post-

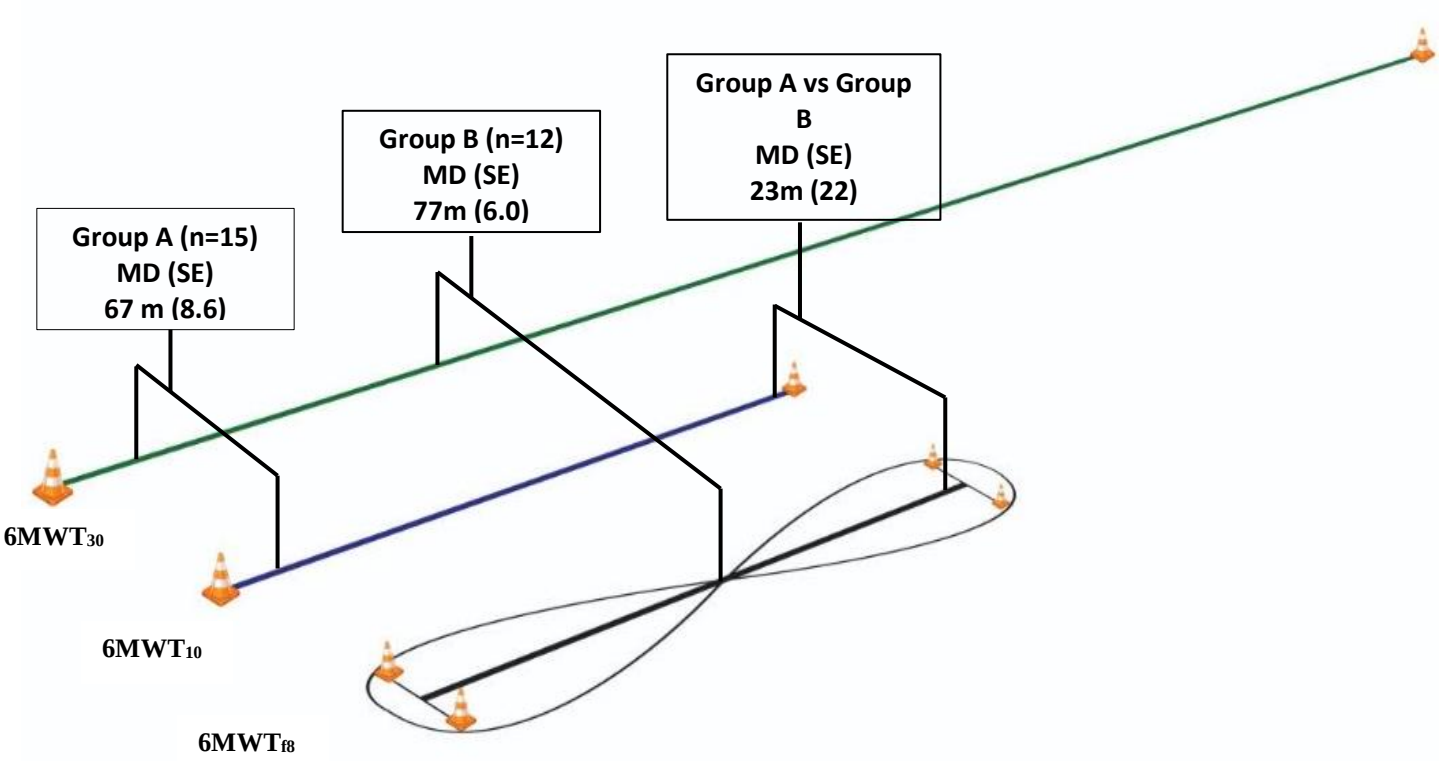

Figure 3.1: 6MWT pathway configuration

6MWT30= as per the ATS guidelines, a straight walkway measuring 30m in length; 6MWT10= straight, shortened walkway measuring 10m in length; 6MWTF8= modified walkway measuring 10m in length; m= meters; MD (SE) = mean difference (standard error). All mean differences will statistically significant ($p<.05$)

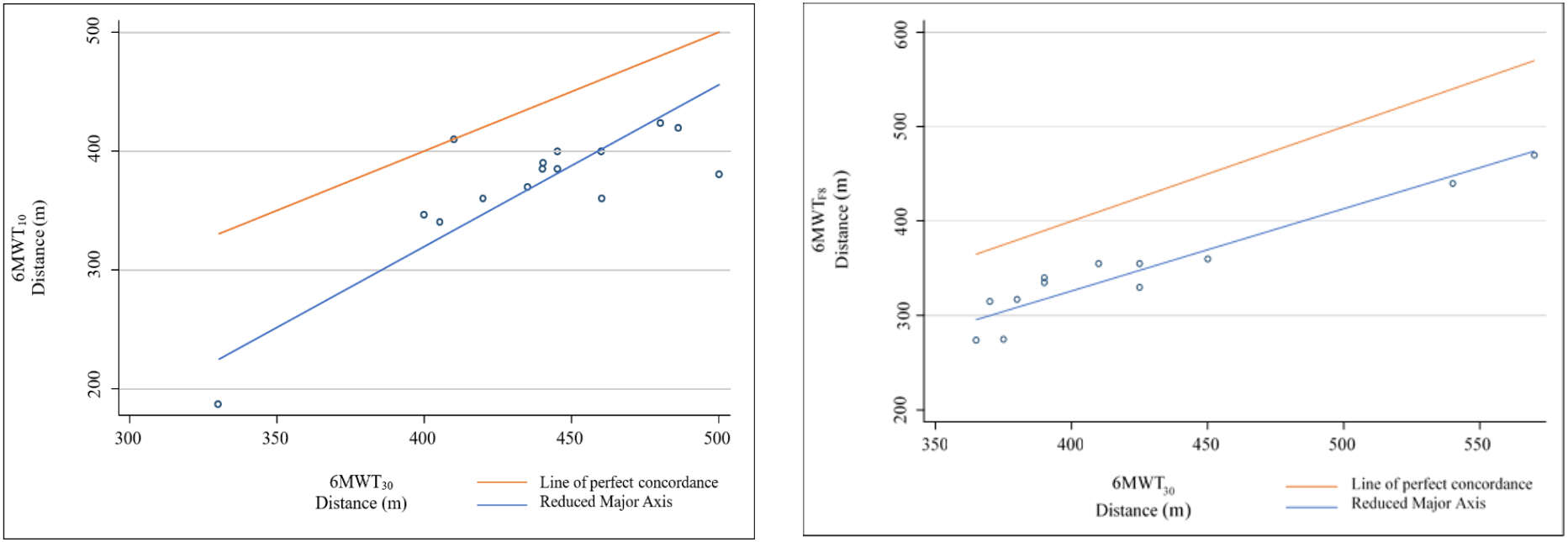

Figure 3.2: Graphical representation of agreement for Group A and Group B.

This figure illustrates the concordance (agreement) of the 6MWD for Group A between 6MWT30 and 6MWT10 and for Group B between 6MWT30 and 6MWTF8. Concordance in Group A is poor while concordance for Group B is moderate.
6MWT30= as per the ATS guidelines, a straight walkway measuring 30m in length; 6MWT10= straight, shortened walkway measuring 10m in length; 6MWTF8= modified walkway measuring 10m in length; m= meters

3.4 Discussion

The aim of this study was to determine the agreement between the standard 6MWT (according to the ATS guidelines) and two alternative pathways. In this study, we showed that a shorter distance, independent of whether configured such that it imposed soft (i.e. figure-of-eight) or hard turns (10m straight) at each end of the lap, led to a significant shorter 6MWD in a small sample of patients with non-communicable disease. This shorter 6MWD had a magnitude greater than what has been reported as the minimal clinical important difference (MCID; 30.5m),(17) and therefore may significantly impact the interpretability of 6MWT findings when using such alternative configurations. In fact, there was a significantly greater 6MWD in those that walked the 6MWT10 relative to the 6MWTF8 which would indicate that choosing to implement soft turns despite a shorter distance, in this population, did not lead to the anticipated greater 6MWD. Additionally, there was low to moderate concordance between the adapted models and the standard 6MWT30. Both models underestimate the 30m distance, however the 6MWTF8 was more consistent in the amount and variance in the underestimation. As shown by the greater mean difference yet, moderate concordance between $6MWT_{30}$ and $6MWT_{F8}$.

To our knowledge, one other study used a figure-of-eight configuration to determine its impact on walking distance and gait parameters (e.g. stride length) albeit in healthy adults of different age groups. Barnett et al. report that the standard 30 m 6MWT resulted in the largest 6MWD and highest gait speeds. Second to this is the 10m figure-of-eight 6MWT and 15m 6MWT, producing a greater 6MWD than 10m 6MWT, recommending the figure-of-eight 6MWT when faced with space limitations. Another element to consider is the effect of course configuration on gait variability and the gait strategy adopted by participants. A study investigating gait variability in older and younger women found greater gait variability in repeated walking path trials vs continuous walking trials with higher SDs in the older (64 ±6.3years) women.(75) The results in this study agree with the finding, by Barnett et al., that the 30m straight pathway produces the greatest 6MWD. However, as reported using the continuous pathway eliminating the hard and frequent turning produced a significantly smaller 6MWD compared to the standard 30m 6MWT in this study. Additionally, the mean distance achieved on the 10m figure-of-eight 6MWT was smaller than the mean distance achieved on the 10m straight 6MWT. The findings in this study does not support the use of a 10m figure-of-eight 6MWT as a substitute of the standard 30m 6MWT in this patient population.

Interestingly, while the 6MWT is regarded as a field walk test of sub maximal intensity, the results in this relatively small sample of patients with NCD showed no significant change in any of the measured cardiorespiratory variables (e.g. Heart Rate) regardless of the 6MWT layout. One previous study compared the cardiorespiratory response in patients with Type II Diabetes Mellitus and matched controls. Both groups walked a similar distance (590(75) vs. 605(69) m; p = 0.458) and reported similar ratings of perceived exertion (RPE) after the 6MWT (4.19(1.56) vs. 3.65(1.54); P = 0.147). However, the group with Type II diabetes Mellitus, at the end of the 6MWT had a higher heart rate (108(23) vs. 95(18) beats per minute; p= 0.048) and systolic blood pressure (169(26) vs. 147(22)mmHg; p= 0.003).(76)While the use of modified and alternative pathways (e.g. $6MWT_{F8}$) may affect these variables, the standard 30m walk test did not produce noticeable changes in cardiorespiratory variables either. The reasoning for the reduced response needs to be explored. One such reason may pertain to the understanding of the instructions.

A study investigating the influence of alternate instructions on 6MWD concluded that when using phrases such as “walk as fast as you can” instead of the standardised “walk as far as you can” results in a larger 6MWD.(77) The ability to make an informed “judgement” as to what is required to walk as “far” as you can requires a level of abstract thinking that may be jeopardized specifically when growing up or living in a low-resource setting (i.e. lack of education). This notion is supported by studies reporting the interaction between 6MWD and contextual factors like the level of education and socio-economic status.(28,78) The Bishop Lavis community (Cape Town, South Africa) is a structurally marginalised community exposed to a variety of aspects one could refer to as being of “low-resource”. These include lack of (quality) education, poverty, unemployment, multiple comorbidities, and violence.(69,79) Considering these factors, it is plausible to believe that the instructions “walk as far as you can” may be ambiguous and subsequently questions the validity of the test, and specifically its instructions, to solicit a submaximal measure of functional exercise capacity in this setting. Surprisingly, only a few studies (n = 11) have adapted instructions when using the 6MWT in low-resource settings.(66) However, it was unclear what the rationale was behind the specific changes from the literature or author correspondence. Future research may explore the impact of socio-economic factors like education on 6MWD, and alternative instructions may be proposed that are more conducive to those patients that may struggle with more abstract language.

Measuring functional capacity is an important component of managing patients with various pathologies and the 6MWT is a widely accepted field test to do so. Its clinical utility, in part, depends on the availability of normative values that assist in interpretation and provide a guideline for exercise prescription. As most normative values are based on an ATS guided 6MWT, including a 30-meter lap length, a variety of settings may encounter challenges in using the test when such a configuration is unavailable. While the use of the 6MWT continues to grow in both clinical and research settings, however, strict adherence to the ATS guidelines is not always practical, especially in LRS. Clinicians and researchers alike need to be cognisant of the adaptations they make when implementing the 6MWT especially when interpreting the test and using it to determine prognosis and inform exercise prescription. Additionally, thorough documentation of the protocols used is important especially for the continuum of care and for others intending to adopt similar methods for a specific population.

3.4.1 Limitations

This study has some limitations. First, as a result of COVID-19 countermeasures we were required to terminate the overarching study early, limiting the sample size for this sub study. As a consequence, restrictions were implemented as to the complexity of analyses available. It would be particularly interesting to explore parameters which may explain the variance in 6MWD between the 6MWT30 and the modified pathways. A second limitation, albeit also a strength, is the heterogeneity in NCD profiles, including multiple co-morbidities, in our sample. While this speaks to the pragmatic nature of our enquiry and the settings in which the study was performed, it may dilute our ability to infer conclusions for specific medical conditions (e.g. stroke). Finally, a third limitation is the lack of spatio-temporal gait parameters during the walking test, including time spent at optimal walking pace, stride variability, and balance disruptions using hard and/or soft turns. This could provide additional information around the gait strategies such as pace on the different configuration and if and how they differed. However, one could argue whether such analysis would not require a more controlled testing environment than the community-based health centre which was the current testing site.

3.4.2 Conclusion

Independent of configuration, requiring hard turns (6MWT10) or soft turns (6MWTF8) using a shorter pathway reduces the 6MWD relative to the expected 6MWD of the ATS standard 6MWT30. The shorter distance found when reducing the space requirement for a 6MWT impacts its use in conjunction with established reference values. Furthermore, the lack of response in cardiorespiratory variables during the 6MWT question its intended submaximal

nature in this population. In light of the burden of chronic disease, establishing context/configuration specific reference values, or developing and validating alternative measures of functional exercise capacity in low-resource settings should be considered.

Chapter: 4 Discussion

The objective of this thesis was to evaluate the application and procedures used when conducting the 6MWT in LRS, especially when access to the gold standard of exercise capacity testing is inaccessible. Assessing the body's response to exercise in individuals with various diseases is an important tool that assists in diagnosis, prognosis, and informs patient management. However, the scarcity of both physical and human resources within LRS as well as the constraints experienced by patients and their ability to access care may affect the ability to offer standardised forms of testing even for the simpler of field walk tests.

Given these challenges, amongst others, ensuring that health care professionals are equipped with pragmatic yet valid tools to use in clinical practice that can assist clinical decision making and monitoring the efficacy of the treatment provided is vital. Being able to assess functional capacity, using a pragmatic field test, can be such a tool.

Therefore, in Chapter 2 we conducted a scoping review to see what adaptations to a standardized (ATS guidelines) 6MWT were reported, specifically in settings of low resource. Our findings concur with the notion that in particular, space constraints may limit the use of an ATS standard 6MWT, as changes were reported in lap length and configuration. Subsequently, in Chapter 3, we tested the agreement of the standard 30m 6MWT and two adapted pathways, a straight 10m 6MWT and a 10m figure-of-eight 6MWT. The 6MWT using a figure-of-eight configuration was of particular interest due to its potential in alleviating the "loss of distance" attributed to a higher number of hard turns and variability in speed with a conventional straight 10m lap length. The latter has been proposed as the main reason for a loss in 6MWD when comparing a straight 10 versus 30m 6MWT. If this hypothesis was true, the 6MWD achieved through the 6MWTF8 could be used in conjunction with normative values for the 6MWT derived from an ATS standard 6MWT and thereby opening opportunity for the use of the 6MWT in LRS without the need for developing new normative values. Unfortunately, the results described in Chapter 3 disproved that hypothesis. Although the figure-of-eight 6-MWT distance showed moderate concordance with the ATS standard 6MWT distance both, 6MWT10 and 6MWTF8, pathways led to a shorter 6MWD at a magnitude greater than the minimally clinical important difference. While this is, to our knowledge, the first report of using such a configuration (6MWTF8) in a patient population, these findings concur with a report by Barnett et al in a healthy adult population.

Furthermore, the validity of functional capacity testing using the 6MWT (although relatively simple) in a LRS may need to be relooked; in particular in relation to the instructions used. The basis of this finding is the lack of change in any of the physiological parameters that were obtained pre-to-post 6MWT, independent of the configuration. This finding was further substantiated by personal experiences in conducting the 6MWT in various populations and the perceived lack of comprehension in understanding the 6MWT instructions.

An alternative way to reduce any space constraints, is using a real-world, GPS based, walking test. This would be in line with some of the technological advances that also trickle through to historically low-resource settings. However, to our knowledge, no standardization of such a GPS-based 6MWT have been proposed yet. Future studies could invest in developing normative values or reference equations for more commonly used configuration and lengths, including a free-moving GPS based model. Alternatively, other or new field tests, that require less physical and/or human resources can be considered and specifically tailored to LRS.

Stringent adherence to the ATS guidelines for the 6MWT is challenging. Clinicians and researchers, when using the 6MWT should be cognisant of the effect that implementing adaptations impacts the outcome and potentially, the clinical applications of the test. In absence of a pragmatic yet working model for the 6MWT, it may be important to ensure that at a minimum, identical formats of the 6MWT across the continuum of care in a specific setting; meaning that the same configuration for the 6MWT is used at a tertiary, secondary and primary care level in a specific setting and for a specific patient. A revision of the ATS guidelines, specific for low-resource settings may assist the field further. Additionally, alternative methods for testing functional capacity should be explored.

4.1 Conclusion

There is extensive evidence that describes the impact of adapting the methods when conducting the 6MWT.(Chapter 1) However, as a result of the constraints experienced by both health care providers and those who make use of the services offered, adaptations are implemented (Chapter 2). In the absence of access to the gold standard CPET for functional capacity testing, in this population, conducting the 6MWT according to the ATS guidelines (30m) results in the best performance within each participant (Chapter 3). Additionally, this allows for interpretation according to existing reference equations. Within the confines of LRS we need to explore the development of reference equations that take into consideration the course length as well as the configuration. However, it can be argued that developing a set of reference equations for every variation of the test may not be feasible. An alternative method for

functional capacity testing within the context and confines of LRS needs to be considered and validated. This option may prove more pragmatic within this context.

References

1. Ubuane PO, Animasahun BA, Ajiboye OA, Kayode-Awe MO, Ajayi OA, Njokanma FO. The historical evolution of the six-minute walk test as a measure of functional exercise capacity: a narrative review. J Xiangya Med. 2018;3(3):40–40.

2. Thompson PD, Arena R, Riebe D, Pescatello LS. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Curr Sports Med Rep. 2013;12(4):215–7.

3. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Postgrad Med J. 2007;83(985):675–82.

4. Noonan V, Dean E. Submaximal exercise testing: Clinical application and interpretation. Phys Ther. 2000;80(8):782–807.

5. Pichurko BM. Exercising your patient: Which test(s) and when? Respir Care. 2012;57(1):100–13.

6. Ajiboye O, Anigbogu C, Ajuluchukwu J, Jaja S. Prediction equations for 6-minute walk distance in apparently healthy Nigerians. Hong Kong Physiother J. 2014;32:65–72.

7. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley S 0., Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure sur sa capacite dans les activites de la vie quotidienne. colleagues'0 introduced the 12-minute walking test, in. Can Med Assoc J. 1985;132:919–23.

8. Faria Júnior NS de, Nakata CH, Oliveira LVF de, Chiappa GR, Cipriano Júnior G. Evaluation of the best environment for the six-minute walk test. Fisioter em Mov. 2015;28(3):429–36.

9. Crapo R, Enright P, Zeballos J. American Thoracic Society ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002;166:111–7.

10. Dunn A, Marsden D, Nugent E, Van Vliet P, Spratt N., Attia J, et al. Protocol variations and six-minute walk test performance in stroke survivors: A systematic review with meta-analysis. Stroke Res Treat [Internet]. 2015;2015. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L601976302%5Cnhttp://dx.doi.org/10.1155/2015/484813

11. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: Validity, reliability and responsiveness-a systematic review. Physiother (United Kingdom) [Internet]. 2012;98(4):277–86. Available from: http://dx.doi.org/10.1016/j.physio.2011.11.003

12. Bellet RN, Francis RL, Jacob JS, Healy KM, Bartlett HJ, Adams L, et al. Repeated six-minute walk tests for outcome measurement and exercise prescription in outpatient cardiac rehabilitation: A longitudinal study. Arch Phys Med Rehabil [Internet]. 2011;92(9):1388–94. Available from: http://dx.doi.org/10.1016/j.apmr.2011.04.014

13. Salbach NM, Brien KK, Brooks D, Irvin E, Martino R, Takhar P, et al. Reference values for standardized tests of walking speed and distance: A systematic review. Vol. 41, Gait and Posture. Elsevier; 2015. p. 341–60.

14. Casillas JM, Hannequin A, Besson D, Benaïm S, Krawcow C, Laurent Y, et al. Walking

tests during the exercise training: Specific use for the cardiac rehabilitation. Ann Phys Rehabil Med. 2013;56(7–8):561–75.

15. Chetta A, Zanini A, Pisi G, Aiello M, Tzani P, Neri M, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. Respir Med. 2006;100(9):1573–8.

16. Nusdwinuringtyas N, Widjajalaksmi, Yunus F, Alwi I. Reference equation for prediction of a total distance during six-minute walk test using Indonesian anthropometrics. Acta Med Indones. 2014;46(2):90–6.

17. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. J Eval Clin Pract. 2017;23(2):377–81.

18. Salvi D, Poffley E, Orchard E, Tarassenko L. The mobile-based 6-minute walk test: Usability study and algorithm development and validation. J Med Internet Res. 2020;22(1):1–15.

19. Chatterjee AB, Rissmiller RW, Meade K, Paladenech C, Conforti J, Adair NE, et al. Reproducibility of the 6-minute walk test for ambulatory oxygen prescription. Respiration. 2009;79(2):121–7.

20. Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, et al. Six-Minute Walk Distance in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2003;167(11):1522–7.

21. Barnett CT, Bisele M, Jackman JS, Rayne T, Moore NC, Spalding JL, et al. Manipulating walking path configuration influences gait variability and six-minute walk test outcomes in older and younger adults. Gait Posture [Internet]. 2016;44:221–6. Available from: http://dx.doi.org/10.1016/j.gaitpost.2015.12.022

22. Beekman E, Mesters I, Hendriks EJM, Klaassen MPM, Gosselink R, van Schayck OCP, et al. Course length of 30 metres versus 10 metres has a significant influence on six-minute walk distance in patients with COPD: An experimental crossover study. J Physiother [Internet]. 2013;59(3):169–76. Available from: http://dx.doi.org/10.1016/S1836-9553(13)70181-4

23. Klein SR, Gulart AA, Venâncio RS, Munari AB, Gavenda SG, Martins ACB, et al. Performance difference on the six-minute walk test on tracks of 20 and 30 meters for patients with chronic obstructive pulmonary disease: validity and reliability. Brazilian J Phys Ther [Internet]. 2020;(xx):1–8. Available from: https://doi.org/10.1016/j.bjpt.2020.01.001

24. Bansal V, Hill K, Dolmage TE, Brooks D, Woon LJ, Goldstein RS. Modifying track layout from straight to circular has a modest effect on the 6-min walk distance. Chest. 2008;133(5):1155–60.

25. Brooks D, Solway S, Weinacht K, Wang D, Thomas S. Comparison between an indoor and an outdoor 6-minute walk test among individuals with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2003;84(6):873–6.

26. Wevers LEG, Kwakkel G, Van De Port IGL. Is outdoor use of the six-minute walk test with a global positioning system in stroke patients' own neighbourhoods reproducible and valid? J Rehabil Med. 2011;43(11):1027–31.

27. Dourado VZ, Tanni SE, Antunes LCO, Paiva SAR, Campana AO, Renno ACM, et al.

Effect of three exercise programs on patients with chronic obstructive pulmonary disease. Brazilian J Med Biol Res [Internet]. 2009 Mar;42(3):263–71. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-65549130493&doi=10.1590%2FS0100-879X2009000300007&partnerID=40&md5=fe2c8fa59298152c73f1eb62db87bc15

28. Ben Saad H, Prefaut C, Tabka Z, Hadj Mtir A, Chemit M, Hassaoune R, et al. 6-Minute walk distance in healthy North Africans older than 40 years: Influence of parity. Respir Med. 2009;103(1):74–84.

29. van der Leeden M, Stuiver MM, Huijsmans R, Geleijn E, de Rooij M, Dekker J. Structured clinical reasoning for exercise prescription in patients with comorbidity. Disabil Rehabil [Internet]. 2018;0(0):1–6. Available from: https://doi.org/10.1080/09638288.2018.1527953

30. Anderson E, Durstine JL. Physical activity, exercise, and chronic diseases: A brief review. Sport Med Heal Sci [Internet]. 2019;1(1):3–10. Available from: https://doi.org/10.1016/j.smhs.2019.08.006

31. Ng SS, Yu PC, To FP, Chung JS, Cheung TH. Effect of walkway length and turning direction on the distance covered in the 6-minute walk test among adults over 50 years of age: A cross-sectional study. Physiother (United Kingdom) [Internet]. 2013;99(1):63–70. Available from: http://dx.doi.org/10.1016/j.physio.2011.11.005

32. Beekman E, Mesters I, Hendriks EJM, Klaassen MPM, Gosselink R, van Schayck OCP, et al. Course length of 30 metres versus 10 metres has a significant influence on six-minute walk distance in patients with COPD: An experimental crossover study. J Physiother [Internet]. 2013;59(3):169–76. Available from: http://dx.doi.org/10.1016/S1836-9553(13)70181-4

33. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schünemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. Eur Respir J. 2008;32(3):637–43.

34. Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-plata V, Miller BE, et al. Six-Minute-Walk Test in Chronic Obstructive Pulmonary Disease Minimal Clinically Important Difference for Death or Hospitalization.

35. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theory Pract. 2005;8(1):19–32.

36. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med. 2018;169(7):467–73.

37. Heine M, Lupton-Smith A, Pakosh M, Grace SL, Derman W, Hanekom SD. Exercise-based rehabilitation for major non-communicable diseases in low-resource settings: A scoping review. BMJ Glob Heal. 2019;4(6):1–10.

38. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 5.1.0. Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 177 p. Available from: www.handbook.cochrane.org.

39. World Bank. The World Bank [Internet]. 2018 [cited 2020 Mar 11]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-

country-and-lending-groups

40. Enright PL. The Six-Minute Walk Test Introduction Standards and Indications 6-Minute Walk Test Versus Shuttle Walk Test Safety Variables Measured Conducting the Test Ensuring Quality Factors That Influence 6-Minute Walk Distance Interpreting the Results Improving the. Respir Care [Internet]. 2003;48:783–5. Available from: http://rc.rcjournal.com/content/respcare/48/8/783.full.pdf

41. Sogbossi ES, Thonnard JL, Batcho CS. Assessing locomotion ability in West African stroke patients: Validation of ABILOCO-benin scale. Arch Phys Med Rehabil. 2014;95(8).

42. Rao NA, Irfan M, Haque AS, Sarwar Zubairi A Bin, Awan S. Six-minute walk test performance in healthy adult Pakistani volunteers. J Coll Physicians Surg JCPSP [Internet]. 2013;23(10):720–5. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=24112258&site=ehost-live&scope=site

43. Locks RR, Costa TC, Koppe S, Yamaguti AM, Garcia MC, Gomes ARS. Effects of strength and flexibility training on functional performance of healthy older people. Brazilian J Phys Ther [Internet]. 2012 Jun;16(3):184–90. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84863794809&doi=10.1590%2FS1413-35552012000300003&partnerID=40&md5=bb302cd62e446f9e411d97994f9db09a

44. Zaky LA, Hassan WF. Effect of partial weight bearing program on functional ability and quadriceps muscle performance in hemophilic knee arthritis. Egypt J Med Hum Genet [Internet]. 2013 Oct;14(4):413–8. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00913753/full

45. Harikesavan K, Chakravarty RD, Maiya AG, Hegde SP, Y. Shivanna S. Hip Abductor Strengthening Improves Physical Function Following Total Knee Replacement: One-Year Follow-Up of a Randomized Pilot Study. Open Rheumatol J [Internet]. 2017 Mar 31;11(1):30–42. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=28567148&site=ehost-live&scope=site

46. Harikesavan K, Chakravarty RDD, Maiya AG. Influence of early mobilization program on pain, self-reported and performance based functional measures following total knee replacement. J Clin Orthop Trauma [Internet]. 2019 Mar;10(2):340–4. Available from: https://doi.org/10.1016/j.jcot.2018.04.017

47. Mohamed AR, Shaban MM. Role of laser acupuncture in chronic respiratory diseases. Egypt J Chest Dis Tuberc. 2014;63(4):1065–70.

48. Worringham C, Rojek A, Stewart I. Development and Feasibility of a Smartphone, ECG and GPS Based System for Remotely Monitoring Exercise in Cardiac Rehabilitation. Miranda JJ, editor. PLoS One [Internet]. 2011 Feb 9;6(2):e14669. Available from: https://dx.plos.org/10.1371/journal.pone.0014669

49. Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, et al. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: Under-recognised phenomena. PLoS One. 2013;8(11):1–11.

50. Laing S, Lythgo N, Lavranos J, Lee PVS. Transtibial Prosthetic Socket Shape in a

Developing Country: A study to compare initial outcomes in Pressure Cast hydrostatic and Patella Tendon Bearing designs. Gait Posture [Internet]. 2017 Oct;58(August):363–8. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=28869901&site=ehost-live&scope=site

51. Sen S, Bandyopadhyay B, Eriksson P, Chattopadhyay A. Functional Capacity Following Univentricular Repair-Midterm Outcome. Congenit Heart Dis [Internet]. 2012 Sep;7(5):423–32. Available from: http://doi.wiley.com/10.1111/j.1747-0803.2012.00640.x

52. Agrawal SR, Joshi R, Jain A. Correlation of severity of chronic obstructive pulmonary disease with health-related quality of life and six-minute walk test in a rural hospital of central India. Lung India [Internet]. 2015;32(3):233. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=25983408&site=ehost-live&scope=site

53. Ben Saad H, Ben Hassen I, Ghannouchi I, Latiri I, Rouatbi S, Escourrou P, et al. 6-Min walk-test data in severe obstructive-sleep-apnea-hypopnea-syndrome (OSAHS) under continuous-positive-airway-pressure (CPAP) treatment. Respir Med [Internet]. 2015;109(5):642–55. Available from: http://dx.doi.org/10.1016/j.rmed.2015.03.001

54. Guessogo WR, Mandengue SH, Ndemba PBA, Medjo UO, Minye EE, Ahmaidi S, et al. Physical and functional follow-up of tuberculosis patients in initial intensive phase of treatment in Cameroon using the 6-min walk test. J Exerc Rehabil [Internet]. 2016 Aug 26;12(4):333–9. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=27656631&site=ehost-live&scope=site

55. Khan NA, Kumar N, Daga MK. Effect of dietary supplementation on body composition, pulmonary function and health-related quality of life in patients with stable COPD. Tanaffos. 2016;15(4):225–35.

56. Mahmoud HH, Mohamed NG, Mohamed AR, Ewas EB. Adipokines response to continuous versus interval aerobic training in ischaemic heart disease patients. Int J pharmtech Res [Internet]. 2016;9(10):53–9. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01475215/full

57. Ranjita R, Hankey A, Nagendra HR, Mohanty S. Yoga-based pulmonary rehabilitation for the management of dyspnea in coal miners with chronic obstructive pulmonary disease: A randomized controlled trial. J Ayurveda Integr Med. 2016;7(3):158–66.

58. Agrawal MB, Awad NT. Cardiac Effect of Interstitial Lung Disease Correlated with Spirometry and Six Minute Walk Test. J Clin DIAGNOSTIC Res [Internet]. 2017;11(2):OC14–7. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=28384908&site=ehost-live&scope=site

59. Daabis R, Hassan M, Zidan M. Endurance and strength training in pulmonary rehabilitation for COPD patients. Egypt J Chest Dis Tuberc [Internet]. 2017 Apr;66(2):231–6. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01380158/full

60. Sanyahumbi AES, Hosseinipour MC, Guffey D, Hoffman I, Kazembe PN, McCrary M,

et al. HIV-infected Children in Malawi Have Decreased Performance on the 6-minute Walk Test With Preserved Cardiac Mechanics Regardless of Antiretroviral Treatment Status. Pediatr Infect Dis J [Internet]. 2017 Jul;36(7):659–64. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=28060042&site=ehost-live&scope=site

61. Tripathi RK, Dethe PD, Bhojne SK, Raut AA, Rege NN. A prospective, randomized, placebo-controlled, double-blind comparative pilot study to evaluate the efficacy of Chlorophytum borivilianum on physical performance. Indian J Pharmacol. 2019;51(3):150–6.

62. Thaweewannakij T, Wilaichit S, Chuchot R, Yuenyong Y, Saengsuwan J, Siritaratiwat W, et al. Reference Values of Physical Performance in Thai Elderly People Who Are Functioning Well and Dwelling in the Community. Phys Ther [Internet]. 2013 Oct 1;93(10):1312–20. Available from: https://academic.oup.com/ptj/article-lookup/doi/10.2522/ptj.20120411

63. Heller DJ, Kumar A, Kishore SP, Horowitz CR, Joshi R, Vedanthan R. Assessment of Barriers and Facilitators to the Delivery of Care for Noncommunicable Diseases by Nonphysician Health Workers in Low- and Middle-Income Countries: A Systematic Review and Qualitative Analysis. JAMA Netw open. 2019;2(12):e1916545.

64. Travensolo C, Goessler K, Poton R, Pinto RR, Polito MD. Measurement of physical performance by field tests in programs of cardiac rehabilitation: a systematic review and meta-analysis. Rev Port Cardiol [Internet]. 2018;37(6):525–37. Available from: http://dx.doi.org/10.1016/j.repce.2017.07.007

65. Maldonado-Martín S, Brubaker PH, Eggebeen J, Stewart KP, Kitzman DW. Association Between 6-Minute Walk Test Distance and Objective Variables of Functional Capacity After Exercise Training in Elderly Heart Failure Patients With Preserved Ejection Fraction: A Randomized Exercise Trial. Arch Phys Med Rehabil. 2017;98(3):600–3.

66. Fell B, Hanekom S, Heine M. (In preperation) Six-minute walk test (6MWT) protocol variations in low-resource settings – A scoping review. 2020.

67. Beekman E, Mesters I, Gosselink R, Klaassen MPM, Hendriks EJM, Van Schayck OCP, et al. The first reference equations for the 6-minute walk distance over a 10 m course. Thorax. 2014;69(9):867–8.

68. Govender T, Miji G. The profile of disability grant applicants in Bishop Lavis, Cape Town. South African Fam Pract. 2009;51(3):228–36.

69. City of Cape Town – 2011 Census Suburb Bishop Lavis [Internet]. 2013. Available from: https://resource.capetown.gov.za/

70. Booysen BL, Schlemmer AC. Reasons for diabetes patients attending Bishop Lavis Community Health Centre being non-adherent to diabetes care. South African Fam Pract. 2015;57(3):166–71.

71. McBride G. A proposal for strength-of-agreement criteria for Lin's Concordance Correlation Coefficient. NIWA Client Rep. 2005;45(1):307–10.

72. Barnhart HX, Lokhnygina Y, Kosinski AS, Haber M. Comparison of concordance correlation coefficient and coefficient of individual agreement in assessing agreement. J Biopharm Stat. 2007;17(4):721–38.

73. Douglas G. Altman. Douglas G. Altman - Practical statistics for medical research-Chapman & Hall_CRC (1991).pdf. 1991. p. 611.

74. Lin LI. A Concordance Correlation Coefficient to Evaluate Reproducibility Author (s): Lawrence I-Kuei Lin Published by : International Biometric Society Stable URL : http://www.jstor.org/stable/2532051 REFERENCES Linked references are available on JSTOR for thi. Biomatrics. 1989;45(1):255–68.

75. Paterson K, ND L, Hill K. Gait variability in younger and older adult women is altered by overground walking protocol. Age Ageing. 2009;38(6):741–5.

76. Senefeld JW, D'Astice SE, Harmer AR, Hunter SK. Increased Cardiovascular Response to a 6-Minute Walk Test in People With Type 2 Diabetes. Diabetes Spectr. 2020;33(1):104–10.

77. Weir NA, Brown AW, Shlobin OA, Smith MA, Reffett T, Battle E, et al. The influence of alternative instruction on 6-min walk test distance. Chest [Internet]. 2013;144(6):1900–5. Available from: http://dx.doi.org/10.1378/chest.13-0287

78. Joobeur S, Rouatbi S, Latiri I, Sfaxi R, Saad H Ben. influencing factors of the 6-min walk distance in adult arab populations : a literature review . les facteurs influençant la distance de marche de 6 minutes des populations adultes arabes : revue de la littérature . 2016;(September).

79. Heine M, Fell BL, Robinson A, Abbas M, Derman W, Hanekom S. Patient-centred lifestyle rehabilitation for non-communicable disease in a low-resource setting : a feasibility and proof-of-concept randomized clinical trial. BMJ Open. 2019;9(4):1–30.

Addenda

Addendum A: PUBMED Search Strategy

Addendum B: BMJ Open- Patient-centred rehabilitation for noncommunicable disease in a low-resource setting: study protocol for a feasibility and proof-of-concept randomised clinical trial- Protocol

Addendum C: Ethical approval -Stellenbosch University Health Research and Ethics Council (M17/09/031)

Addendum D: Western Cape Department of Health Approval

Addendum E: Case Report Form

Addendum F: Informed Consent

Addendum G: Afrikaans 6MWT Instructions

Addendum A: PUBMED Search Strategy

#	Search Terms
#1	Afghan*" OR "Armenia*" OR "Bangladesh*" OR "Basutoland" OR "Basuto*" OR "Benin*" OR "Bhutan*" OR "Bolivia*" OR "Burkina Faso" OR "Burma" OR "Burmes*" OR "Burundi*" OR "Cabo Verde*" OR "Cambodia*" OR "Cameroon*" OR "Cape Verde*" OR "Central African Republic" OR "Central America*" OR "Ceylon" OR "Chad*" OR "Comoro Islands" OR "Comoros" OR "Comorian*" OR "Congo*" OR "Cote d'Ivoire" OR "Djibouti*" OR "Egypt*" OR "El Salvador*" OR "Eritrea*" OR "Ethiopia*" OR "French Somaliland" OR "Gambia*" OR "Gaza*" OR "Georgia"* OR "Ghana*" OR "Gold Coast" OR "Guatemala*" OR "Guinea*" OR "Guinea-Bissau*" OR "Haiti*" OR "Honduras" OR "Honduran*" OR "Ifni" OR "India*" OR "indigenous" OR "Indonesia*" OR "Ivory Coast" OR "Kenya*" OR "Kirghizia*" OR "Kirghiz" OR "Kyrgyz" OR "Kirgizstan*" OR "Kiribati" OR "Democratic People's Republic of Korea" OR "North Korea*" OR "Kosovo" OR "Kyrgyzstan" OR "Kyrgyz Republic" OR "Lao PDR" OR "Laos" OR "Laotian*" OR "Latin America*" OR "Lesotho" OR "Mosotho*" OR "Liberia*" OR "Madagascar" OR "Malagasy" OR "Malawi*" OR "Mali*" OR "Mauritania*" OR "Mayotte" OR "Melanesia*" OR "Micronesia*" OR "Moldova" OR "Moldovia*" OR "Morocco" OR "Moroccan*" OR "Nicaragua*" OR "Niger*" OR "Nigeria*" OR "Nyasaland" OR "Pakistan*" OR "Papua New Guinea" OR "Philipines" OR "Filipinas" OR "Filipino*" OR "Philippines" OR "Phillipines" OR "Phillippines" OR "Ruanda-Urundi" OR "Rwanda*" OR "Samoa*" OR "Sao Tome*" OR "Samoan Islands" OR "Senegal*" OR "Sierra Leone" OR "Sri Lanka*" OR "Solomon Islands" OR "Somalia*" OR "Sudan*" OR "Swaziland" OR "Swazi*" OR "Syria*" OR "Tadjikistan*" OR "Tadzhik*" OR "Tadzhikistan*" OR "Tajikistan*" OR "Tanzania*" OR "Timor-Leste" OR "Togo*" OR "Togolese Republic" OR "Uganda*" OR "Ukrain*" OR "Upper Volta" OR "Urundi" OR "Uzbek*" OR "Uzbekistan" OR "Vanuatu" OR "Ni-Vanuatu" OR "Viet Nam" OR "Vietnam*" OR "West Bank" OR "Yemen*" OR "Zaire" OR "Zambia*" OR "Zimbabwe*"
#2	("low-resource setting" OR "resource-constrained setting" OR "resource poor setting" OR "resource-poor setting" OR "resource limited setting" OR "resourcelimited setting" OR "low-resource settings" OR "resource-constrained settings" OR "resource poor settings" OR "resource-poor settings" OR "resource limited settings" OR "resource-limited settings")
#3	(developing countries[MeSH]) AND (developing OR "less* developed" OR "under developed" OR underdeveloped OR "middle income" OR "low* income" OR underserved OR deprived OR poor* AND countr* OR nation* OR population*)
#4	#1 or #2 or #3
#5	"six minute walk test" OR "six-minute walk test" OR "6 minute walk test" OR "6-minute walk test" OR "6MWT" OR "6-MWT"
#6	#4 AND #5

BMJ Open

Patient-centred rehabilitation for non-communicable disease in a low-resource setting: study protocol for a feasibility and proof-of-concept randomised clinical trial

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ABSTRACT

Introduction Non-communicable diseases (NCDs) are the leading cause of death globally. Even though NCD disproportionally affects low-to-middle income countries, these countries including South Africa, often have limited capacity for the prevention and control of NCDs. The standard evidence-based care for the long-term management of NCDs includes rehabilitation. However, evidence for the effectiveness of rehabilitation for NCDs originates predominantly from high-income countries. Despite the disproportionate disease burden in low-resourced settings, and due to the complex context and constraints in these settings, the delivery and study of evidence-based rehabilitation treatment in a low-resource setting is poorly understood. This study aims to test the design, methodology and feasibility of a minimalistic, patient-centred, rehabilitation programme for patients with NCD specifically designed for and conducted in a low-resource setting.

Methods and analysis Stable patients with cancer, cardiovascular disease, chronic respiratory disease and/or diabetes mellitus will be recruited over the course of 1 year from a provincial day hospital located in an urban, low-resourced setting (Bishop Lavis, Cape Town, South Africa). A postponed information model will be adopted to allocate patients to a 6-week, group-based, individualised, patient-centred rehabilitation programme consisting of multimodal exercise, exercise education and health education; or usual care (ie, no care). Outcomes include feasibility measures, treatment fidelity, functional capacity (eg, 6 min walking test), physical activity level, health-related quality of life and a patient-perspective economic evaluation. Outcomes are assessed by a blinded assessor at baseline, postintervention and 8-week follow-up. Mixed-method analyses will be conducted to inform future research.

Ethics and dissemination This study has been approved by the Health Research and Ethics Council, Stellenbosch University (M17/09/031). Information gathered in this research will be published in peer-reviewed journals, presented at national and international conferences, as well as local stakeholders.

Trial registration number PACTR201807847711940; Pre-results.

Strengths and limitations of this study

- This is the first feasibility study of patient-centred rehabilitation for non-communicable disease, specifically tailored to the context of an urban, low-resource setting.
- This study uses a postponed information randomisation model to avoid randomising patients to usual care.
- This study will inform feasibility and cost–benefits to upscale rehabilitation for non-communicable disease in low-resource settings.
- The experimental group size is dependent on the patient's willingness to participate in the rehabilitation programme.
- Generalisation of results to other low-resourced settings needs to be explored.

INTRODUCTION

Non-communicable diseases (NCDs) are the leading cause of death globally. Almost three quarters of NCD-related deaths occur in low-income and middle-income countries (LMICs).[1] Moreover, approximately 60% of NCD deaths occur before the age of 70 with 82% of these 'premature' deaths occurring in LMICs.[1] Cardiovascular diseases account for most NCD deaths (17.5 million annually), followed by cancer (8.2 million), respiratory diseases (4 million) and diabetes (1.5 million). These four groups of diseases account for 82% of all NCD deaths and 54% of loss in disability-adjusted life years; however, they share important commonalities in terms of modifiable risk factors.[1]

South Africa is facing evolving healthcare needs moving from a predominantly communicable disease profile towards a NCD profile. This cannot be contributed solely to the remarkable improvements concerning

the prevention and control of HIV/AIDS and tuberculosis, but also to increased urbanisation and economic growth.[2 3] Accordingly, as of 2011, NCDs are the leading cause of death in South Africa, which makes the prevention and control of NCD paramount. Even though NCD disproportionally affects LMICs, these countries, including South Africa, often have limited capacity for the prevention and control of NCD.[1] The rapid rise in NCDs is predicted to impede poverty reduction initiatives in low-income countries, particularly by increasing household costs associated with healthcare. Not much is known about the true economic and societal costs of NCDs in South Africa. The WHO recently estimated the loss of economic output associated with chronic diseases in 23 LMICs. It was estimated that in South Africa between 2006 and 2015, cumulative gross domestic product losses due to heart disease, stroke and diabetes alone amounted to US$1.88 billion.[4]

Rehabilitation can be defined as the 'sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible physical, mental and social conditions, so that they (patients) may by their own efforts, preserve or resume when lost, as normal a place as possible in the society'.[5] The core components of rehabilitation for patients with NCD include baseline patient assessment, educational interventions, risk factor modification, psychosocial interventions, physical activity counselling and exercise training.[5–11] However, the unmet need for rehabilitation globally, and especially in LMICs is profound,[12 13] and thought to be a direct function of the lack of reimbursement and governmental funding. The reasons are complex, and include healthcare budgetary issues (particularly for lower-income countries), inadequate legislation, lack of trained healthcare providers and a dearth of evidence from randomised controlled trials (RCTs) evaluating the effects of rehabilitation in LMICs such as those that are available in high-income countries.[14] While there is substantial evidence for the benefits of exercise-based rehabilitation in high-resource settings,[15–18] the study, delivery and implementation of evidence-based rehabilitation in low-resourced settings are poorly understood. Hence, it is important to determine a minimalistic yet effective rehabilitation intervention and accompanying research methodology to optimise the (cost) benefits and sustainability of rehabilitation services in a low-resource setting.[19] An effective, evidence-based, rehabilitation paradigm, specifically for resource-limited settings, is essential in terms of attaining United Nations' sustainable development goal 3 'Ensure healthy lives and promote well-being for all at all ages' in the context of an NCD epidemic.[20] The role of rehabilitation is instrumental for effective implementation of a variety of global action plans including the Global Strategy and Action Plan on Ageing and Health (2016–2020), and Framework on Integrated People-centred Health Services.[12]

A particularly important aspect regarding rehabilitation in a low-resource setting, and in specifically in South Africa, is the influence of multiple comorbidities on the outcome of rehabilitation; that is, 'quadruple burden of disease' (communicable, non-communicable, perinatal and maternal, and injury-related disorders).[2 21–23] Despite the widespread development of clinical practice guidelines, comorbidity remains a known barrier to the application of such guidelines in various settings and across conditions.[24 25] The robust evidence on which most clinical practice guidelines are founded is primarily based on short-term RCTs, which exclude those with comorbid conditions.[23 26] This limits the ability to generalise their results to settings with a high disease burden. For instance, a patient may present herself with simultaneous chronic obstructive pulmonary disorder and diabetes in the presence of an HIV infection with secondary cardiomyopathy as a side effect of HIV treatment. Such complex patients argue against a 'disease'-specific rehabilitation approach (eg, cardiac rehabilitation and pulmonary rehabilitation). Thus, there is a clear need for a patient-centred approach, incorporating the complexity of multiple comorbidities in a single-personalised rehabilitation programme. A study by Derman and colleagues on patient-centred rehabilitation for patients with NCD in a high-resource LMIC setting found significant improvements in a variety of outcomes including lipid profile, muscle strength and walking capacity.[27] However, the translation of this programme to a low-resource setting is limited due to the aforementioned quadruple burden of disease, but also setting-specific barriers and facilitators for treatment adherence (patient) and treatment fidelity (therapist). The transition to a patient-centred approach has been identified as the crux to the reimagined future of 2030 by the WHO through their #REHAB2030 call for action.[12]

The aim of this study is therefore to (i) test the feasibility[28] and key characteristics of a minimalistic patient-centred rehabilitation intervention that is designed specifically for the low-resource setting and (ii) inform the research methodology and study design for a full-scale randomised clinical trial on the effectiveness of patient-centred rehabilitation for NCD in a low-resource setting.

These aims can be structured according to the following objectives:

- To assess the feasibility and acceptance of a minimalistic patient-centred rehabilitation programme in a low-resource setting.
- To assess recruitment processes including attrition, retention and study uptake to inform a definitive RCT.
- To assess the feasibility of using a postponed information randomisation model in the context of a low-resource setting.
- To assess barriers and facilitators for treatment adherence (patient) and fidelity (therapist and physician).
- To assess the clinical relevance and validity of various outcomes in a low-resource community to inform the selection of primary and secondary outcomes, and sample size calculations for a full-scale RCT.

- To assess the feasibility of a patient-perspective economic evaluation in the context of a low-resource setting.
- To demonstrate proof of principle by gathering information about the process of change between the two treatment arms.

METHODS AND ANALYSIS

Design

This is a randomised pilot study[28] with blinded assessments to evaluate the feasibility of a patient-centred lifestyle rehabilitation programme in addition to usual care, compared with usual care alone, in a low-resource setting over the course of a 1-year timespan (2019).

Setting

Bishop Lavis is a densely populated, urban area—home to ~54 000 people living mostly in formal dwellings.[29] Only 66% of the economically active population (aged 15–65 years) of this community is employed. Approximately half of these (47%) earn between 0 and 544$ (purchase power parity) per household (average ~4.4 dependents per household) per month.[30] In contrast, the gross average monthly household wage in South Africa is ~3231$. The dominant types of occupation in Bishop Lavis are those classified as elementary occupations, for example, machine operators and assemblers, craft and related trades workers, and clerks. Crime rates in the area are high, with Bishop Lavis being in the top 10 of neighbourhoods in terms of murders, attempted murder, robbery and drug-related or gang-related crimes.[31]

The Bishop Lavis Rehabilitation Centre (BLRC) is a university-driven service learning centre that provides physiotherapy, occupational therapy, dietetics, as well as speech and language therapy to the community of Bishop Lavis and its surroundings. However, no structural patient-centred rehabilitation programme is in place for people with NCD. The BLRC was opened in January 1994 as a collaboration between the University of Stellenbosch, the Provincial Administration of the Western Cape and the Bishop Lavis local authority.

Patient and public involvement

Patients were not directly involved in the design of this study; however, their input was voiced through the >25 year experience of the BLRC staff (see acknowledgements) working in this environment. All components of this study, including intervention and assessments, have been tested using volunteers at the BLRC. Feedback with respect to study findings will be provided during a patient-information day on completion of this study.

Participants

Inhabitants of the Bishop Lavis community diagnosed with at least one of the four major NCDs, namely cardiovascular diseases (eg, heart failure and stroke), cancers, chronic respiratory diseases (including chronic obstructive pulmonary disorder) and diabetes will be recruited through the Bishop Lavis Day Care hospital physician and nursing staff for the study. This study will take place over 1 year between January 2019 and December 2019. Overseen by the family physician (MA) at the Bishop Lavis clinic, physician and nursing staff will determine eligibility of the patient based on the following eligibility criteria, as well as verify contact details.

1. Cardiovascular disease, cancer, diabetes and/or chronic respiratory disease.
2. Stable medical condition.
3. Agree to be contacted by research team.

The eligible patient will subsequently be contacted by the assessor (BLF), who will provide an oral explanation of the study and if interested, invite the eligible patient for a baseline assessment. During baseline assessment, the assessor (BLF) will determine inclusion/exclusion based on the following criteria, and obtain written informed consent for the observational study at this stage (consent 1) prior to any outcome measure testing.

Inclusion criteria

1. At least 18 years of age or older (ie, adult).
2. Able to perform some weight-bearing or non-weight-bearing exercise.
3. Minimal of one confirmed diagnosis according to the WHO classification[32] of cardiovascular disease (ICD: I0-99), chronic respiratory disease (ICD: J30-98), malignant neoplasms (ICD: C00-97) or diabetes (E10-E14; excluding those with complications [E10.2-E10.29, E11.2-E11.29, E12.2, E13.2-E13.29 and E14.2]).

Exclusion criteria

1. No generic contraindications for exercise training or disease-specific contraindications for exercise training (table 1).[33]
2. Other contraindications for exercise prescription as determined by the physiotherapist.
3. Structured exercise training at regular intervals (more than once per week) at a moderate-to-vigorous intensity in the previous 3 months.
4. Psychiatric concerns, substance abuse or known history of violence that would jeopardise the safe conduct of this programme.
5. Pregnancy.

Data management and randomisation logistics

Data collection and randomisation are facilitated through http://www.castoredc.com. Castor EDC is an intuitive and secure cloud-based electronic data capture platform that facilitates defined user roles, advanced monitoring, participant management and powerful calculations. Data storage is compliant with all relevant regulations including good clinical practice.

Randomisation is conducted using a postponed-information model (figure 1).[34 35] After inclusion in the observational cohort study, an appointment is made for baseline assessment (1) and followed by the extended (additional to the inclusion screening) medical history. Demographics and outcomes will be evaluated by the

Table 1 Generic and disease-specific contraindications to be considered during enrolment

	Generic	Disease specific			
		ICD: C00-97	ICD: E10-14	ICD: I0-99	ICD: J30-98
Factors related to treatment		▶ Severe tissue reaction to radiation therapy			
Haematologic	▶ Electrolyte abnormalities ▶ Severe arterial hypertension (SBP >200 mm Hg and/or DBP >110 mm Hg) at rest	▶ Platelets <50×10^{9}·L-1 ▶ White cell count <3 ×10^{9}·L-1 ▶ Haemoglobin <100 g·L^{-1}			
Musculoskeletal	▶ Neuromuscular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise ▶ Physical impairment leading to inability to exercise adequately	▶ Bone, back or neck pain of recent origin ▶ Unusual muscular weakness ▶ Severe cachexia ▶ Unusual/extreme fatigue ▶ Poor functional status			
Systemic	▶ Acute systemic infection, accompanied by fever, body aches or swollen lymph glands ▶ Uncontrolled metabolic disease (eg, diabetes, thyrotoxicosis or myxoedema) ▶ Chronic infectious disease (eg, mononucleosis, hepatitis and AIDS)	▶ Acute infections ▶ Febrile illness: fever >38°C ▶ General malaise ▶ Resting SBP >145 mm Hg and/or DBP >95 mm Hg	▶ Uncontrolled diabetes (ie, HbA_{1c} >7.0%)	▶ Uncontrolled hypertension (ie, SBP >180 and/or DBP >110) at rest ▶ Orthostatic BP drop >20 mm Hg with symptoms ▶ Acute systemic illness or fever ▶ Uncontrolled diabetes mellitus ▶ Other metabolic conditions such as acute thyroiditis, hypokalaemia, hyperkalaemia or hypovolaemia	
Gastrointestinal		▶ Severe nausea ▶ Vomiting or diarrhoea within 24–36 hours ▶ Dehydration ▶ Poor nutrition: inadequate fluid and/or intake			
Cardiovascular	▶ **Recent (2 days) significant ischaemia, myocardial infarction, cardiac surgery or another acute cardiac event** ▶ **Unstable angina** ▶ **Uncontrolled cardiac dysrhythmias causing symptoms or haemodynamic compromise** ▶ **Symptomatic severe aortic stenosis** ▶ **Uncontrolled symptomatic heart failure** ▶ **Acute myocarditis or pericarditis** ▶ Left main coronary stenosis ▶ Moderate stenotic valvular heart disease ▶ Tachydysrhythmia or bradydysrhythmia ▶ Hypertrophic cardiomyopathy and other forms of outflow tract obstruction	▶ Chest pain ▶ Resting HR >100 bpm or <50 bpm ▶ Irregular heart rate ▶ Swelling of ankles		▶ **Recent (5 weeks)*significant ischaemia, myocardial infarction, cardiac surgery or another acute cardiac event** ▶ Critical aortic stenosis (ie, peak SBP gradient of >50 mm Hg with an aortic valve orifice area of <0.74 cm^{2} in an average-size adult) ▶ Uncontrolled atrial or ventricular dysrhythmias ▶ Uncontrolled sinus tachycardia (>120 bpm) ▶ Uncompensated chronic heart failure ▶ Third-degree atrioventricular block without pacemaker ▶ Active pericarditis or myocarditis ▶ Resting ST-segment depression or elevation (>2 mm)	
Pulmonary	▶ Acute pulmonary embolus or pulmonary infection	▶ Severe dyspnoea ▶ Cough, wheezing ▶ Chest pain increased deep breath		▶ Recent embolism ▶ Thrombophlebitis	
Neurologic	▶ Suspected or known dissecting aneurysm ▶ Mental impairment leading to inability to exercise adequately (ie, neglect, aphasia and severe depression)	▶ Significant decline in cognitive status ▶ Dizziness/light headedness ▶ Disorientation ▶ Blurred vision ▶ Ataxia (ie, inability to coordinate voluntary movement)			

The absolute contraindications to exercise participation and direct exclusion are highlighted in bold. All other criteria are reviewed on a case-by-case basis by the medical practitioner at the time of inclusion if applicable. BP, Blood Pressure; bpm, beat per minute; DBP, Diastolic Blood Pressure; HR, Heart Rate; ICD, International Classification of Disease; SBP, Systolic Blood Pressure
*While endurance training can start within 2 days of a cardiac event, the guidelines for resistance training indicate a minimum of 2–3 weeks following transcatheter procedures, and a minimum of 5 weeks after myocardial infarction or cardiac surgery.

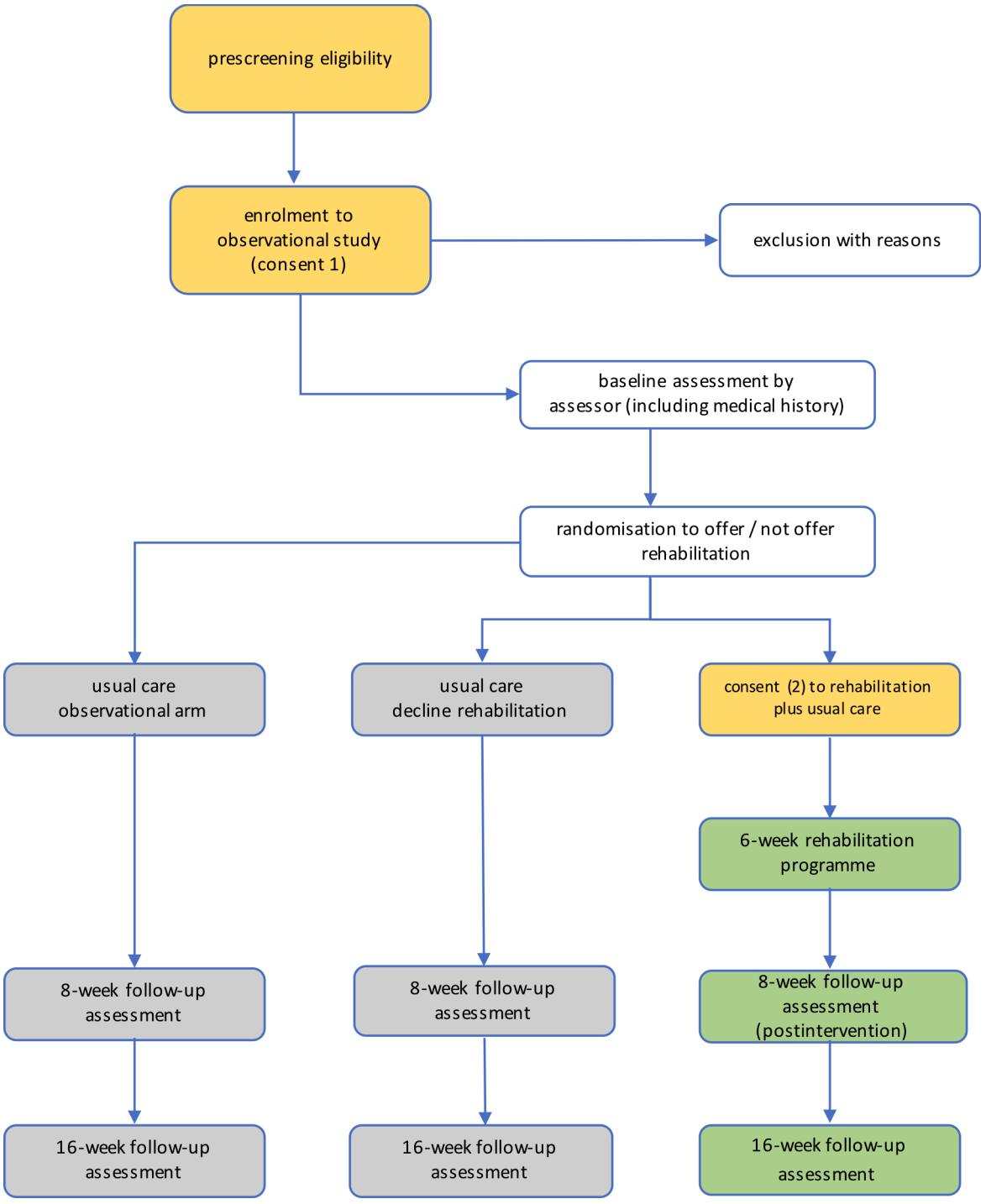

Figure 1 Study flow chart of postponed information model. Blinded follow-up assessments of all outcomes at 8 weeks, 16 weeks postrandomisation. The 6-week rehabilitation programme starts ~2 weeks after randomisation to allow for logistical arrangements.

blinded assessor at the initial assessment. At this time, also follow-up assessments will be scheduled. Subsequently, the participant will be 'silently' (ie, unknowingly) randomised to being offered or not being offered the rehabilitation programme (consent 2) using a 3:1 centralised and concealed allocation scheme. The assessor (BLF) will trigger randomisation through Castor EDC online (but will not have access to the outcome), and the coordinating physiotherapist (AR) will contact the patient with the randomisation outcome to ensure blinding of the assessor. This procedure entails three potential outcomes:

1. The participant is not offered the rehabilitation programme, and as such is unaware of its existence. The participant will remain in the observational arm.
2. The participant is offered the rehabilitation programme but declines to consent to the rehabilitation programme. The participant will continue the study in the observational arm.

3. The participant is offered the rehabilitation programme and agrees to participate (consent 2). The participant will provide the second informed consent and is subsequently contacted by the physiotherapist to initiate the rehabilitation programme (based at the BLRC).

It is hypothesised that the postponed information model reduces the ethical boundaries to allocate patients to a control condition (as is the case in this specific setting, where structured rehabilitation for NCDs is non-existent), while maintaining the recruitment efficiency and robustness of a conventional RCT.[34 35] This model also ensures that a participant makes an informed decision to participate in an intervention, without the risk of being randomised to usual care, and therefore resembles clinical practice more closely. It can be hypothesised that patients who provide the second consent to participate in the rehabilitation programme are subsequently more motivated to engage in the intervention. It can be postulated that by resembling clinical practice more closely, translation from research into clinical practice is more likely. Finally, this model also allows the assessment of patients who decline to participate or discontinue the intervention, providing additional insights into the feasibility of the intervention. The present study will therefore inform, through qualitative (eg, focus group interviews) and quantitative (eg, retention rate, acceptance rate) research techniques, whether or not a postponed information model is a viable randomisation strategy and reduces some of the methodological constrains for conducting an RCT in a low-resource setting. Participants will be informed about the full extent of this model during a patient-information day on completion of the study.

Outcomes and participant characteristics

Due to the feasibility nature of this RCT, no a-priori primary outcome is identified or power-analysis conducted. Outcomes have been selected based on their clinical relevance, pragmatic implementation in a low-resource setting and expected lack of dependency on the health-literacy of the patient. All outcomes will be assessed at baseline, 8 weeks postrandomisation (ie, postintervention) and 16 weeks postrandomisation by an assessor blinded to treatment allocation (see table 2 for the assessment schedule).

Participants' characteristics

The following participants' characteristics will be recorded to describe the study sample: demographics (eg, age), socioeconomic status and lifestyle-related factors (eg, smoking).

Medical history

A qualified physiotherapist (BLF) will take a detailed medical history, which is double checked offline against exclusion criteria by the family physician (MA). A disease severity classification is included in the medical history for cardiovascular disease,[36] cancer (https://cancerstaging.org) and diabetes (type 1 and type 2).[37] Disease severity for chronic respiratory disease is determined after inclusion, during the physical examination (according to the patient's forced expiratory volume [FEV1]).

Physical examination and lifestyle inventory

Each participant will undergo a basic physical examination by the assessor who is blinded to treatment allocation during follow-up assessments. The examination includes the measurement and recording of height (m), weight (kg), hip and waist circumference (cm), resting blood pressure (mm Hg), lung spirometry (FEV and Force Vital Capacity) and resting heart rate (beats per minute). Lifestyle risk factors including tobacco consumption (one selected item), alcohol consumption (one selected item), diet (four items), and selected items from the violence module (two items), will be assessed using components of the WHO STEPS instrument.[38] Separate questionnaires are included for physical activity and quality of sleep.

Physical activity

The International Physical Activity Questionnaire (IPAQ) is a 27-item self-reported measure of physical activity for use with individual adult patients aged 15–69 years old. Duration (minutes) and frequency (days) of physical activity in the last 7 days is measured in domains of job-related, transportation, housework, house maintenance, caring for family, recreation, sport and leisure-time, and time spent sitting. The IPAQ has acceptable psychometric properties relative to other self-report measures.[39]

Quality of sleep

Quality of sleep is assessed using the Pittsburgh Sleep Quality Index (PSQI). The PSQI differentiates 'poor' from 'good' sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction over the last month. The PSQI has shown moderate to excellent psychometric properties in clinical and non-clinical samples.[40]

Functional capacity

Six-minute walk test

The primary mode of transport for most people living in a low-resource setting (eg, Bishop Lavis) is walking.[29] It is evident that having one or more NCDs has a severe impact on mobility, and therefore daily life and participation. The six-minute walk test (6MWT) has been shown to be a valid, reliable and responsive measure across various patient groups.[41] The 6MWT is a functional walking test that requires the participant to walk around a measured and demarcated (eg, pylons or coloured tape to mark turning points) 30 m track for 6 min continuously when conducted in accordance with published guidelines.[42] Due to resource-constraints (space), a 10 m lap distance will be used instead. The 6MWT will be conducted twice during baseline testing to reduce the learning effect,

Table 2 Assessment and treatment schedule

Weeks	**0**		**1–2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11–16**	**17**	**18**
Phase	Inclusion	Baseline	Scheduling	Treatment/usual care						Postintervention			Follow-up	
Inclusion/exclusion criteria	X													
Medical history	X													
Outcomes														
Physical examination		X								X			X	
Lifestyle risk factors		X								X			X	
IPAQ		X								X			X	
PSQI		X								X			X	
6MWT		X (n=2)								X			X	
TUG		X								X			X	
SSST		X								X			X	
HRQOL		X								X			X	
Economic evaluation		X								X			X	
Treatment type				Treatment/usual care										
Exercise				X	X	X	X	X	X					
Education					X		X		X					
Adherence				X	X	X	X	X	X					
Treatment fidelity				Continuous evaluation										

6MWT, six-minute walk test (assessed twice at baseline to correct for a learning effect); HRQOL, health-related quality of life; IPAQ, International Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SSST, six-spot step test; TUG, timed up and go test.

which has been reported to be as large as 27–35 m in patients with chronic heart failure.[43]

Timed up and go test

The timed up and go (TUG) test is a measure of function which closely corresponds with balance and fall risk.[44] The participant is asked to stand up from an armed chair, walk 3 m and return to the chair as quickly as they feel *safe and comfortable*. Each participant will get one practice run, and two runs that count. The best run is used as the outcome. The test has shown excellent test–retest reliability (Intraclass Correlation[ICC} Coefficient=0.93), and moderate concurrent validity with the 6MWT (r=−0.81).[45]

Six-spot step test

The six-spot step test (SSST) is a relatively new quantitative test of ambulation with components of coordination, dynamic balance and lower-limb function.[46 47] The SSST is performed in a 5 m rectangular field with five marked circles (diameter 20 cm) which contain a wooden block (4×8 cm^2, 140 g).[47] From the starting line, the participant is instructed to walk to the other side as quickly as safe and comfortable, kicking the wooden blocks out of the circles in the process. The assessor first provides a demonstration, after which the participant does two runs with the dominant and two with the non-dominant leg. The SSST combines straight walking with bouts of single-leg standing (during kicking), making it unique from other common walking tests (including 6MWT and TUG).

Health-related quality of life (EQ-5D-5L)

The EQ-5D-5L is a 5-item, self-report questionnaire to assess self-care, mobility, pain/discomfort, anxiety/depression and usual activities on a 1–5 scale of perceived problems in these domains. In addition, general health is scored using a visual-analogue-scale. Combined, these six items form a profile of health-related quality of life. The EQ-5D-5L is essential in terms of the economic evaluation. The EQ-5D-5L is widely used and validated in a surplus of chronic medical conditions, most recently in a large cohort of the elderly.[48]

Cost–benefits

While the provider-perspective economic evaluation is generally feasible in a low-resource setting (eg, clinical record review), most studies conducted in a low-resource setting refrain from economic evaluations from a patient-perspective. In the present study, we aim to test the feasibility of a patient-perspective economic evaluation in addition to key provider statistics (personnel, equipment, inpatient visits, outpatient visits and drug use). To that extent, the following outcomes will be included: direct costs related to transportation (patient or caregiver), direct medical costs (ie, over the counter drugs and supplements), strategies to pay for out-of-pocket expenses (ie, medical poverty trap)[49] and patient-reported productivity costs based on the Productivity Cost Questionnaire.[50 51]

Treatment adherence and fidelity

Each patient will keep a paper and pen-based exercise diary/file in which the moderate-to-vigorous physical activity and resistance exercises are logged, if applicable photos are added to illustrate proper execution of the exercises and patients keep note of the extent (frequency, duration, intensity and repetitions) to which they have completed their physical activity targets and prescribed resistance exercises (see programme description below). These records will then be reviewed during each supervised session, and where necessary, the patient will be encouraged to improve his/her adherence. Barriers that limit adherence will be recorded.

Treatment fidelity practices are related to study design, training providers and delivery of treatment.[52 53] To optimise fidelity of treatment provision, all treatment providers will receive a 1-day training, which will cover the study protocol, and considerations for exercise-based rehabilitation in cardiovascular disease, cancer, chronic respiratory disease and diabetes. The standardised training will reduce the likelihood of a provider×treatment interaction. Adherence to the prescribed intervention from a patient perspective is recorded during the intervention (frequency, dose and intensity). Participants will receive a 'graduation diploma' if they complete and adhere to 90% of the supervised exercise and education sessions. During the conduct of the intervention, providers will sign-off on the delivered components of the intervention following each session. An independent physiotherapist will review 10% of the therapy sessions, convene with the therapy provider to ensure protocol adherence and address potential provider differences due to level of education, skill level or background.

The patient-centred rehabilitation programme

There is no consensus as to the minimum duration of an exercise-based rehabilitation programme to lead to clinically relevant improvements. However, rehabilitation programmes as short as 3–5 weeks have shown clinical relevant improvements walking capacity (mean difference=30.9 m, 95% CI 9.4 to 52.4, p=0.005).[54 55] Rather than the duration per se, the effectiveness of exercise-based rehabilitation should mostly be attributed to the extent the exercises are specific for the desired goal, and to the extent in which the exercises and dose are individualised to the patients' functional capacity at baseline and progresses over time. In the present study, we aim to develop a treatment paradigm that, on the one hand, potentially results in clinically relevant and sustained improvements in body function, activity and participation, while, on the other hand, keeping the cost–benefits optimal. To that end, the rehabilitation programme for the present feasibility study has been limited to 6 weeks, designed with respect to the anticipated difficulties related to the low-resource setting,[56] while still addressing the core components of rehabilitation in terms of risk factor analysis, exercise and patient-education.[57]

Exercise component

The rehabilitation programme will start ~2 weeks after randomisation to allow for appropriate scheduling. The supervised exercise prescription will be tailored to each patient's initial functional capacity, profile of comorbidities, use of medication and active disease status and consist of an aerobic and resistance component. The exercise component of the intervention will consist of one 60 min supervised group session (max five per group) per week, and two 30 min home-based sessions, and will progress in terms of intensity throughout the 6 weeks according to the patient's (increasing) ability. Each group session will entail a 10 min group-based warm-up, 20 min aerobic-type training with a specific educational component (see below) and 30 min of resistance training. Even though the supervised sessions are group-based, each patient will follow his or her own individualised, patient-centred, exercise programme. Group sessions will be offered once daily. Participants need to sign-up at which timeslot they wish to attend the following week. It is hypothesised that by giving the participant this flexibility, and given anticipated barriers related to the low-resource setting, adherence to the supervised sessions will be higher.

The primary exercise component is to enable the patient to be health-enhancing, moderately-to-vigorously active, five times a week for 30 min or a combined minimum of 150 min/week in a home environment, at completion of the 6-week intervention, in accordance with the American College of Sports Medicine (ACSM) guidelines for physical activity.[33] To ascertain this goal, each supervised 60 min practical exercise sessions has a specific theme (see box 1).

It is hypothesised that by introducing an educational theme to the supervised aerobic exercise component, this relatively short rehabilitation programme is more likely to result in sustainable benefits.

The secondary exercise component will entail the participants engaging in two-to-three progressive resistance type exercises, involving large muscle groups for improving specific muscle and/or gait function. This is in line with recent suggestions for a stronger focus on resistance training (compared with higher intensity aerobic exercise-based rehabilitation) might be a more viable paradigm to improve health outcomes.[58] Resistance training exercises can be general exercises to improve stability, balance or muscle strength or can be more specified to the health condition, for instance in patients with hemiplegia or respiratory muscle weakness. Progression and intensity of exercise are based on the aim (eg, muscle strength, endurance and power) in accordance with the ACSM guidelines for resistance training (table 3). Each participant will be requested to keep a paper-based exercise diary during the intervention phase. All prescribed exercises, both aerobic as well as resistance type exercises, should be viable with no or minimal equipment.[59] Leaflets will be handed out to the participants with preferred, key exercises to promote proper conduct of the exercise in a home-environment.

Box 1 Six different themes addressed during the supervised exercise sessions

1. Exercise and safety; recognising body responses to exercise and safety warnings.
2. Home-based exercise options.
3. What entails moderate intensity exercise (*individualised moderate intensity reference*).
4. What entails vigorous intensity exercise (*individualised upper intensity reference*).
5. Alternative community exercise modalities.
6. Long-term goal setting–continuing a physically active lifestyle.

Educational component

Each patient will be requested to enrol in each of the three educational sessions through the course of the 6-week programme to facilitate informed healthy choices.[57] Topic one will be presented during week 1 of the intervention, topic two during week 3 and topic three during week 6. Each topic will be presented daily throughout that week and patients can sign-up according to their availability. It is hypothesised that providing this flexibility, adherence will be higher. Each session consisted of a 15–30 min standardised educational part, and a 15–30 min group discussion to enable vicarious learning (ie, learning by the experiences of peers)[60] and address perceived facilitators and barriers with respect to the subject at hand.

1. NCDs of lifestyle.
2. Heart-health behaviour (eg, tobacco-use and nutrition).
3. Health benefits of physical activity.

Usual care

Usual care at the Bishop Lavis Day Clinic is directed mainly towards ongoing medical management of community members with chronic disease. Referral to the (in-house) rehabilitation centre is limited, and not standardised. An optional education session for patients with NCD is hosted monthly, with shifting themes.

Sample size

There are no precise estimates on the prevalence of NCD in Bishop Lavis per se. However, results from the Global Health Action indicate a prevalence of ~52% NCDs in South Africa.[61] Approximately 22% of these patients reported the presence of ≥2 chronic conditions. Among others, cultural background and living in an urban area are considered risk factors for a higher prevalence of NCD. If we translate these numbers to the Bishop Lavis community (54 006 inhabitants), one may estimate that the population of people with NCD is roughly 28 083. It is hypothesised that using the 3:1 allocation (offer vs non-offer) ratio, this will approximately result into a 1:1 group allocation; in other words, for every three patients who will be offered the rehabilitation programme, two will consent and one will decline. The study will be conducted

Table 3 Different types of resistance training schemes according to the ACSM (https://www.acsm.org/docs/brochures/resistance-training.pdf)

Muscle strength	Muscle power	Muscle endurance
▲ Load: 60%–70% 1RM for novice to intermediate; 80%–100% for advanced. ▲ Volume: 1–3 sets of 8–12 repetitions for novice to intermediate; 2–6 sets of 1–8 repetitions for advanced. ▲ Rest period: 2–3 min for higher intense exercises that use heavier loads; 1–2 min between the lower intense exercises with light loads.	▲ Load: 30%–60% 1RM for upper body exercises; 0%–60% 1RM for lower body exercises. ▲ Volume: 1–3 sets of 3–6 repetitions per exercise. ▲ Rest period: 2–3 min for higher intense exercises that use heavier loads; 1–2 min between the lower intense exercises with light loads.	▲ Load: lower than 70% of 1RM. ▲ Volume: 2–4 sets of 10–25 repetitions. ▲ Rest period: 30 s to 1 min between each set.

1RM, one-repetition maximum; ACSM, American College of Sports Medicine.

over the course of 1 year, with the final group starting in week 40. As such, recruitment, reasons for non-participation or adherence can be evaluated within the context of an entire year (eg, seasonal changes). The theoretical maximum capacity of the programme is 25 patients per week, five complete treatment cycles of 8 weeks within 40 weeks, leading to 125 patients in the experimental group.

Data analysis

- The feasibility of the postponed-information model and recruitment strategy in a low-resource setting will be evaluated quantitatively based on the eligible patients, participant and retention rate, group-allocation ratio, drop-out rate and treatment adherence.
- Treatment fidelity is assessed by reviewing 10% of the provided treatment sessions against the study protocol by an independent rehabilitation specialist.
- Feasibility of the different treatment components is assessed by reviewing the training dairies and adherence rates for both the supervised exercise sessions, as well as education sessions.
- Feasibility of the various endpoints is assessed by performing a preliminary longitudinal data-analysis (ie, random-coefficient analysis or generalised estimating equations) to determine the time-by-group interaction for each outcome measure and based on an intention-to-treat principle. It has been shown that both these longitudinal data techniques are robust to missing data in the analysis of continuous outcomes.[62 63] If appropriate, analyses will be adjusted for patient characteristics that differ between the two groups. Independent variables (covariates) can be added to the model to assess and estimate their impact on the dependent variable. Among others, this may include the overall treatment adherence to estimate the extent in which protocol deviations may bias the results. The longitudinal analysis will be performed blinded to treatment allocation.
- Acceptance of the programme is evaluated using group-based focus interviews with both participants of the intervention and participants that declined the intervention.

ETHICS AND DISSEMINATION

All of the participants will be recruited through voluntary participation, and written informed consent forms from all trial participants will be obtained by researchers in accordance with the Declaration of Helsinki.[64] Each participant will receive a unique identifier to ensure confidentiality before, during and after the trial.

Safety

Patients will be asked to report any adverse events (AEs) during the home-based training at each supervised session. All AEs that occur during testing or rehabilitation treatment will be recorded and reviewed by the medical practitioner to determine seriousness and relation to the provided treatment. Patients will be asked to report any

AEs during the home-based training at each supervised session. Muscle soreness and increased levels of a fatigue are only reported as AEs if lasting >48 hours. Serious AEs will be expedited to the medical ethics committee as per good clinical practice. This study is covered by Stellenbosch University's no-fault study insurance, a medical doctor is on the study team, and both testing and supervised treatment are conducted in a hospital environment, ensuring prompt and adequate treatment of any issues or injuries arising during the conduct of the study.

Reimbursement of participants

Each participant will receive a monetary token for participating in this study to the value of R100 per completed assessment visit (R300 in total per participant). There are a number of arguments to justify the amount per visit. First, given the low-resource environment (average income of ZAR1600/month) of the Bishop Lavis community, a higher reimbursement will substantially increase the likelihood of undue influence in signing informed consent. Second, all visits (assessment and treatment) will take place within the Bishop Lavis community, substantially reducing the time, inconvenience and travel requirements. Third, the inconvenience of the assessment battery is reduced to a minimum and does not entail invasive procedures. No reimbursement will be provided for the *supervised treatment visits (n=6[exercise]+3[education])*. First, this will increase the undue influence for patients to sign consent based on the monetary revenue it would entail. But more importantly, this will significantly limit the ecological validity, sustainability and implementation of the rehabilitation model studied into clinical practice, if shown feasible.

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Contributors MH, WD and SH were involved in the conception and design of the study. AR and BLF will be coordinating the intervention and assessments, respectively, and are anticipated to obtain an MSc in Physiotherapy on the basis of this study. MA is the family physician at the community clinic, and will oversee the recruitment and safety of participants. MH obtained ethical approval from the Stellenbosch University Health and Research Council. MH secured funding for this study. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol has been reviewed by the Stellenbosch University Health Research and Ethics Committee and has been approved on 16 May 2018 (reference number: M17/09/031).

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REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases, 2014. http://www.who.int/nmh/publications/ncd-status-report-2014/en/ (accessed 25 Jun 2018).
2. Mayosi BM, Flisher AJ, Lalloo UG, *et al*. The burden of non-communicable diseases in South Africa. *Lancet* 2009;374:934–47.
3. Pillay-van Wyk V, Msemburi W, Laubscher R, *et al*. Mortality trends and differentials in South Africa from 1997 to 2012: second National Burden of Disease Study. *Lancet Glob Health* 2016;4:e642–53.
4. Abegunde DO, Mathers CD, Adam T, *et al*. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* 2007;370:1929–38.
5. World Health Organization. Rehabilitation after cardiovascular diseases, with special emphasis on developing countries. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1993;831:1-122.
6. Balady GJ, Williams MA, Ades PA, *et al*. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115:2675–82.
7. Buckley JP, Furze G, Doherty P, *et al*. BACPR scientific statement: British standards and core components for cardiovascular disease prevention and rehabilitation. *Heart* 2013;99:1069–71.
8. Grace SL, Turk-Adawi KI, Contractor A, *et al*. Cardiac Rehabilitation Delivery Model for Low-Resource Settings: An International Council of Cardiovascular Prevention and Rehabilitation Consensus Statement. *Prog Cardiovasc Dis* 2016;59:303–22.
9. Piepoli MF, Corrà U, Adamopoulos S, *et al*. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol* 2014;21:664–81.
10. Woodruffe S, Neubeck L, Clark RA, *et al*. Australian Cardiovascular Health and Rehabilitation Association (ACRA) core components of cardiovascular disease secondary prevention and cardiac rehabilitation 2014. *Heart Lung Circ* 2015;24:430–41.
11. Kachur S, Chongthammakun V, Lavie CJ, *et al*. Impact of cardiac rehabilitation and exercise training programs in coronary heart disease. *Prog Cardiovasc Dis* 2017;60:103–14.
12. World Health Organization. *Rehabilitation 2030: A Call for Action*: WHO. http://www.who.int/rehabilitation/rehab-2030/en/ (accessed 22 Mar 2018).
13. Pesah E, Supervia M, Turk-Adawi K, *et al*. A Review of Cardiac Rehabilitation Delivery Around the World. *Prog Cardiovasc Dis* 2017;60:267–80.
14. Babu AS, Lopez-Jimenez F, Thomas RJ, *et al*. Advocacy for outpatient cardiac rehabilitation globally. *BMC Health Serv Res* 2016;16:471.
15. Anderson L, Thompson DR, Oldridge N, *et al*. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016:CD001800.
16. Long L, Anderson L, Dewhirst AM, *et al*. Exercise-based cardiac rehabilitation for adults with stable angina. *Cochrane Database Syst Rev* 2018;2:CD012786.
17. Puhan MA, Gimeno-Santos E, Cates CJ, *et al*. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. In: *The Cochrane Library*: John Wiley & Sons, Ltd, 2016;59.
18. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. In: *The Cochrane Library*: John Wiley & Sons, Ltd, 2017.
19. Lavie CJ, Kachur S, Milani RV. Making cardiac rehabilitation more available and affordable. *Heart* 2019;105:94–95.
20. United Nations - Sustainable development goals. United Nations Sustainable Development. https://www.un.org/sustainabledevelopment/sustainable-development-goals/ (accessed 25 Jun 2018).
21. Nelson ML, Grudniewicz A, Albadry S. Applying Clinical Practice Guidelines to the Complex Patient: Insights for Practice and Policy from Stroke Rehabilitation. *Healthc Q* 2016;19:38–43.
22. Arokiasamy P, Uttamacharya U, Jain K, *et al*. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? *BMC Med* 2015;13:178.

23. Glynn LG, Buckley B, Reddan D, *et al*. Multimorbidity and risk among patients with established cardiovascular disease: a cohort study. *Br J Gen Pract* 2008;58:488–94.
24. Fortin M, Contant E, Savard C, *et al*. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Pract* 2011;12:74.
25. Boyd CM, Darer J, Boult C, *et al*. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716–24.
26. Jadad AR, To MJ, Emara M, *et al*. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA* 2011;306:2670–2.
27. Derman W, Schwellnus M, Hope F, *et al*. Description and implementation of U-Turn Medical, a comprehensive lifestyle intervention programme for chronic disease in the sport and exercise medicine setting: pre-post observations in 210 consecutive patients. *Br J Sports Med* 2014;48:1316–21.
28. Eldridge SM, Lancaster GA, Campbell MJ, *et al*. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS One* 2016;11:e0150205.
29. De la Cornillere W-L. *Participants' experience of the Bishop Lavis Rehabilitation Centre stroke group*, 2007.
30. PPP conversion factor, GDP (LCU per international $). Data. https://data.worldbank.org/indicator/PA.NUS.PPP (accessed 25 Jun 2018).
31. Crime Stats SA - Crime Stats Simplified. http://crimestatssa.co.za/ (accessed 25 Jun 2018).
32. World Health Organization. *WHO methods and data sources for global burden of disease estimates 2000-2011*. Geneva: Department of Health Statistics and Information Systems, 2013.
33. Garber CE, Blissmer B, Deschenes MR, *et al*. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334–59.
34. Gallo C, Perrone F, De Placido S, *et al*. Informed versus randomised consent to clinical trials. *Lancet* 1995;346:1060–4.
35. Young-Afat DA, Verkooijen HA, van Gils CH, *et al*. Brief Report: Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design. *Epidemiology* 2016;27:389–92.
36. New York Heart Association. *Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis*: Little, Brown, 1964.
37. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33(Suppl 1)S62–S69.
38. World Health Organization. *The WHO STEPwise approach to noncommunicable disease risk factor surveillance (STEPS)*. Geneva: World Health Organization, 2003.
39. Craig CL, Marshall AL, Sjöström M, *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
40. Mollayeva T, Thurairajah P, Burton K, *et al*. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Med Rev* 2016;25:52–73.
41. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81.
42. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
43. Uszko-Lencer N, Mesquita R, Janssen E, *et al*. Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure. *Int J Cardiol* 2017;240:285–90.
44. Hafsteinsdóttir TB, Rensink M, Schuurmans M. Clinimetric properties of the Timed Up and Go Test for patients with stroke: a systematic review. *Top Stroke Rehabil* 2014;21:197–210.
45. Hwang R, Morris NR, Mandrusiak A, *et al*. Timed up and go test: a reliable and valid test in patients with chronic heart failure. *J Card Fail* 2016;22:646–50.
46. Kreutzfeldt M, Jensen HB, Ravnborg M, *et al*. The six-spot-step test - a new method for monitoring walking ability in patients with chronic inflammatory polyneuropathy. *J Peripher Nerv Syst* 2017;22:131–8.
47. Nieuwenhuis MM, Van Tongeren H, Sørensen PS, *et al*. The six spot step test: a new measurement for walking ability in multiple sclerosis. *Mult Scler* 2006;12:495–500.
48. Lutomski JE, Krabbe PF, Bleijenberg N, *et al*. Measurement properties of the EQ-5D across four major geriatric conditions: Findings from TOPICS-MDS. *Health Qual Life Outcomes* 2017;15:45.
49. McIntyre D, Thiede M, Dahlgren G, *et al*. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? *Soc Sci Med* 2006;62:858–65.
50. Bouwmans C, Krol M, Severens H, *et al*. The iMTA Productivity Cost Questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health* 2015;18:753–8.
51. Bouwmans C, Krol M, Brouwer W, *et al*. IMTA Productivity Cost Questionnaire (IPCQ). *Value Health* 2014;17:A550.
52. Bellg AJ, Borrelli B, Resnick B, *et al*. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychol* 2004;23:443–51.
53. Borrelli B. The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. *J Public Health Dent* 2011;71:S52–S63.
54. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness—a systematic review. *Physiotherapy* 2012;98:277–86.
55. Sherrington C, Pamphlett PI, Jacka JA, *et al*. Group exercise can improve participants' mobility in an outpatient rehabilitation setting: a randomized controlled trial. *Clin Rehabil* 2008;22:493–502.
56. Baumann LC. Insights on conducting research in low-resource settings: examples from Vietnam and Uganda. *Transl Behav Med* 2011;1:299–302.
57. Grace SL, Turk-Adawi KI, Contractor A, *et al*. Cardiac rehabilitation delivery model for low-resource settings. *Heart* 2016;102:1449–55.
58. Steele J, Fisher J, Skivington M, *et al*. A higher effort-based paradigm in physical activity and exercise for public health: making the case for a greater emphasis on resistance training. *BMC Public Health* 2017;17:300.
59. Alison JA, McKeough ZJ. Pulmonary rehabilitation for COPD: are programs with minimal exercise equipment effective? *J Thorac Dis* 2014;6:1606–14.
60. Roberts D. Vicarious learning: a review of the literature. *Nurse Educ Pract* 2010;10:13–16.
61. Phaswana-Mafuya N, Peltzer K, Chirinda W, *et al*. Self-reported prevalence of chronic non-communicable diseases and associated factors among older adults in South Africa. *Glob Health Action* 2013;6:20936.
62. Twisk JW. Longitudinal data analysis. a comparison between generalized estimating equations and random coefficient analysis. *Eur J Epidemiol* 2004;19:769–76.
63. Twisk J, de Boer M, de Vente W, *et al*. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. *J Clin Epidemiol* 2013;66:1022–8.
64. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent* 2014;81:14–18.

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Health Research Ethics Committee (HREC)

Approval Notice

New Application

16/05/2018

Project ID : 0913

HREC Reference #: M17/09/031

Title: Patient-centred lifestyle rehabilitation for management of non-communicable disease in a low-resource setting: a randomized pilot study

Dear Dr Martin Heine,

The **Response to Deferral** received on 13/04/2018 10:48 was reviewed at a convened meeting of **Health Research Ethics Committee 2 (HREC2)** on 16/05/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your **Project ID [0913]** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/913

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Francis Masiye ,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

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Amendment Approval Letter

12/09/2018

Project ID: 0913

Ethics Reference #: M17/09/031

Title: Patient-centred lifestyle rehabilitation for non-communicable disease in a low-resource setting: a feasibility and proof-of-concept randomized clinical trial

Dear Dr Martin Heine ,

Your amendment request and the response to the requested modifications dated 12 September 2018 refer.

The Health Research Ethics Committee (HREC) reviewed and approved the amended documentation through an expedited review process.

The following amendments were reviewed and approved:

1. Amended Protocol Version 3 Dated 28 August 2018
2. Translated Informed Consent Forms in Afrikaans (part 1 and 2)
3. Health Passport
4. Addition of Mrs Brittany Fell to the Research Team as a Sub-Investigator (Research Assistant).

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your **Project ID [0913]** and ethics reference number **[M17/09/031]** on any documents or correspondence with the HREC concerning your research protocol.

National Health Research Ethics Council (NHREC) Registration Numbers: REC-130408-012 for HREC1 and REC-230208-010 for HREC2

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005240 for HREC1

Institutional Review Board (IRB) Number: IRB0005239 for HREC2

The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Department of Health).

Yours sincerely,

Francis Masiye,

Coordinator,

Health Research Ethics Committee 2 (HREC2).

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Approval Letter
Progress Report

20/02/2019

Project ID: 0913

Ethics Reference #: M17/09/031

Title: Patient-Centred Rehabilitation for non-communicable disease in a Low-Resource Setting: a feasibility and proof-of-concept randomized clinical trial

Dear Dr Martin Heine,

Your request for extension/annual renewal of ethics approval dated 06/02/2019 12:44 refers.

The Health Research Ethics Committee (HREC) reviewed and approved the annual progress report you submitted at a convened meeting of HREC2 on 20 February 2019.

The approval of this project is extended for a further year.

Approval date: 20 February 2019

Expiry date: 19 February 2020

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your **Project ID [0913]** and Ethics Reference Number **[M17/09/031]** on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

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Approval Letter
Amendment

17/09/2019

Project ID: 0913

Ethics Reference No: M17/09/031

Project Title: Patient-centred lifestyle rehabilitation for non-communicable disease in a low-resource setting: a feasibility and proof-of-concept randomized clinical trial

Dear Dr Martin Heine,

Your amendment request dated 11 September 2019 refers.

The Health Research Ethics Committee (HREC) reviewed and approved the amended documentation through an expedited review process.

The following amendments were reviewed and approved:

1. Amended DEF_protocol version 3.0 dated 11 September 2019
2. Additions of Dr Mumtaz Abbas as co-investigator and Miss Ashleigh Robinson as a Research Assistant (Physiotherapist) to the study team.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project ID **[0913]** andethics reference number **[M17/09/031]** on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African *Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition)*; as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

Western Cape Government
Health

Health impact Assessment
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www.capegateway.gov.za)

REFERENCE: WC_201806_027
ENQUIRIES: Dr Sabela Petros

Stellenbosch University

Tygerberg Campus

Francie Van Zijl Drive

Parow Valley

Cape Town

7305

For attention: Dr Martin Heine, Prof Susan Hanekom, Prof Wayne Derman

Re: **Patient-Centred Lifestyle Rehabilitation for Non-Communicable Disease in A Low-Resource Setting: A Feasibility and Proof-of-Concept Randomized Clinical Trial**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following person to assist you with any further enquiries in accessing the following site:

Bishop Lavis CDC	**Rachel Carelse**	**021 934 6051**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. By being granted access to provincial health facilities, you are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of your project. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR J EVANS

ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 2016/10/12

BISHOP study - version 44.37

Printed on 04-12-2020 11:22:44 by Martin Heine

1. Inclusion - Inclusion

Number	Question	Answers
1.1	Please provide todays date:	☐☐ ☐☐ ☐☐☐☐ *(dd-mm-yyyy)*
1.2	Date of Birth	☐☐ ☐☐ ☐☐☐☐ *(dd-mm-yyyy)*
1.3	Sex	◯ Male ◯ Female
1.4	Age *Exclude patient if field's value is smaller than 18 with message: 'Exclude patient'*	
1.5	Day hospital file available during inclusion (if applicable)?	◯ Yes ◯ No
1.6	Does the patient has one or more of the following medical conditions? (tick all that apply) *Exclude patient if field's value is equal to No with message: 'Please complete other in/exclusion criteria prior to excluding the patient from study participation'*	☐ Cardiovascular disease (ICD: I0-99) ☐ Cancer (ICD: C00-97) ☐ Chronic Respiratory Disease (ICD:J30-98) ☐ Diabetes (E10-E14; excluding those with complications) ☐ No
1.6.1	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Cardiovascular disease (ICD: I0-99)' answer this question:*** Please specify the Cardiovascular Disease	0 / 1 / 2 / 3 / 4 CVD 1 --- ☐ ☐ ☐ --- CVD 2 --- ☐ ☐ ☐ --- CVD 3 --- ☐ ☐ ☐ --- Row Number 4 --- ☐ ☐ ☐ ---
1.6.2	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Chronic Respiratory Disease (ICD:J30-98)' answer this question:*** Please specify the Chronic Respiratory Disease	0 / 1 / 2 / 3 CRD 1 --- ☐ ☐ ☐ CRD 2 --- ☐ ☐ ☐ CRD 3 --- ☐ ☐ ☐ Row Number 4 --- ☐ ☐ ☐
1.6.3	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Cancer (ICD: C00-97)' answer this question:*** Please specify the Cancer	0 / 1 / 2 / 3 / 4 Cancer 1 --- ☐ ☐ ☐ --- Cancer 2 --- ☐ ☐ ☐ --- Cancer 3 --- ☐ ☐ ☐ --- Row Number 4 --- ☐ ☐ ☐ ---
1.6.4	***If 'Does the patient has one or***	0 / 1 / 2 / 3

	more of the following medical conditions? (tick all that apply)' is equal to 'Diabetes (E10-E14; excluding those with complications)' answer this question: Please specify the Diabetes	Diabetes ---
1.7	Is the patient able to perform in some weight-bearing or non-weight-bearing exercise? *Exclude patient if field's value is equal to No with message: 'Please complete other in/exclusion criteria prior to excluding the patient from study participation'*	◯ Yes ◯ No

2. Inclusion - Exclusion

Number	Question	Answers
2.1	***If 'Sex' is equal to 'Female' answer this question:*** Is the patient currently pregnant? *Exclude patient if field's value is equal to Yes with message: 'Please complete other in/exclusion criteria prior to excluding the patient from study participation'*	◯ Yes ◯ No
2.2	Did the patient engage in structured exercise training at regular intervals (more than once per week) at a moderate-to-vigorous intensity in the previous 3 months? *Exclude patient if field's value is equal to Yes with message: 'Please complete other in/exclusion criteria prior to excluding the patient from study participation'*	◯ Yes ◯ No
2.3	Are there strict contraindications for physical activity participation?	☐ No ☐ Recent (2 days) significant ischemia, myocardial infarction, or other acute cardiac event ☐ Unstable angina ☐ Uncontrolled cardia dysrhythmias causing symptom or hemodynamic compromise ☐ Symptomatic severe aortic stenosis ☐ Uncontrolled symptomatic heart failure ☐ Acute myocarditis or pericarditis
2.4	Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?	☐ Electrolyte abnormalities ☐ Severe arterial hypertension (SBP > 200mmHg and/or DBP > 110 mmHg) at rest ☐ Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise ☐ Physical impairment leading to inability to exercise adequately ☐ Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands ☐ Uncontrolled metabolic disease (e.g. diabetes, thyrotoxicosis, or myxoedema) ☐ Chronic infectious disease (e.g. mononucleosis, hepatitis, AIDS) ☐ Left main coronary stenosis ☐ Moderate stenotic valvular heart disease ☐ Tachydysrhytmia or bradydysrythmia ☐ Hyperthrophic cardiomyopathy and other forms of outflow tract obstruction ☐ Acute pulmonary embolus or pulmonary infection ☐ Suspected or known dissecting aneurysm ☐ Mental impairment leading to inability to exercise adequately (i.e. neglect, aphasia, severe depression)
2.4.1	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Electrolyte abnormalities' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.2	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Severe arterial hypertension (SBP > 200mmHg and/or DBP > 110 mmHg) at rest' answer this question:***	◯ Yes ◯ No

Warrants exclusion?

2.4.3	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.4	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Physical impairment leading to inability to exercise adequately' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.5	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.6	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncontrolled metabolic disease (e.g. diabetes, thyrotoxicosis, or myxoedema)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.7	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Chronic infectious disease (e.g. mononucleosis, hepatitis, AIDS)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.8	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Left main coronary stenosis' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.9	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Moderate stenotic valvular heart disease' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.10	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Tachydysrhytmia or bradydysrythmia' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.11	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Hyperthrophic cardiomyopathy and other forms of outflow tract obstruction' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.12	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Acute pulmonary embolus or pulmonary infection' answer this question:***	◯ Yes ◯ No

	Warrants exclusion?	
2.4.13	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Chronic infectious disease (e.g. mononucleosis, hepatitis, AIDS)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.14	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Suspected or known dissecting aneurysm' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.4.15	***If 'Based on your clinical opinion, are any of the following general contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Mental impairment leading to inability to exercise adequately (i.e. neglect, aphasia, severe depression)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Cardiovascular disease (ICD: I0-99)' answer this question:*** Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?	☐ Uncontrolled hypertension (ie. SBP > 180 and/or DBP > 110) at rest ☐ Orthostatic BP drop > 20 mmHg with symptoms ☐ Acute systemic illness or fever ☐ Uncontrolled diabetes mellitus ☐ Other metabolic conditions such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia. ☐ Critical aortic stenosis (ie. peak SBP gradient of >50 mmHg with an aortic valve orifice area of <0.74cm2 in an average size adult) ☐ Uncontrolled atrial or ventricular dysrythmias ☐ Uncontrolled sinus tachycardia (>120bpm) ☐ Uncompensated chronic heart failure ☐ Third degree atrioventricular (AV) block without pacemaker ☐ Active pericarditis or myocarditis ☐ Resting ST-segment depression or elevation (>2mm) ☐ Recent embolism ☐ Thrombophlebitis
2.5.1	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncontrolled hypertension (ie. SBP > 180 and/or DBP > 110) at rest' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.2	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Orthostatic BP drop > 20 mmHg with symptoms' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.3	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Acute systemic illness or fever' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.4	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncontrolled diabetes***	◯ Yes ◯ No

	mellitus' answer this question: Warrants exclusion?	
2.5.5	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Other metabolic conditions such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia.' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.6	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Critical aortic stenosis (ie. peak SBP gradient of >50 mmHg with an aortic valve orifice area of <0.74cm2 in an average size adult)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.7	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncontrolled atrial or ventricular dysrythmias' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.8	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncontrolled sinus tachycardia (>120bpm)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.9	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Uncompensated chronic heart failure' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.10	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Third degree atrioventricular (AV) block without pacemaker' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.11	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Active pericarditis or myocarditis' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.12	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Resting ST-segment depression or elevation (>2mm)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.13	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Recent embolism' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.5.14	***If 'Based on your clinical opinion, are any of the following CVD-specific contraindications for physical activity participation present that warrant exclusion from this study?' is equal to 'Thrombophlebitis' answer this question:*** Warrants exclusion?	◯ Yes ◯ No

2.6	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Cancer (ICD: C00-97)' answer this question:*** Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?	☐ Severe tissue reaction to radiation therapy ☐ Platelets <50000 ☐ White blood cells < 3000 ☐ Haemoglobin < 10 mg/dl ☐ Bone, back or neck pain of recent origin ☐ Unusual muscular weakness ☐ Severe cachexia ☐ Unusual / extreme fatigue ☐ Poor functional status ☐ Acute infections ☐ Febrile illness: fever > 38 degrees ☐ General malaise ☐ Resting SBP > 145mmHg and/or DBP > 95 mmHg ☐ Severe nausea ☐ Vomiting or diarrhea within 24-36 hours ☐ Dehydration ☐ Poor nutrition: inadequate fluid and/or food intake ☐ Chest pain ☐ Resting HR > 100bpm or < 50bpm ☐ Irregular heart rate ☐ Swelling of ankles ☐ Severe dyspnea ☐ Cough, wheezing ☐ Chest pain increased with deep breath ☐ Significant decline in cognitive status ☐ Dizziness / light headedness ☐ Disorientation ☐ Blurred vision ☐ Ataxia (ie. inability to coordinate voluntary movement)
2.6.1	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Severe tissue reaction to radiation therapy' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.2	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Platelets <50000' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.3	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'White blood cells < 3000' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.4	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Haemoglobin < 10 mg/dl' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.5	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Bone, back or neck pain of recent origin' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.6	***If 'Based on your clinical opinion, are any of the following Cancer-***	◯ Yes

	specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Unusual muscular weakness' answer this question: Warrants exclusion?	◯ No
2.6.7	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Severe cachexia' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.8	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Unusual / extreme fatigue' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.9	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Poor functional status' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.10	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Acute infections' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.11	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Febrile illness: fever > 38 degrees' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.12	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'General malaise' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.13	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Resting SBP > 145mmHg and/or DBP > 95 mmHg' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.14	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Severe nausea' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.15	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Vomiting or diarrhea within 24-36 hours' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.16	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Dehydration' answer this question:*** Warrants exclusion?	◯ Yes ◯ No

2.6.17	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Poor nutrition: inadequate fluid and/or food intake' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.18	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Chest pain' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.19	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Resting HR > 100bpm or < 50bpm' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.20	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Irregular heart rate' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.21	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Swelling of ankles' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.22	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Severe dyspnea' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.23	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Cough, wheezing' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.24	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Chest pain increased with deep breath' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.25	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Significant decline in cognitive status' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.26	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Dizziness / light headedness' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.27	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Disorientation' answer this question:***	◯ Yes ◯ No

	Warrants exclusion?	
2.6.28	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Blurred vision' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.6.29	***If 'Based on your clinical opinion, are any of the following Cancer-specific contraindications or physical activity participation present that warrant exclusion from this study?' is equal to 'Ataxia (ie. inability to coordinate voluntary movement)' answer this question:*** Warrants exclusion?	◯ Yes ◯ No
2.7	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Diabetes (E10-E14; excluding those with complications)' answer this question:*** Is there a presence of uncontrolled diabetes (i.e. blood glucose > 250 mmol and presence of ketones; or HbAC1 > 7.0%)	◯ Yes ◯ No
2.8	Is there a known history of psychiatric disorders, substance abuse or violence that would jeopardize the safe conduct of this program? *Exclude patient if field's value is equal to Yes with message: 'Please complete other in/exclusion criteria prior to excluding the patient from study participation'*	◯ Yes ◯ No
2.9	Based on your clinical opinion, are there any other reasons for this patient not to participate in this study?	

3. Inclusion - Consent 1

Number	Question	Answers
3.1	Please confirm that the patient has met the in / exclusion criteria *Exclude patient if field's value is equal to No with message: 'Exclude patient'*	◯ Yes ◯ No
3.2	Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)	◯ Yes ◯ No
3.3	Version:	◯ V1 (Afrikaans) ◯ V1 (English)
3.2.1	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** Surname	
3.2.2	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** First name	
3.2.3	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** Primary contact number	
3.2.4	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** Emergency contact	
3.2.5	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** Email (if available)	
3.2.6	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** WCDOH file number	
3.2.7	***If 'Please confirm that oral and written consent to the observational part of this study have been obtained (consent 1)' is equal to 'Yes' answer this question:*** Address	

30. Follow-up 2 (16 weeks) - Testing conditions

Number	Question	Answers
30.1	Temperature in hour before assessment	[ ] Degrees Celcius
30.2	Rain forecast in hour prior to assessment	[ ] mm
30.3	Test setting for 6MWT and SSST	◯ Inside ◯ Outside
30.4	How busy is the test site during time of visit?	Dead quiet (0.00) ... Extremely busy (10.00)

31. Follow-up 2 (16 weeks) - Physical Examination

Number	Question	Answers
31.1	Body weight?	Kg
31.2	Height?	cm
31.3	Body Mass Index:	
31.4	Waist circumference	cm
31.5	Hip circumference	cm
31.6	Waist to Hip ratio	
31.7	WHR chart	
	Resting blood pressure and heart rate; Please have the patient seated, in rest, for 5 minutes prior to assessment	
31.8	Cuff size used?	○ XS ○ S ○ M ○ L ○ XL
31.9	Blood pressure and resting heart rate	**0** **1** **2** Reading 1 Reading 2 Reading 3
31.10	***If 'Does the patient has one or more of the following medical conditions? (tick all that apply)' is equal to 'Diabetes (E10-E14; excluding those with complications)' answer this question:*** Blood glucose concentration	
	Lung spirometry	
	Using the MicroLab Spirometer, three attempts for Forced Maximal Expiratory capacity are made. From that, FEV1 and FVC can be calculated. During each attempt, the subject is seated. In patients with diagnosed COPD, assessment are made post bronchodilator if applicable..	
31.11	Lung spirometry	**0** **1** **2** Attempt 1 Attempt 2 Attempt 3

32. Follow-up 2 (16 weeks) - 6MWT(4)

Number	Question	Answers
	Make sure you have the following equipment ready: HR monitor, Stopwatch, Clipboard with BORG scale and scoring form, a chair, and portable oxygen if needed.	
32.1	6MWT lap distance	◯ 10 meter normal ◯ 10 meter f8 ◯ 30 meter ATS
32.2	Does the patient use a walking aid during the 6MWT?	◯ Cane (Left) ◯ Cane (Right) ◯ Two canes ◯ Orthosis / Brace (Left) ◯ Orthosis / Brace (Right) ◯ Orthosis / Brace (Left and Right) ◯ Walker ◯ None
32.3	Six minute walk test 1	0 / 1 Time Heart Rate Dyspnea (BORG) Fatigue (BORG) SpO2 (%)
32.4	Stopped or paused before 6 minutes?	◯ Yes ◯ No
32.4.1	***If 'Stopped or paused before 6 minutes?' is equal to 'Yes' answer this question:*** Stopped or paused?	☐ Stopped before 6 minutes, not continued ☐ Paused and continued
32.4.2	***If 'Stopped or paused before 6 minutes?' is equal to 'Yes' answer this question:*** Provide reason for stopping or pausing during 6 minutes:	
32.5	Distance walked *Warning shown if field's value is larger than or equal to 600: 'High value for patients with NCD, please check'*	
32.6	Other symptoms at end of exercise	☐ angina ☐ dizziness ☐ hip, leg or calf pain

33. Follow-up 2 (16 weeks) - Six-Spot Step Test

Number	Question	Answers
33.1	SSST	
33.2	Does the patient use a walking aid during the SSST?	◯ Cane (Left) ◯ Cane (Right) ◯ Two canes ◯ Orthosis / Brace (Left) ◯ Orthosis / Brace (Right) ◯ Orthosis / Brace (Left and Right) ◯ Walker ◯ None
33.3	Six Spot Step Test	**0** **1** Run 1 (seconds; two decimals) [ ] [ ] Run 2 (seconds; two decimals) [ ] [ ]

34. Follow-up 2 (16 weeks) - Timed Up & Go Test

Number	Question	Answers
	Patients wear their regular footwear and can use a walking aid if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters. Instructions to the patient: When I say “Go,” I want you to: 1. Stand up from the chair 2. Walk to the line on the floor at your normal pace 3. Turn 4. Walk back to the chair at your normal pace 5. Sit down again	
34.1	Does the patient use a walking aid during the TUG test?	◯ Cane (Left) ◯ Cane (Right) ◯ Two canes ◯ Orthosis / Brace (Left) ◯ Orthosis / Brace (Right) ◯ Orthosis / Brace (Left and Right) ◯ Walker ◯ None
34.2	Practice run	[ ] seconds (2 decimals)
34.3	Run 1	[ ] seconds (2 decimals)
34.4	Run 2	[ ] seconds (2 decimals)

35. Follow-up 2 (16 weeks) - Questionnaire 1: IPAQ

Number	Question	Answers		
	We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport. Please answer each question even if you do not consider yourself to be an active person. In answering the following questions, vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.			
35.1	During the past 7 days	**0**	**1**	**2**
	How many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?	---		
	How many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.	---		
	How many days did you walk for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking	---		

		that you did solely for recreation, sport, exercise or leisure.
	The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.	
35.2	4. During the last 7 days, how much time in total did you usually spend sitting on a week day?	[Hours.Minutes] / per day

36. Follow-up 2 (16 weeks) - Questionnaire 2: PSQI

Number	Question	Answers
36.1	When have you usually gone to bed?	: *(hh:mm)*
36.2	How long (in minutes) has it taken you to fall asleep each night?	Minutes
36.3	What time you usually gotten up in the morning?	: *(hh:mm)*
36.4	How many hours of actual sleep did you get at night?	: *(hh:mm)*
36.5	How many hours were you in bed?	: *(hh:mm)*
	During the past month, how often have you had trouble sleeping because you	
36.6	A. Cannot get to sleep within 30 minutes	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.7	B. Wake up in the middle of the night or early morning	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.8	C. Have to get up to use the bathroom	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.9	D. Cannot breathe comfortably	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.10	E. Cough or snore loudly	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.11	F. Feel too cold	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.12	G. Feel too hot	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.13	H. Have bad dreams	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.14	I. Have pain	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.15	J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.15.1	***If 'J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):' is not equal to 'Not during the past month' answer this question:*** Describe other	
36.16	During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	Not during the past month / Less than once a week / Once or twice a week / Three or more times a week
36.17	During the past month, how often have you had trouble staying awake while	Not during the past month / Less than once a week

	driving, eating meals, or engaging in social activity?	◯ Once or twice a week ◯ Three or more times a week
36.18	During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
36.19	During the last month, how would you rate the quality of your sleep overall?	◯ Very good ◯ Fairly good ◯ Fairly bad ◯ Very bad

37. Follow-up 2 (16 weeks) - Questionnaire 3: EQ-5D

Number	Question	Answers
37.1	I have .... in walking about.	◯ no problems ◯ slight problems ◯ moderate problems ◯ severe problems ◯ unable
37.2	I have .... washing or dressing myself	◯ no problems ◯ slight problems ◯ moderate problems ◯ severe problems ◯ unable
37.3	I have ... doing my usual activities	◯ no problems ◯ slight problems ◯ moderate problems ◯ severe problems ◯ unable
37.4	I have .... pain or discomfort.	◯ No ◯ Slight ◯ Moderate ◯ Severe ◯ Extreme
37.5	I am ... anxious or depressed	◯ no ◯ slightly ◯ moderately ◯ severely ◯ extremely
37.6	EQ5D - General health	
37.7	General Health	The worst health you can imagine (0.00) — The best health you can imagine (100.00)

38. Follow-up 2 (16 weeks) - Health Economics

Number	Question	Answers
38.1	Do you have one of the following types of medical insurance?	◯ I don't have medical insurance ◯ Basic hospital plan ◯ Extended hospital plan with benefits ◯ Other

38.2 Please list any use of <inpatient> hospital services over the last 2 months.

	0	1	2	3
Acute psychiatric ward				
Psychiatric rehabilitation ward				
Long-stay ward				
Emergency / crisis centre				
General medical ward				
Other (1)				
Other (2)				
Other (3)				
Other (4)				
Other (5)				

38.3 Please list any use of < outpatient> hospital services over the last 2 months.

	0	1	2	3	4	5
Physician (e.g. cardiologist)						
Physiotherapist						
Occupational Therapist						
Speech Therapist						
Dietist						
Other (1)						
Other (2)						
Other (3)						
Other (4)						
Other (5)						

38.4 Please list any drugs taken of the past one month

	0	1	2	3
Row Number 1				---
Row Number 2				---
Row Number 3				---
Row Number 4				---
Row Number 5				---
Row Number 6				---
Row Number 7				---
Row Number 8				---
Row Number 9				---
Row Number 10				---

38.5 In order to pay out of pocket expenses (if applicable) related to your illness in the past 2

- ☐ Mobilize savings
- ☐ Reduce consumption (e.g. food)
- ☐ Sale of assets
- ☐ Borrow (e.g. from family)
- ☐ Engage in other activities than normal work to diversify income

	months, have you used any of the following strategies?	
	Productivity cost questionnaire (https://www.imta.nl)	
38.6	Do you have paid work?	◯ Yes ◯ No
38.6.1	***If 'Do you have paid work?' is equal to 'No' answer this question:*** Were you, because of your illness, unable to seek employment?	◯ Yes ◯ No
38.6.2	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** Does this work entail a formal contract with an employer?	◯ Yes ◯ No
38.6.3	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** What is your occupation?	
38.6.4	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** How many hours a week do you work? Count only the hours that you get paid.	
38.6.5	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** How many	

	days a week do you work?	
38.6.6	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** Have you missed work in the last 4 weeks as a result of being sick?	◯ Yes ◯ No
38.6.6.1	***If 'Have you missed work in the last 4 weeks as a result of being sick?' is equal to 'Yes' answer this question:*** If yes, how many days of work have you missed?	
38.6.7	***If 'Do you have paid work?' is equal to 'Yes' answer this question:*** During the last 4 weeks have there been days in which you worked but during this time were bothered by physical or psychological problems?	◯ Yes ◯ No
38.6.7.1	***If 'During the last 4 weeks have there been days in which you worked but during this time were bothered by physical or psychological problems?' is equal to 'Yes' answer this question:*** How many days at work	

	were you bothered by physical or psychological problems? (Only count the days at work in the last 4 weeks)		
38.6.7.2	***If 'During the last 4 weeks have there been days in which you worked but during this time were bothered by physical or psychological problems?' is equal to 'Yes' answer this question:*** On the days that you were bothered by these problems, was it perhaps difficult to get as much work finished as you normally do? On these days how much work could you do on average? Look at slider below. A 10 means that you were able to do as much work as you normally do. A 0 means that you were unable to do any work on these days. Select the number that fits best.	On these days I could not do anything (0.00)	I was able to do just as much as I normally do (10.00)

Explanation Even for unpaid work, you can be bothered by physical or psychological problems. Sometimes as a result you (might) do less. For example you have trouble caring for your children or doing voluntary work. Or you are unable to run errands and pick up groceries, or to work in the garden. The following questions refer to this.

38.7	Were there days in which you were forced to do less unpaid	◯ Yes ◯ No

	work because of physical or psychological problems? Only days in the last four weeks.	
38.7.1	***If 'Were there days in which you were forced to do less unpaid work because of physical or psychological problems? Only days in the last four weeks.' is equal to 'Yes' answer this question:*** How many days did this happen? Only count the days in the last 4 weeks.	
38.7.2	***If 'Were there days in which you were forced to do less unpaid work because of physical or psychological problems? Only days in the last four weeks.' is equal to 'Yes' answer this question:*** Imagine that somebody, for example your partner, family member or friend helped you on these days, and he or she did all the unpaid work that you were unable to do for you. How many hours on average did that person spend doing	

	this on these days?	
38.8	In the past 4 weeks, did a family member or friend have to stop or reduce usual work / activities to provide care to you?	◯ Yes ◯ No
38.8.1	***If 'In the past 4 weeks, did a family member or friend have to stop or reduce usual work / activities to provide care to you?' is equal to 'Yes' answer this question:*** If yes, what type of work was foregone?	
38.8.2	***If 'In the past 4 weeks, did a family member or friend have to stop or reduce usual work / activities to provide care to you?' is equal to 'Yes' answer this question:*** How many days did the member or a friend above stop or reduce usual work / activities to provide care to your?	

39. Follow-up 2 (16 weeks) - 6MWT(5)

Number	Question	Answers
	Make sure you have the following equipment ready: HR monitor, Stopwatch, Clipboard with BORG scale and scoring form, a chair, and portable oxygen if needed.	
39.1	6MWT lap distance	◯ 10 meter normal ◯ 10 meter f8 ◯ 30 meter ATS
39.2	Does the patient use a walking aid during the 6MWT?	◯ Cane (Left) ◯ Cane (Right) ◯ Two canes ◯ Orthosis / Brace (Left) ◯ Orthosis / Brace (Right) ◯ Orthosis / Brace (Left and Right) ◯ Walker ◯ None
39.3	Six minute walk test 2	0 / 1 Time Heart Rate Dyspnea (BORG) Fatigue (BORG) SpO2 (%)
39.4	Stopped or paused before 6 minutes?	◯ Yes ◯ No
39.4.1	***If 'Stopped or paused before 6 minutes?' is equal to 'Yes' answer this question:*** Stopped or paused?	☐ Stopped before 6 minutes, not continued ☐ Paused and continued
39.5	***If 'Stopped or paused before 6 minutes?' is equal to 'Yes' answer this question:*** Provide reason for stopping or pausing during 6 minutes:	
39.6	Distance walked *Warning shown if field's value is larger than or equal to 600: 'High value for patients with NCD, please check'*	
39.7	Other symptoms at end of exercise	☐ angina ☐ dizziness ☐ hip, leg or calf pain

40. Follow-up 2 (16 weeks) - Notes

Number	Question	Answers
40.1	Notes	

41. Adverse events (Treatment) - Log (S)AE

Number	Question	Answers
41.1	(Serious) Adverse Events	

42. Adverse events (Assessments) - Log (S)AEs

Number	Question	Answers
42.1	(Serious) Adverse Events	

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT: Patient-centred lifestyle rehabilitation for non-communicable disease in a low-resource setting

REFERENCE NUMBER:

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You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

This study will take place at the Bishop Lavis Clinic and Rehabilitation Centre over the course of one year. We anticipate that during that year, approximately 200 patients will be recruited to participate in this study.

For this study we're are looking for patients with one (or more) of the following medical conditions: cardiovascular disease, cancer, diabetes and/or chronic respiratory disease. These conditions are also referred to as "diseases of lifestyle" and often related to low levels of physical activity, poor nutrition, or other poor lifestyle habits like smoking and/or alcohol use. The Bishop Lavis Clinic provides routine medical care and additional education sessions to assist patients in managing their medical condition. Up to date, we don't know if patients benefit, for instance in terms of mobility or quality of life, from these usual care services provided at the Bishop Lavis Clinic. The aim of this study is therefore to evaluate the routine services provided at the Bishop Lavis Clinic for the long-term management of these medical conditions.

You will be asked to undergo a variety of tests: walking tests, a physical examination, as well as answer questionnaires about your health and quality of life. You will be required to do this three times: at the beginning, after 8 weeks, and after 16 weeks. By repeating these tests, we can better understand if and how the services offered at Bishop Lavis benefit you as a patient or where these services may be improved. What do these tests look like?

- Walking tests: The physical tests are all related to walking and your ability to move. We think your ability to move from A to B is very relevant for living in the Bishop Lavis community, as well as to your health. The following tests are included: a 6-minute walking test, the timed up-and-go test, and the six-spot-step-test. Each of these tests approaches walking/mobility slightly different. If you use a walking aid, you can use this during these tests as well. A research assistant will conduct the tests and make sure the testing-environment is safe.
    - For the 6-minute walk test you will be wearing a heart-rate monitor. Over the course of 6 minutes you will be asked to walk as far as possible at a safe walking speed. We will use a quiet hallway with two pylons spaced 30 meters apart. You can take a rest in between if needed. At the end of the test you will be asked to give a score for how tired you were after walking these 6 minutes and we record the total distance you've walked.
    - For the timed up-and-go test, you will be seated in a chair with arm-rests. When the assessor signals "go", you will get up out of the chair and walk a short 5-meter stretch as fast and safely as possible. We will record your best time out of three attempts.
    - For the six-spot-step-test, you will be asked to walk 5 meters. However, during those 5 meters you will asked to kick away small wooden blocks that are placed on the ground. First with your left leg, and then again with your right leg. An assessor will demonstrate this to you first. We will record your best time for each leg out of three attempts.
- Physical examination: During the physical examination we measure your height, body weight, waist circumference, resting blood pressure, resting heart rate, and lung function. All these tests are without risk and harm (i.e. no needles etc.). For the lung function test, you will need to breath in and out very deeply into a small device. You may feel a bit out of breath following the lung function test. We expect the walking tests and physical examination to take about 45 minutes.
- Questionnaires: You will be asked to answer range of questions regarding you and where you live, your medical condition, about your daily life and lifestyle, how you feel about the quality of your life, and how physically active you are. We also ask you to report any visits to the hospital or other medical professionals during the period preceding the visit with the researcher. The researcher can assist you if necessary or if you are uncertain on how to answer a question. All information will be treated as confidential. We expect that completing all questions will take about 45 minutes as well.
- Once all of this is done, testing is complete!

Why have you been invited to participate?

You have been invited because you are 18 years or older and diagnosed with one or more of the four major non-communicable disease: cardiovascular disease, cancer,

chronic respiratory disease or diabetes. Your physician at the Bishop Lavis Day Clinic has cleared you to participate in this study.

What will your responsibilities be?

Your responsibility is to attend the three scheduled assessments with the research assistant over this 16 week period, to answer all questions to the best of your ability, and to bring forward any adverse events that happened during 16 week period.

Will you benefit from taking part in this research?

There is no direct short-term benefit for you in participating in this study. The various assessments may provide you with more information and knowledge regarding your medical condition and general health. For each completed assessment, you will receive a token of appreciating worth R100 to a maximal of R300 in total.

Are there in risks involved in your taking part in this research?

- **Medical emergencies:** Unexpected medical emergencies (collapse, fainting, injury during testing)
- **Testing related risks:** Fall, shortness of breath
- All of these risks will be minimized as much as possible, and treated on-site if they happen. All testing is done in a medical environment, and medical personnel will be on site to assist if necessary. Patients with unstable and high-risk medical conditions are excluded from this study.

If you do not agree to take part, what alternatives do you have?

If you do not agree to take part, you will continue to receive care as usual.

Who will have access to your medical records?

- The information collected in this study will be treated as confidential and will be stored in password protected computers and back-up drives. When your information is exported from our data sheets for analysis, you will receive a number and your name will be deleted, to further protect your identity.
- When this study is published, no identifying information will be included in the publication.
- Only the testing team will have access to your information.
- If, for some reason, this research is inspected by co-investigators, ethics committee members or auditors, no identifying information will be included.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

This study is covered by Stellenbosch University's no-fault insurance policy. There is a qualified medical doctor part of the study team who will address injury occurring during testing. Injuries or adverse events are considered due to the study if they occur during testing and the investigator is informed of the injury during the testing session. If an injury occurs, you are asked to seek medical attention first and then contact Dr. Heine immediately so that your injury can be recorded for insurance purposes, according to ABPI guidelines.

Will you be paid to take part in this study and are there any costs involved?

For each completed assessment, you will receive a token of appreciating worth R100 to a maximal of R300 in total.

Is there any thing else that you should know or do?

- We may invite you to an additional part of this research project. If this is the case, this will be explained to you in detail at that stage. If you decline this addition, this will not affect your routine medical care of your participation in this part of the research.
- You can contact [RESEARCH ASSISTANT] if you have any further queries or encounter any problems.
- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled “Patient-centred lifestyle rehabilitation for non-communicable disease in a low-resource setting”

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be invited to an additional part of this research project to be explained later if applicable. I can decline participation in in this additional part without it affecting my routine medical care, or my participation in this section of the research project.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…….…….. on (*date*) ……..…….. 20__.

.....	.....
Signature of participant	**Signature of witness**

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If a interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 20__.

.....	.....
Signature of investigator	**Signature of witness**

Addendum G: Afrikaans 6MWT Instructions

INSTRUKSIE TEKS (Gebruik 'n egalige toon)

AANVANKLIKE INSTRUKSIE: "Die doel van hierdie toets is om so ver as moontlik te stap vir 6 minute. Jy gaan op en af loop in die gang. Ses minute is 'n lang tyd so jy gaan hoe vereistes stel aan jou liggaam. Jy sal waarskynlik moeg en uitasem word. Jy mag enige tyd stadiger loop, of heeltemal stop en rus as dit nodig is. Jy kan teen die muur leun om te rus maar begin weer loop sodra jy kan. Jy gaan heen en weer om die twee bakens loop. Ek gaan die hele tyd agter jou loop om seker te maak dat jy veilig is. Loop flink om elke baken en keer dan terug sonder om te huiwer. Nou gaan ek jou wys. Kyk asb na die manier waarop ek draai sonder om te huiwer.

Demontreer aan die pasient deur een rondte te stap. Veral die draai om die bakens is belangrik. **GAAN VOORT** "Is jy gereed om dit te doen? Ek gaan hierdie horlosie gebruik om die rondtes te tel wat jy voltooi. Ek gaan hierdie knoppie druk elke keer as jy om die eerste baken gaan. Onthou die doel is om so ver as moontlik vir 6 minute te loop, maar moenie begin draf of hardloop nie. Jy kan begin sodra jy gereed is.

NA DIE EERSTE MINUUT: "Jy doen goed. Jy het 5 minute om te gaan."

4 MINUTE OOR: Hou aan met die goeie werk. Jy het 4 minute om te gaan.

3 MINUTE OOR: "Wel gedaan. Jy is nou halfpad daar

2 MINUTE OOR: Hou aan met die goeie werk. Jy het net 2 minute om te gaan. **1 MINUTE OOR:** "Jy doen goed. Net een minuut om te gaan

15 SEKONDES VOOR DIE EINDE: "Binne enkele oomblikke gaan ek jou vra om te stop. Wanneer ek dit doen wil ek he jy moet onmiddelik stop net waar jy is. Ek sal dan vir jou 'n stoel bring

INDIEN DIE PATIENT OPHOU OM TE STAP: "Jy kan teen die muur leun as jy wil; en begin dan maar net weer loop sodra jy voel jy kan. Ek kan ook vir jou 'n stoel bring om op te sit as jy wil.

DIE BORG SKAAL

0	Hoegenaamd niks
0,5	Baie, baie min (net-net merkbaar)
1	Baie gering
2	Effens (lig)
3	Gematigd
4	Effens straf
5	Straf (swaar)
6	
7	Baie straf
8	
9	
10	Baie, baie straf