School of Physiotherapy and Exercise Science

Optimising Assessment and Rehabilitation in People Hospitalised with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Fatim Tahirah Mirza Mohd Tahir Beg

This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

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Fatim Tahirah Mirza Mohd Tahir Beg

Date: 04/04/2016

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy at Curtin University, Western Australia. Studies were undertaken between September 2011 and April 2016, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Physiotherapy Departments at Sir Charles Gairdner Hospital (Perth), Hospital Selayang (Malaysia) and Institute of Respiratory Medicine (Malaysia), community groups in the Batu sub-district (Malaysia), and the Faculty of Health Sciences, Universiti Teknologi MARA (Malaysia).

This research project was developed in association with my supervisors who have been involved in editing both this thesis and all associated publications. All material presented in this thesis is original.

ABSTRACT

This doctoral research program comprised three separate prospective studies. Data collection was completed on 139 participants.

Study 1:

Two-minute walk test (2MWT): measurement properties and comparison of the cardiorespiratory and symptom responses with the six-minute walk test (6MWT) in people with moderate to severe chronic obstructive pulmonary disease (COPD)

Background: Although the 6MWT is commonly used to measure functional exercise capacity in people with COPD, it does not appear to be routinely used among clinicians involved in the management of patients hospitalised with an acute exacerbation of COPD (AECOPD). This may be because clinicians consider the 6MWT to be an inefficient use of their time as the severe dyspnoea that accompanies an exacerbation results in patients often need to rest frequently, or for prolonged periods during the test. Therefore, in the context of patients who experience severe dyspnoea on exertion, such as in some of those with moderate to severe COPD who are clinically stable or in those who are hospitalised for an AECOPD, the 2MWT may be an appropriate alternative to the 6MWT for assessing functional exercise capacity. However, there is a paucity of data pertaining to the measurement properties of the 2MWT and no studies have compared the cardiorespiratory responses between the 2MWT and the 6MWT. **Aims:** In people with moderate to severe COPD who experience severe dyspnoea exertion, to; (i) report the measurement properties of the 2MWT (i.e. effect of test repetition, coefficient of repeatability [COR] and validity), (ii) determine whether or not the two-minute walk distance (2MWD) is interchangeable with one third of the six-minute walk distance (6MWD) and, (iii) compare the cardiorespiratory responses and levels of symptoms elicited during the 2MWT with the 6MWT. **Methods:** Participants were recruited from patients who had been referred to the out-patient pulmonary rehabilitation program at Sir Charles Gairdner Hospital, Perth, Western Australia. All participants attended two testing sessions that were separated by a minimum of 48 hours and a maximum of 14 days. The sessions included completing three 2MWTs during the

first testing session, and one 2MWT and one 6MWT during the second testing session. **Results:** Twenty participants (nine [45%] males; age [mean ± SD] 72.5 ± 8.3yr) with moderate to severe COPD (forced expiratory volume in one second [FEV_1] 28 ± 13% predicted) completed this study. The 2MWD increased by a mean of 6m; 95% confidence interval (CI), 2m to 9m between walk 1 and walk 2, and by a mean of 4m; 95% CI, 2m to 6m between walk 2 and walk 3. When expressed as a percentage of difference from baseline, the 2MWD increased by a mean of 4%; 95% CI, 1% to 7% between walk 1 and walk 2 and a mean of 3%; 95% CI, 1% to 4% between walk 2 and walk 3. The bias and COR for the 2MWD were 1m and 14m, respectively. There was a strong linear relationship ($r = 0.67$, $p < 0.01$) between the 2MWD and the 6MWD. The participants walked 31 ± 22m (27%) further during the 2MWT than one third of the 6MWD ($p < 0.001$). Two (11%) participants rested during the 2MWT and 13 (72%) rested during the 6MWT ($p < 0.001$). Compared with data collected during the 6MWT, the 2MWT elicited significantly lower cardiorespiratory responses, demonstrated by lower peak heart rate (HR [107 ± 13bpm vs. 112 ± 15bpm]) and higher nadir percutaneous oxygen saturation (SpO_2 [86 ± 6% vs. 82 ± 7%]) and less peak dyspnoea (Borg, 4.1 ± 2.0 vs. 5.0 ± 1.8) (all $p < 0.05$). **Discussion and conclusions:** The 2MWT had a very small learning effect which appears to be smaller than the learning effect for the 6MWD reported in previous studies. Therefore, a practice walk for the 2MWT may be less important and may not be necessary in people who may not be able to complete two 2MWTs within a day. The COR of 14m indicates that clinicians can be 95% confident that a difference of greater than 14m in response to an intervention is likely to represent a 'true' change in this outcome as it exceeds measurement error and the natural variability inherent in this test. The strong relationship between the 2MWD and the 6MWD supports the concurrent validity of the 2MWT as a measure of functional exercise capacity. The finding that the participants walked significantly further during the 2MWT than one third of the 6MWD indicates that these two values are not interchangeable. This information is particularly important for clinicians who evaluate the effect of an intervention (e.g. exercise program) using the 6MWT at baseline and are tempted to use the 2MWT on completion of the program in patients who develop an exacerbation or because the clinicians are under time pressure. Even though the 6MWT is three times as long as the 2MWT, comparing one third of the distance walked during the 6MWT performed at baseline with the 2MWD measured

post-intervention will lead to an over-estimation of the effects of the intervention on this outcome. The findings that a smaller proportion of participants rested during the 2MWT compared with the 6MWT and the 2MWT elicited a lower peak HR, less oxygen desaturation and lower peak dyspnoea responses compared to the responses during the 6MWT, provides some evidence that the 2MWT is better tolerated than the 6MWT in people with moderate to severe COPD.

Study 2:

Regression equations to estimate the 2MWD in Malaysian adults aged 40 to 75 years

Background: The use of the 2MWT to assess functional exercise capacity has recently risen in popularity. However, the distance achieved during the test (i.e. the 2MWD) may be difficult to interpret in the absence of normative data in a healthy local population. To date, there are only two regression equations available to estimate the 2MWD; one was derived from a sample of Brazilian adults and the other one was derived from a sample of American adults. Earlier studies that established equations to estimate the 6MWD in one ethnicity appear to be of limited accuracy in other ethnicities. Therefore, it is likely that the two equations previously published to estimate the 2MWD will be of limited accuracy in a sample of Malaysian adults. **Aim:** In Malaysian adults aged between 40 and 75 years who present with no significant disease, to (i) develop regression equations to estimate the 2MWD and, (ii) ascertain differences between the measured 2MWD with that estimated using the two previously published regression equations. **Methods:** Participants were volunteers who responded to flyers distributed in four villages located in the Batu sub-district, Gombak, Malaysia. All participants attended a single 3-hour session and completed two 2MWTs. Using a stepwise linear regression analysis, the best 2MWD was used as the dependent variable and age, gender, height, weight and change in HR (ΔHR) during the test were used as independent variables. **Results:** Eighty seven participants (43 [49%] males; age 57.1 ± 9.6yr) completed this study. The 2MWDs measured during the two consecutive 2MWTs were 193 ± 33m and 199 ± 34m, respectively, with the best 2MWD being 200 ± 34m. Males achieved a greater 2MWD compared with females (217 ± 31m vs. 184 ± 28m; $p < 0.001$). The predictor variables that explained the largest proportion of variance in the 2MWD were gender, age and ΔHR during the test. The following equation explained 73% of the

variance in 2MWD, m: 196 - (1.1 × age, yr) + (1.0 × ΔHR) + (31.2 × gender [males = 1, females = 0]). When ΔHR was excluded from the equation, age and gender explained 47% of the variance in 2MWD, m: 279 - (1.7 × age, yr) + (35.9 × gender [males = 1, females = 0]). The 2MWD estimated using the equation derived from an American sample significantly under-estimated the 2MWD measured in the sample of Malaysian adults by 23 ± 27m ($p < 0.001$). Although the average 2MWD estimated using the equation derived in a sample of Brazilian adults was similar to the 2MWD measured in Malaysian adults, the Bland and Altman plots showed the presence of proportional error between the 2MWD measured in the sample of Malaysian adults and the 2MWD estimated using both existing equations.

Discussion and conclusions: The equations derived in this study allow the main outcome of the 2MWT (i.e. the 2MWD) in clinical populations in Malaysia, as well as countries with similar cultural backgrounds and anthropometric characteristics to Malaysia, such as Indonesia, Singapore and Southern Thailand to be interpreted as a percentage of the value estimated in a person without significant disease (i.e. % predicted). Expressing the 2MWD as a % predicted value provides individuals and healthcare professionals with an indication of the magnitude of functional exercise capacity lost as the consequence of their condition. Inclusion of ΔHR in the first regression model explained an additional 26% of the variance in the 2MWD and is therefore likely to produce a more accurate estimate than the equation that does not include ΔHR. However, the second regression equation, which does not include ΔHR is more likely to be appropriate when interpreting the 2MWD in clinical populations who have factors known to influence the HR response during exercise, such as certain cardiovascular medications. Disparity between the measured 2MWD with that estimated using both of the existing equations highlights the importance of using regression equations derived in a local sample.

Study 3:

A randomised controlled trial of exercise training in people hospitalised with an AECOPD

Background: Acute exacerbations of COPD are important events in the clinical course of people with COPD and they represent a major burden to patients as well as healthcare systems. Severe AECOPDs which necessitate hospitalisation have been demonstrated to impair functional exercise capacity, quadriceps muscle force (QMF)

and levels of physical activity (PA). Most importantly, one exacerbation increases the risk of recurrent exacerbations and the frequency of AECOPDs is associated with worse prognosis in this population. Therefore, strategies are needed to minimise the negative consequences of severe AECOPDs and the risk of further AECOPDs. In people with stable COPD, exercise training reduces dyspnoea and fatigue, feelings of anxiety and depression, improves exercise capacity, health-related quality of life (HRQoL) and reduces healthcare utilisation. However, in contrast to the large body of evidence supporting exercise training in people with stable COPD, evidence to support its benefits in people hospitalised for an AECOPD is limited. **Aims:** In people hospitalised with an AECOPD, to; (i) evaluate the effects of an exercise program comprising walking and resistance exercises, initiated within two days of hospitalisation, on exercise capacity (2MWD), QMF, functional performance (i.e. Sit to Stand Test [STST] and Timed Up and Go [TUG]) test and PA and, (ii) compare the level of adherence to supervised and unsupervised training sessions. **Methods:** Participants were recruited from patients who were hospitalised for an AECOPD in two general hospitals in Kuala Lumpur, Malaysia (Hospital Selayang and Institute of Respiratory Medicine). Within two days of hospital admission, participants completed baseline testing and were randomised to either a control group (CG) or an exercise group (EG). Participants in the CG received standard usual care (e.g. medical and nursing care, airway clearance and encouragement to mobilise). In addition to standard usual care, participants in the EG performed individualised, progressive walking and functional resistance exercises throughout the hospitalisation period. They were prescribed with one supervised and one unsupervised training session each day. Primary outcomes were 2MWD and QMF. Secondary outcomes were the STST, TUG test and daily steps recorded using a Stepwatch Activity Monitor. **Results:** Thirty two participants (31 males [97%]; age 64.2 ± 7.8yr; FEV_1 33 ± 14% predicted) completed all the measurements during baseline and re-assessment. Median [interquartile range] hospital length of stay in the EG and CG were 8 [6 to 9] and 7 [6 to 8] days, respectively (p = 0.64). Those in the EG completed 4 ± 1 (range 2 to 6) supervised and 4 ± 1 (range 2 to 7) unsupervised exercise sessions. Compared with changes seen in the CG group, those in the EG demonstrated greater gains in 2MWD (33 ± 15m vs. 20 ± 13m; p = 0.01) and QMF (5.9 ± 3.4kg vs. 3.1 ± 3.6kg; p = 0.03). No between-group differences were seen in the magnitude of change in the STST or TUG test. Compared with the CG, the EG

spent less time being sedentary (median [interquartile range] 1154 [1082 to 1275] min per day vs. 1261 [1177 to 1342] min per day; p = 0.04) and more time walking at a low intensity (248 [143 to 307] min per day vs. 126 [84 to 221] min per day; p = 0.03). No between-group differences were observed in the amount of time they spent walking at a moderate intensity or the average number of steps taken per day. Adherence to supervised and unsupervised sessions was similar (96 ± 9% vs. 92 ± 13%; p = 0.22). **Discussion and conclusions:** In people hospitalised with an AECOPD, an individualised, progressive exercise program that comprised walking and resistance exercises significantly reduced the deleterious effects of an AECOPD on exercise capacity and QMF. In contrast with other randomised controlled trials of exercise training in people hospitalised with an AECOPD which demonstrated no effect on exercise capacity, the program prescribed in this study used a combination of both walking and resistance training and was powered to detect between-group differences in exercise capacity and QMF. The lack of between-group difference in STST and TUG test may reflect the fact that participants in this study did not present with substantial impairment in these outcomes at the time of recruitment. The training program also appears to have positive effect on levels of PA. The EG spent less time being sedentary and more time walking at low intensity compared to the CG. The lack of between-group difference in the average number of steps taken per day over the hospitalisation period may reflect a Type II error in the analysis. The high level of adherence to the training sessions as well as the similar adherence to supervised and unsupervised exercise sessions suggest that exercise intervention initiated within two days of hospital admission was well tolerated.

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LIST OF ABBREVIATIONS

1-RM	one-repetition maximum
2MWD	two-minute walk distance
2MWT	two-minute walk test
6MWD	six-minute walk distance
6MWT	six-minute walk test
12MWT	twelve-minute walk test
ADL	activities of daily living
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ANZCTR	Australian New Zealand Clinical Trial Registry
ATS	American Thoracic Society
BMI	body mass index
BODE	body mass index, airflow obstruction, dyspnoea and exercise capacity index
BP	blood pressure
bpm	beats per minute
BTS	British Thoracic Society
CAT	COPD Assessment Test
CG	control group
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COR	coefficient of repeatability
CPG	clinical practice guidelines
CV	coefficient of variation
DH	dynamic hyperinflation
CRP	C-reactive protein
CRQ	Chronic Respiratory Questionnaire
DOMS	delayed onset muscle soreness
EELV	end-expiratory lung volume
EG	exercise group
ERS	European Respiratory Society
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HHD	hand-held dynamometer
hr	hours
HR	heart rate
HREC	Human research ethics committee
HRmax	heart rate maximum
HRQoL	health-related quality of life
HS	Hospital Selayang
ht	height

ICC	intraclass correlation coefficient
ICU	intensive care unit
IGF-I	insulin-like growth factor-I
IL-6	interleukin-6
IL-8	interleukin-8
IQR	interquartile range
IRM	Institute of Respiratory Medicine
ISWT	incremental shuttle walk test
kg	kilograms
L	litres
LLN	lower limit of normal
LTOT	long term oxygen therapy
m	metres
MCID	minimal clinically important difference
MD	mean difference
min	minutes
mMRC	modified Medical Research Council
MMT	manual muscle testing
mRNA	messenger RNA
MTS	Malaysian Thoracic Society
MVC	maximum voluntary contraction
NICE	National Institute of Health and Clinical Excellence
NIV	non-invasive ventilation
PaO_2	partial pressure of oxygen in arterial blood
PA	physical activity
PRP	pulmonary rehabilitation program
QMF	quadriceps muscle force
RCT	randomised controlled trial
RM-ANOVA	repeated measures analysis of variance
RPE	rating of perceived exertion
RT	resistance training
s	seconds
SAM	Stepwatch™ Activity Monitor
SCGH	Sir Charles Gairdner Hospital
SD	standard deviation
SEM	standard error of measurement
SGRQ	St George's Respiratory Questionnaire
SF-36	36-item Short-Form survey
SpO_2	percutaneous oxygen saturation
SPSS	Statistical Package for the Social Sciences
STST	Sit to Stand Test
TSANZ	Thoracic Society of Australia and New Zealand
TUG	Timed Up and Go
USA	United States of America

VAS	visual analogue scale
VIF	variance inflation factors
VO_2	oxygen consumption
V/Q	ventilation perfusion
wt	weight
yr	years

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While my name may be alone on the front cover of this thesis, I am by no means its sole contributor. Rather, there are a number of people behind this piece of work who deserve to be both acknowledged and thanked.

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Manuscripts under preparation

Tahirah F, Hill K, Cecins N & Jenkins S. Two-Minute Walk Test (2MWT): measurement properties and cardiorespiratory responses in people with moderate to severe chronic obstructive pulmonary disease.

Tahirah F, Jenkins S, Justine M, Cecins M & Hill K. Regression equations to estimate the two-minute walk distance in Malaysian adults aged 40 to 75 years.

Tahirah F, Jenkins S, Othman SK, Ismail R, Ismail T & Hill K. A randomised controlled trial of individualised, progressed early exercise in people hospitalised with an acute exacerbation of chronic obstructive pulmonary disease.

Published abstracts

Tahirah F, Jenkins S, Othman SK, Ismail R, Ismail T & Hill K. A randomised controlled trial of individualised, progressed early exercise in patients hospitalised with an acute exacerbation of chronic obstructive pulmonary disease. European Respiratory Journal 2015; 46: Supplement 59, PA 743.

Tahirah F, Jenkins S, Cecins N, Justine M & Hill K. Regression equations to estimate the two-minute walk distance in Malaysian adults aged 40 to 75 years. Respirology 2015; 20: Supplement 3, page 112, ID604.

Presentations

Tahirah F, Cecins N, Jenkins S & Hill K. Two-Minute Walk Test (2MWT): Measurement properties and cardiorespiratory responses in severe chronic obstructive pulmonary disease (COPD). Poster presentation at Malaysian Thoracic Society Annual Congress (14^{th} -16^{th} June 2013). http://www.mts.org.my/download/MTS2013_Report.pdf.

Tahirah F, Cecins, N, Jenkins S & Hill K. Comparison of the cardiorespiratory and symptom responses to the 2MWT and the 6MWT in patients with COPD. Oral presentation at Lung Institute of Western Australia, November 2012, Perth, WA.

Tahirah F, Hill K & Jenkins S. Overview of the two-minute walk test in COPD. Oral presentation at Sir Charles Gairdner Hospital, November 2011, Perth, WA.

Tahirah F, Jenkins S, Cecins N, Justine M & Hill K. Regression equations to estimate the two-minute walk distance in Malaysian adults aged 40 to 75 years. Oral presentation at Asia Pacific Society of Respirology (Young Investigator Session), Kuala Lumpur Convention Centre, 5th December 2015, Kuala Lumpur, Malaysia.

Papers co-authored during the period of PhD study (Appendix 1)

AWARDS

2015:

European Respiratory Society Young Investigator Award - Asia Pacific Society of Respirology

Awarded at the 20th APSR Annual International Congress (3rd - 6th Dec)

Travel grant - Asia Pacific Society of Respirology/European Respiratory Society

Awarded a travel grant for the 20th APSR Annual International Congress (3rd - 6th Dec)

2014:

Travel grant - Malaysian Thoracic Society

Awarded a travel grant for the 16th MTS Annual Congress (12th - 15th June)

2013:

Best poster presentation - Malaysian Thoracic Society

Awarded at the 15th MTS Annual Congress (14th - 16th June)

Research grant - Malaysian Thoracic Society (incentive category)

Awarded a research grant of RM10, 000

CONFERENCE PRESENTATIONS – INVITED SPEAKER

2014:

2014 MTS Annual Congress - Pulmonary Rehabilitation (PR) Workshop

Title: The six-minute walk test in pulmonary rehabilitation

2013:

Malaysia Asia Pacific Occupational Therapy Students Congress 2013

Title: Discoveries in the field of research and innovations

CHAPTER 1
INTRODUCTION

This program of research focuses on the assessment and rehabilitation of people with chronic obstructive pulmonary disease (COPD), who are characterised by profound dyspnoea on exertion. Two prospective cross-sectional studies and one randomised controlled trial (RCT) were conducted in a total of 139 participants. Study 1 evaluated the measurement properties of the two-minute walk test (2MWT), including the effect of test repetition, coefficient of repeatability and validity, the difference between the distance walked during the 2MWT and one third of the distance walked during the six-minute walk test (6MWT) and compared the cardiorespiratory responses and the severity of dyspnoea and leg fatigue reported during the 2MWT and the 6MWT. Study 2 developed regression equations to estimate the two-minute walk distance (2MWD) in Malaysian adults who presented with no significant disease. Study 3 evaluated the effectiveness of an exercise program in people hospitalised with an acute exacerbation of COPD (AECOPD) in Malaysia. The exercise program comprised both walking and resistance exercise and was evaluated in terms of its effect on outcomes such as functional exercise capacity, quadriceps muscle force (QMF), functional performance and levels of physical activity (PA).

This chapter provides a rationale for the development of each research question. The hypotheses for each research question are described (where appropriate) and the significance of the research program is discussed. The order of the research questions described is consistent with the order in which Chapters 3 to 5 are presented.

1.1 Study 1

2MWT: measurement properties and comparison of the cardiorespiratory and symptom responses with the 6MWT in people with moderate to severe COPD

1.1.1 Background

The 2MWT and the 6MWT were introduced in 1982 as alternatives to the original twelve-minute walk test (12MWT) as they were considered to be less burdensome for patients with respiratory disease and less time consuming for clinicians (1, 2). The 6MWT was subsequently proposed as the test of choice as it was better tolerated by patients with cardiorespiratory diseases than the 12MWT, and was believed to more accurately reflect the requirements of daily living activities than the shorter 2MWT (1). Nevertheless, the uptake of this test is poor among people hospitalised with an AECOPD (3). This may be because clinicians consider the 6MWT to be an inefficient use of their time as the severe dyspnoea that accompanies an exacerbation results in patients taking frequent and/or prolonged rests during the test. Earlier work has shown that at least 20% of those who are clinically stable require between one and four rests during the 6MWT (4-6). It seems likely that this proportion would be greater in those hospitalised with an AECOPD. Therefore, in the context of patients who experience severe dyspnoea on exertion, such as those who are hospitalised for an AECOPD or even in some of those with moderate to very severe disease, the 2MWT may be an appropriate alternative to the 6MWT in measuring functional exercise capacity.

The first study conducted in this program of research sought to investigate several measurement properties of the 2MWT and compare the cardiorespiratory and symptom responses elicited during the 2MWT and the 6MWT in people with moderate to severe stable COPD.

This study reported the effect of test repetition on 2MWD. Earlier work has reported inconsistent findings with respect to the effect of test repetition on the 2MWD (1, 2, 7, 8), with some, but not all reporting a small but significant increase in the 2MWD with test repetition (1, 2, 7). Information regarding whether or not the 2MWD increases significantly with test repetition is important to clinicians who wish to use the 2MWT to evaluate change in functional exercise capacity following an intervention. If the 2MWD is found to increase significantly with test repetition,

practice test(s) would then be necessary at baseline. Failure to account for the influence of test repetition (if present) on 2MWD would result in an over-estimation of the effect any intervention has on this outcome.

This study also reported the coefficient of repeatability (COR) for the 2MWD. These data are important in order to understand how much the 2MWD may differ with test repetition simply due to inherent error in the test. That is, a change in the 2MWD following an intervention that exceeds the COR means that the clinician can be 95% confident that a difference of this magnitude was due to the intervention as it exceeds the threshold of error inherent in the test.

Data collected in this study also allowed for comparison of measures collected during the 2MWT (i.e. the 2MWD) with measures collected during the 6MWT (i.e. six-minute walk distance [6MWD]). Specifically, these analyses allowed the validity of the 2MWD as an assessment of functional exercise capacity to be explored by determining the strength of the association between the 2MWD and 6MWD. Further, the 2MWD was also compared with one third of the distance in the 6MWD. Determining whether or not these two measurements are interchangeable with each other is important for clinicians who evaluate the effect of an intervention, such as an exercise training program, using the 6MWT. That is, given that the 6MWT is exactly three times as long as the 2MWT, in the event that a patient develops an AECOPD or when time is limited, clinicians might be tempted to use the 2MWT on completion of the program and one third of the 6MWD performed at baseline as the baseline 2MWD. If these two measurements are not interchangeable with each other, comparing one third of the distance walked during the 6MWT performed at baseline with the 2MWD measured post-intervention will lead to either an over- or under-estimation of the effects of the intervention on this outcome.

Finally, this study compared the cardiorespiratory and symptom responses elicited during the 2MWT with those elicited during the 6MWT. Although earlier work (8) suggests that people with stable COPD report a significantly higher rating of perceived exertion (RPE) on completion of the 6MWT compared to the 2MWT, no studies have compared the cardiorespiratory responses (heart rate [HR] and percutaneous oxygen saturation [SpO_2]) elicited during the 2MWT with the 6MWT in people with moderate to severe COPD. Understanding whether or not the 2MWT

elicits less cardiorespiratory and symptom burden when compared with the 6MWT will support the use of the 2MWT as an alternative to the 6MWT in people who experience severe dyspnoea on exertion, such as in some of those with moderate to severe stable COPD or in patients who are hospitalised with an AECOPD.

While all the results in this study are most relevant to patients with moderate to severe stable COPD, it is also possible that the results could be extended to those who are hospitalised for an AECOPD. This is because this study specifically recruited patients who were likely to have similar characteristics as those experiencing an AECOPD, such as profound dyspnoea and oxygen desaturation on exertion and marked impairment in exercise capacity (90% of the participants had severe to very severe COPD, 80% requiring wheeled walker and 80% were on long term oxygen therapy).

1.1.2 Research questions and hypotheses (where appropriate)

1.1.2.1 Primary research question and hypothesis

i) *Research question:*

What is the magnitude of change in the 2MWD with test repetition?

Hypothesis:

The 2MWD will change (i.e. increase) significantly with test repetition.

1.1.2.2 Secondary research questions and hypotheses

ii) *Research question:*

What is the COR for the 2MWD measured over two days?

Hypothesis:

No hypothesis will be tested. The research question will be answered with a descriptive statistic.

iii) *Research question:*

Is the 2MWD associated with the 6MWD?

Hypothesis:

There will be a positive strong association between the 2MWD and the 6MWD.

iv) *Research question:*

Is the distance walked during the 2MWT different to one third of the 6MWD?

Hypothesis:

The distance walked during the 2MWT is different (i.e. greater) than a distance equivalent to one third of the 6MWD.

v) *Research question:*

Does the 2MWT elicit different cardiorespiratory responses and levels of symptoms when compared with the 6MWT?

Hypothesis:

The 2MWT will elicit different (i.e. less) cardiorespiratory responses and different (i.e. lower) levels of symptoms when compared with the 6MWT.

1.2 Study 2

Regression equations to estimate the 2MWD in Malaysian adults aged 40 to 75 years

1.2.1 Background

The 2MWT has been used in people with respiratory diseases (1, 2, 7-9), as well as in other clinical populations, such as in people with poliomyelitis (10), multiple sclerosis (11, 12) and stroke (13), in those undergoing cardiac surgery (14), lower limb amputation (15), and in the healthy elderly (16). However, despite the increasing use of the 2MWT, regression equations to estimate the main outcome of the test (i.e. 2MWD) are still limited. Such equations allow clinicians to estimate the 2MWD in the general population and thereby express the 2MWD in a clinical population as a percentage of the estimated value. Expressing the 2MWD as a percentage of the value estimated in general population allows clinicians to provide people with a health condition with an indication of the degree of impairment in functional exercise capacity that was due to their condition.

To date, there are only two regression equations available to estimate the 2MWD; one was derived from a sample of Brazilian adults (17) and the other one was derived from a sample of American adults (18). This is in contrast to the 6MWT, where at least 20 regression equations are available to estimate the 6MWD in healthy individuals (19-38). Of note, the regression equations published to estimate the

6MWD use different predictors, different coefficients for the same predictors, and produce 6MWDs that differ by as much as 200m for any given individual (23, 26, 27). In addition to differences in the test protocol (i.e. track length, use or not of encouragement), differences in the predictors retained in each equation, and the influence of each predictor in these equations reflects, at least in part, discrepancies in sample characteristics. For example, in two studies where the 6MWT was performed using an identical protocol, by the same team of investigators but in two samples of different ethnicities, the equation derived to estimate the 6MWD in Chinese Singaporean retained different predictors and different coefficients for the same predictors to the equations derived to estimate the 6MWD in Caucasian Australian (21, 39). Factors such as disparities in body composition, cultural and lifestyle differences between Asian and Caucasian populations may explain these differences. Given the fact that the two previously published regression equations (17, 18) that estimate the 2MWD were derived in American (18) and Brazilian samples (17), it is likely that these equations will not be appropriate to estimate the 2MWD in a sample of Malaysian adults. Therefore, the second study conducted in this program of research sought to develop regression equations to estimate the 2MWD in Malaysian adults. This study is important because, in the absence of normative data derived from a local population, the distance achieved during the 2MWT (i.e. the 2MWD) for an individual patient may be difficult to interpret.

1.2.2 Research questions and hypotheses

1.2.2.1 Primary research question and hypothesis

i) Research question:

Can age, gender, height, weight and change in HR (ΔHR [i.e. peak measured HR during the 2MWT - resting HR]) explain at least 50% of variance in the 2MWD?

Hypothesis:

Age, gender, height, weight and ΔHR will account for at least 50% of variance in the 2MWD.

1.2.2.2 Secondary research questions and hypotheses

ii) Research question:

Is the 2MWD measured in Malaysian adults similar to the 2MWDs estimated using the equations derived from Brazilian and American samples?

Hypothesis:

The 2MWD in Malaysian adults is different (i.e. smaller) than the 2MWD estimated using the regression equations derived from Brazilian and American samples.

1.3 Study 3

An RCT of exercise training in people hospitalised with an AECOPD

1.3.1 Background

Acute exacerbations of COPD that necessitate hospitalisation (i.e. severe AECOPD) are important events in the clinical course of people with COPD and account for the largest component of the treatment cost for this condition (40-42). When compared with people who are clinically stable, those who are hospitalised for an AECOPD are characterised by an increase in dyspnoea and fatigue (43, 44), a greater impairment in quadriceps muscle force (QMF) (45-47), worse exercise capacity (48-50), lower levels of PA (47, 51), and poorer health-related quality of life (HRQoL) (40). There is also evidence suggesting that, in some patients, the decrease in exercise capacity and PA levels, and the loss in QMF during hospitalisation for AECOPD have not recovered to the pre-exacerbation values two to three months following hospital discharge (46-48, 52, 53).

Hospitalisation for an AECOPD has also been identified as the single best predictor for both recurrent AECOPDs as well as hospitalisations for AECOPDs (40, 54-56). In a longitudinal study of 295 people with COPD, Hurst et al. (55) found that at least 30% of the 2,189 exacerbations recorded over their 2-year study period were recurrent exacerbations. They also found that AECOPDs were not random events, instead clustering together in time, with the high-risk period for recurrent exacerbation to be within the first 8 weeks after an exacerbation (55). Importantly, hospitalisations for AECOPD are associated with worse prognosis in this population (57-59). Specifically, hospitalisation for an AECOPD has been identified as one of the independent predictors of mortality in people with COPD (57), with the mortality rates amongst those who survive the hospital admission ranging from 22% (57, 58) to 43% (59) at one year following hospital discharge. Therefore, strategies are

needed to minimise the negative consequences of AECOPD and the risk of recurrent exacerbation.

In people with stable COPD, there is strong evidence demonstrating that pulmonary rehabilitation programs (PRPs), which include an exercise training component, lead to an improvement in multiple outcomes including dyspnoea and fatigue, feelings of anxiety and depression, exercise capacity and health-related quality of life (60, 61). There is also evidence demonstrating that PRPs reduce hospitalisations for AECOPDs (62-64). Despite this evidence in people with stable COPD, the evidence to support the role of exercise training during hospitalisation for AECOPD is limited. This is somewhat surprising as it is possible that implementing a program of exercise training during hospitalisation for AECOPD maybe assists in reducing the deleterious effects of an AECOPD and thereby assists in reducing the risk of future AECOPDs. Studies that have explored the effects of exercise training during hospitalisation for an AECOPD have often initiated the exercise program between four and eight days following hospital admission (i.e. once clinical status had been stabilised) (65-67). This limits the generalisability of the results of these studies to countries, such as Malaysia and Australia in which the length of stay for an AECOPD is often less than one week (68, 69).

To date, only three RCTs have explored the effects of exercise training commenced within two to three days of hospitalisation for an AECOPD and evaluated the effect of the intervention prior to hospital discharge (70-72). These RCTs showed that exercise training commenced within two to three days of hospitalisation was safe and feasible (70-72). However, despite the evidence for the benefits of walking-based training on outcomes such as exercise capacity and HRQoL in people in with stable COPD (73, 74), two of these three studies prescribed an exercise training program that comprised exclusively resistance exercise (71, 72). Studies that prescribed a resistance only exercise program reported inconsistent effects on exercise capacity and QMF at the time of discharge from the hospital (71, 72). The only RCT that investigated the effects of an exercise training program that comprised both walking and resistance exercise, initiated within two days of hospitalisation, did not demonstrate significant between-group differences in favour of the intervention group on exercise capacity or QMF (70). The lack of between-group differences was

presumably due to the small sample size available for analyses ($n \leq 11$ per group). Further, none of the three RCTs have investigated the effect of exercise training commenced within two to three days of hospitalisation for an AECOPD on functional outcomes such as the Sit to Stand test (STST) and the Timed Up and Go (TUG) test or have monitored PA on a daily basis throughout the hospitalisation period. Therefore, the third study conducted in this program of research sought to determine the effects of an exercise program that comprised both walking and resistance exercise, initiated within two days of hospitalisation for an AECOPD, on outcomes including QMF, exercise capacity, level of PA, STST and TUG. This RCT was conducted in two general hospitals in Kuala Lumpur, Malaysia. Data collected in this RCT also allowed the level of adherence to supervised and unsupervised training sessions to be compared. Such information is important, as it will allow clinicians to appreciate whether supervision of the training sessions is essential to optimise adherence.

1.3.2 Research questions and hypotheses

1.3.2.1 Primary research question and hypothesis

i) Research question:

Does an exercise program, initiated within two days of hospital admission, that comprises walking and resistance exercise, produce additional benefits in exercise capacity, QMF, functional performance and PA, over and above any changes seen with usual care?

Hypothesis:

Participation in the exercise training will produce significant positive changes in exercise capacity, QMF, functional performance and PA, over and above any changes seen with standard usual care.

1.3.2.2 Secondary research questions and hypotheses

ii) Research question:

Is there a difference in the level of adherence between supervised and unsupervised exercise training sessions?

Hypothesis:

The level of adherence to supervised exercise sessions will be different (i.e. higher) than the level of adherence to unsupervised exercise sessions.

1.4 Significance and novelty of the research

This program of research will contribute novel and important information pertaining to both the assessment and rehabilitation of people with COPD who are characterised by profound dyspnoea on exertion, such as those hospitalised for an AECOPD.

The first study in this program of research investigated the measurement properties of a simple field-based test of functional exercise capacity, the 2MWT. This information can be used by clinicians to guide implementation of this test and interpretation of its results and is most likely to be of use to those working with people with COPD who are characterised by profound dyspnoea on exertion. This is because, in this group of people, the 6MWT may be considered burdensome and in those who need to rest frequently or for long periods, the 6MWT is an inefficient use of both the patient's and clinician's time. This limits the uptake of the 6MWT in people hospitalised with an AECOPD (3). The use of the 2MWT in people for whom the 6MWT is perceived to be burdensome or inefficient, offers clinicians the opportunity to evaluate the effectiveness of interventions, such as exercise training, using an objective measure of functional exercise capacity, the 2MWD. Further, similar to the way in which the 6MWD has been used to prescribe the initial intensity of walking-based exercise training (75), the 2MWD may provide a basis for exercise prescription in those for whom the 6MWT is perceived to be burdensome or inefficient.

The second study in this program of research developed regression equations to estimate the 2MWD in Malaysian adults. These equations are the first to estimate the 2MWD in adults living in the Asian region, and therefore are likely to be the most appropriate to facilitate interpretation of the 2MWD in clinical populations in Malaysia as well as in other Asian countries with similar cultural backgrounds and anthropometric characteristics to Malaysia, such as Indonesia, Singapore and Southern Thailand.

The third study in this program of research evaluated the effects of an exercise program in people hospitalised with an AECOPD on important outcomes such as functional exercise capacity, QMF, functional performance and daily PA. The intervention investigated in this study was initiated within two days of hospital admission and included both walking and resistance exercise. The exercise training

program required minimal equipment and could be easily replicated in areas of low healthcare funding. If the exercise intervention is found to be effective, this study will be the first to demonstrate that an exercise training program initiated early during hospital admission, using minimal equipment, can mitigate the negative consequences of AECOPD on exercise capacity, QMF, functional performance and PA. These findings will contribute importantly to the current evidence for such interventions. Data collected during this RCT also builds on information presented in the first study performed in this program of research by exploring the responsiveness of the 2MWD following exercise training in people hospitalised for an AECOPD. Finally, this program of research is particularly novel given that two of the studies were conducted in Malaysia, a country where very little work in the area of pulmonary rehabilitation has been done in the past.

CHAPTER 2
LITERATURE REVIEW

This literature review is divided into four parts.

Part 1 provides information pertaining to the definition, prevalence, classification of severity, causes, risk factors and cost associated with chronic obstructive pulmonary disease (COPD) and an acute exacerbation of COPD (AECOPD). Part 2 discusses the pulmonary and extra-pulmonary impairments of people with COPD, and includes a description of their clinical characteristics such as dyspnoea and fatigue, decreased exercise capacity, low levels of physical activity (PA) and impaired health-related quality of life (HRQoL), and the impact of hospitalisation for an AECOPD. This section also provides a summary of the assessment techniques commonly used to measure dyspnoea and fatigue, muscle force and endurance, exercise capacity, PA and HRQoL in people with COPD. Part 3 focuses on the literature which has reported data pertaining to the measurement properties of the two-minute walk test (2MWT) as an assessment of functional exercise capacity in people with COPD and tolerance when compared to tests such as the six-minute walk test (6MWT) and the twelve-minute walk test (12MWT). This section also describes the literature which has reported data pertaining to the interpretation of the primary outcome of the 2MWT (i.e. the two-minute walk distance [2MWD]). Part 4 reviews studies which have reported the effects of exercise training in people hospitalised for an AECOPD. Specifically, this section discusses the quality of the studies and the effects of exercise training on exercise capacity, quadriceps muscle force (QMF), PA, HRQoL and healthcare utilisation. This part of the literature review is the longest as; (i) it reviews earlier work related to the most complex study undertaken in this program of research (i.e. the randomised controlled trial which investigated the effects of exercise training initiated in people hospitalised with an AECOPD) and, (ii) there was considerably more literature to review in this area than other topics related to this thesis such as the use of the 2MWT to measure exercise capacity in people with COPD.

2.1 Part 1

Chronic obstructive pulmonary disease is a common and costly condition mostly associated with cigarette smoking (76). Unlike many other common chronic diseases, the prevalence and burden of COPD are predicted to rise due to the continuous exposure to COPD risk factors such as cigarette smoking and air pollution and the ageing of the world's population (76-78). Section 2.1.1 provides the definition and an overview of the prevalence of COPD in Australia and Malaysia. Section 2.1.2 describes the methods used to diagnose and classify the severity of COPD and AECOPDs. Section 2.1.3 provides an overview of the causes and risk factors for COPD and AECOPDs. Section 2.1.4 provides information regarding the cost associated with the management of COPD as well as AECOPD.

2.1.1 Definition and prevalence of COPD

Chronic obstructive pulmonary disease is a preventable and treatable lung disease characterised by persistent airflow obstruction that is usually progressive. The chronic airflow obstruction characteristic of COPD is caused primarily by a combination of small airway diseases (chronic bronchitis) and parenchymal destruction (emphysema), each of which contributes to a varying degree from individual to individual (76). Chronic obstructive pulmonary disease was reported as the sixth leading cause of death worldwide in 1990 (79), fifth in 2002 and is projected to be the third leading cause of death by 2020 (80). The prevalence of individuals with at least moderate COPD in Australia was estimated to be 7.5% for those aged 40 years and over and 29.2% in those aged 75 years and over (81). In 2008, the disease was estimated to affect more than 2.1 million Australians (i.e. nearly 1 in 5 individuals aged > 40 years) (82). Data reporting the prevalence of COPD in Malaysia are limited. Based on model projections, using the prevalence of risk factors for COPD, the prevalence of moderate to severe COPD in Malaysia was estimated to be 4.7% for individuals aged 30 years and over (83). However, this prevalence is likely to be an under-estimation as spirometric data collected in similar regions (i.e. the Philippines) has demonstrated the prevalence of COPD among those aged ≥ 40 years to be 12.5% (84).

2.1.2 Diagnosis and classification of severity of COPD and AECOPD

The diagnosis of COPD is confirmed by spirometry, with the most important measures being the forced vital capacity (FVC) and the forced expiratory volume in

one second (FEV_1) (76). The exact criteria for the diagnosis and classification of the disease severity vary in the literature (Table 2.1). The British Thoracic Society (BTS) (85), National Institute of Health and Clinical Excellence (NICE) (86) and Thoracic Society of Australia and New Zealand (TSANZ) (87) define airway obstruction based on a fixed FEV_1/FVC ratio < 0.70 and FEV_1 below 80% of predicted value in healthy individuals (i.e. % predicted). In contrast, the Global Initiative of Obstructive Lung Disease (GOLD) (76), American Thoracic Society/European Respiratory Society (ATS/ERS) (88) and Malaysia Clinical Practice Guidelines (CPG) (89) define airflow obstruction based only on the fixed FEV_1/FVC ratio < 0.70 with no criteria based on the measurement of FEV_1 expressed as a % predicted.

Table 2.1: Classification of severity of COPD

		FEV_1 % predicted	
GOLD grade	**Description**	GOLD, ATS/ERS and Malaysia CPG	BTS, NICE and TSANZ
I	Mild	≥ 80%	60% to 80%
II	Moderate	≥ 50% to < 80%	40% to 59 %
III	Severe	≥ 30% to < 50%	< 40%
IV	Very severe	< 30% or < 50% with chronic respiratory failure	

Abbreviations: ATS/ERS, American Thoracic Society/European Respiratory Society; BTS, British Thoracic Society; CPG, Clinical Practice Guidelines; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NICE, National Institute for Health and Care Excellence; TSANZ, Thoracic Society Australia and New Zealand.

The clinical course of COPD includes periods of clinical stability punctuated by periods of acute worsening, known as AECOPDs. An AECOPD is defined as a period during which people with COPD experience a sustained (i.e. ≥ 24 hours) worsening of symptoms beyond their normal day-to-day variation, that is acute in onset and necessitates a change in their regular medications (90). Symptoms of an AECOPD vary between individuals (91), with the most common being increased dyspnoea, cough, wheezing and chest tightness and increased sputum volume and purulence. Non-specific symptoms such as fatigue and general malaise are also common during an AECOPD (76). The severity of an AECOPD is often classified based on the utilisation of healthcare resources by patients (90). A mild exacerbation is characterised when a patient has an increased need for medication but he/she can manage the condition in own normal environment. A moderate exacerbation is

characterised when a patient has an increased need for medication and feels the need to seek additional medical assistance. A severe exacerbation is characterised when a patient or caregiver recognises obvious and/or rapid deterioration in condition which requires hospitalisation (90).

2.1.3 Causes and risk factors for COPD and AECOPD

Both environmental and genetic risk factors have been identified in the development and progression of COPD (76). With regard to the environmental risk factors, exposure to cigarette smoke has been estimated to account for approximately 85% of the risk of developing COPD (92), and thus is the most important risk factor. However, it is important to note that that not all people with the same smoking history will develop COPD. Thus, there are factors other than exposure to cigarette smoke that play a role in the development of COPD. Genetic factors such as deficiency of the serine protease α1-antitrypsin enzyme, exposure to other environmental hazards (e.g. air pollution or occupational dusts) and advancing age have also been shown to increase the risk of COPD (93).

Regarding the causes and risk factors for AECOPD, published data suggest that 50 - 70% of exacerbations are due to bacterial or viral infections, 10% are from environmental pollution and about 30% are of unknown aetiology (94). Several other factors have also been demonstrated to increase the risk of an AECOPD. These include a history of exacerbations in the previous year (54, 56, 95, 96), more severe airflow limitation (40, 54, 95, 96), older age (54, 96), winter season (40, 55), poor quality of life (40, 95) and underlying comorbidities (e.g. diabetes mellitus, ischaemic heart disease) (96). Of all these risk factors, a history of exacerbation in the previous year has been consistently identified as the single best predictor for both an AECOPD as well as hospitalisation for an AECOPD (40, 54, 56, 95).

2.1.4 Cost of COPD and AECOPD

Chronic obstructive pulmonary disease is associated with a large direct and indirect economic burden. Direct costs are costs that directly relate to the disease such as the costs for in-patient care, physician services, prescription drugs, out-patient visits, special care visits, home healthcare and nursing home care (97). Indirect costs of COPD are costs primarily related to reduced labour force participation such as lost wages of the patient, lost wages of the caregivers, and employer-borne costs such as

absenteeism and sick leave, disability and impaired work performance costs (97). In Australia, the total cost of COPD in 2008 was estimated to be AUD $8.9 billion (approximately USD $6.7 billion). Of this, AUD $0.9 billion (USD $681 million) was reported from direct healthcare expenditure and the remaining AUD $8 billion (USD $6.1 billion) was reported from indirect costs such as lost productivity due to lower employment, absenteeism and premature death (82). Data reporting the direct and indirect costs of COPD in Malaysia are limited. As estimated from the prevalence of COPD National Burden of Disease Study, Ministry of Health Malaysia (98), the total cost of COPD was estimated to be approximately RM2.25 billion (USD $560 million) per annum. This cost includes out-patient visits, travelling costs, annual visits for primary care, specialist care visits and hospitalisation costs. Chronic obstructive pulmonary disease also results in a high economic burden in countries like the United States of America (USA) and the European Union (EU). It was estimated that the direct and indirect costs of COPD in the USA in 2010 were USD $29.5 billion and USD $20.4 billion, respectively (76). Whereas, in the EU, the total direct and indirect costs associated with COPD in 2011 were €23.3 billion (USD $26 billion) and €25.1 billion (USD $28 billion), respectively (99).

The higher costs of COPD in countries like the USA and EU when compared to the costs of COPD in countries like Malaysia and Australia may be partly explained by the differences in the prevalence of the disease as well as the size of the population between these countries. For example, the prevalence of COPD in the USA and EU were estimated to be higher than that estimated for both Malaysia and Australia (i.e. 15.2% and 13.7% (100) vs. 4.7% (83) and 7.5% (81), respectively). Thus, it can be appreciated that the costs would be greater in countries with more people with COPD. In addition to the higher prevalence of COPD, the size of the population in the USA and EU were also at least 10 times greater than the size of the population in Malaysia and Australia. This means that, there would be more people with COPD for every percentage of increase in prevalence in the USA and EU than in Australia and Malaysia. Of note, several studies have reported that the management of an AECOPD accounts for the largest component of the treatment costs of COPD (40-42), representing between 50% and 75% of the total treatment costs of COPD (88).

2.1.5 Summary

Chronic obstructive pulmonary disease is a preventable and treatable chronic lung disease, characterised by persistent airflow obstruction that is usually progressive. The prevalence of COPD is high in developing countries such as Malaysia as well as in developed countries like Australia. The diagnosis of COPD is usually confirmed by spirometry. The clinical course of COPD includes periods of clinical stability (i.e. periods where there have been no change in respiratory symptoms that required a change in medication for ≥ 4 weeks) and periods of acute worsening of respiratory symptoms, known as an AECOPD. The severity of an AECOPD is usually classified based on healthcare utilisation. Severe AECOPD (i.e. exacerbations that necessitate hospitalisation) represent a major burden to patients as well as healthcare systems.

2.2 Part 2

Chronic obstructive pulmonary disease is increasingly recognised as a systemic disease rather than a disease of the respiratory system alone. It is characterised by pulmonary and extra-pulmonary impairments and associated with several chronic comorbidities such as cardiovascular disease, osteoporosis, and anxiety and depression. Section 2.2.1 provides an overview of the pulmonary pathology and its physiological consequences (i.e. pulmonary hyperinflation and gas exchange abnormalities). Section 2.2.2 provides an overview of the systemic pathology that occurs during COPD and describes one extra-pulmonary consequence (i.e. skeletal muscle dysfunction) that has been demonstrated in people with COPD. A detailed discussion of other systemic manifestations and comorbidities described in this clinical population is beyond the scope of this thesis. Section 2.2.3 reviews the clinical characteristics of people with COPD, which include symptoms of dyspnoea and fatigue, impairments in exercise capacity, low levels of PA and poor HRQoL. This section also provides a summary of the assessment techniques commonly used to measure dyspnoea and fatigue, muscle force and endurance, exercise capacity, PA and HRQoL in this population.

2.2.1 Pulmonary pathology and pathophysiology in COPD

2.2.1.1 Pulmonary pathology

Pulmonary pathology in COPD occurs as a result of exposure to noxious particles (e.g. cigarette smoke and/or environmental pollution) which trigger a series of

protective inflammatory responses in the lungs. Repeated injury and repair amplifies the normal protective inflammatory response and results in changes to the central and peripheral airways, lung parenchyma and pulmonary vasculature (93, 101).

Inflammation within the central airways is associated with epithelial, squamous and goblet cell metaplasia, mucous gland hypertrophy, ciliary dysfunction, degeneration of airway cartilage, increased smooth muscle and connective tissue in the airway wall and mucus hypersecretion (93). These changes are responsible for the symptoms of chronic cough and sputum production in people with COPD (102). Inflammation within the peripheral airways results in smooth muscle hypertrophy, remodelling, fibrosis and airway narrowing, and is responsible for airflow obstruction in people with COPD (93). Of note, the structural changes in the wall of the peripheral airway are an important cause of the increase in peripheral airway resistance, which contributes to pulmonary hyperinflation, ventilation-perfusion (V/Q) mismatch and gas exchange abnormalities in COPD (102).

Lung parenchyma includes the area for gas exchange of the lung (i.e. respiratory bronchioles and alveoli) and the pulmonary capillary system. The damage within the lung parenchyma (i.e. dilatation and destruction of the respiratory bronchioles, alveolar walls and pulmonary capillary bed) seen with COPD contributes further to expiratory airflow limitation and gas exchange abnormalities (93, 102). Inflammation within the pulmonary vasculature results in thickening of the vessel wall and is associated with an increase in pulmonary vascular pressure that develops first with exertion and then at rest, and, late in the course of the disease, the development of pulmonary hypertension and cor pulmonale (93). During an episode of AECOPD, the inflammatory response in people with stable COPD is triggered by viral or bacterial infections or air pollutants to further increase the production of eosinophils, neutrophils and several other inflammatory mediators such as cytokines and chemokines and leads to greater respiratory impairments and symptoms (102).

2.2.1.1.1 Pulmonary hyperinflation

In people with COPD, the pulmonary pathology within both the peripheral airways and lung parenchyma reduces lung elastic recoil, which in turn leads to a reduction in the driving pressure for expiratory flow through narrowed airways (102).

Consequently, during resting spontaneous breathing, the end-expiratory lung volume (EELV) increases, a process known as static lung hyperinflation (103). This process worsens during exercise as the increased respiratory demand (i.e. increased minute ventilation) results in insufficient time to allow for a complete expiration because it is interrupted by the next inspiratory effort before the respiratory system has reached the static equilibrium volume. This process is known as dynamic hyperinflation (DH) of the lungs (104). As an AECOPD is often characterised by worsening airway obstruction, both static and dynamic hyperinflation worsen during an AECOPD (103). Regarding measurement, whole body plethysmography is the gold standard for measuring static EELV (103), whereas the rate and magnitude of DH is generally measured in the laboratory by making serial measures of inspiratory capacity during a cycle ergometry test (105). Dynamic hyperinflation is the main factor contributing to the sensation of dyspnoea (see subheading 2.2.3.1.1) and exercise limitation in COPD (103, 104).

2.2.1.1.2 Gas exchange abnormalities

In addition to causing lung hyperinflation, pulmonary pathology within the peripheral airways and lung parenchyma also leads to problems with gas exchange (i.e. V/Q mismatching). For example, in people with a predominantly emphysematous phenotype, there is a greater destruction of parenchyma compared to the changes in peripheral bronchioles, which in turn results in increased ventilation of poorly perfused lung units (i.e. high V/Q ratio) (106). In contrast, people with COPD who have a substantial magnitude of impairment in the airways, are more likely to have a low V/Q ratio resulting from hypoventilation (106). Ventilation/perfusion abnormalities are also one of the most important causes of arterial hypoxemia in people with COPD, which is measured as the partial pressure of oxygen in arterial blood (PaO_2) or indirectly via pulse oximetry (107). The prevalence and magnitude of hypoxemia appear to increase with disease progression and during exertion or an AECOPD (106-108). Rodriguez-Roisin et al. (107) found that the prevalence of mild to moderate hypoxemia (i.e. PaO_2 of < 80mmHg to $\geq$ 60mmHg) increased from 40% to 72% from mild to severe COPD. During an AECOPD, the worsening of the V/Q mismatch or the increase in gas exchange abnormalities is often explained by the increase in airway obstruction due to worsening of airway inflammation, bronchospasm or mucus secretions. These

changes result in a greater proportion of blood flow diverted through the poorly-ventilated lung units and a decrease in mixed venous oxygen tension due to greater oxygen consumption by the respiratory muscles (108). The presence of hypoxaemia in COPD has been associated with the development of pulmonary hypertension and polycythaemia as well as skeletal muscle dysfunction in people with COPD (106).

2.2.2 Systemic pathology

Chronic obstructive pulmonary disease is associated not only with an abnormal inflammatory response in the lungs, but also with evidence of systemic inflammation. That is, when compared to healthy controls, people with COPD have an increased in systemic oxidative stress (109, 110), enhanced chemotaxis in the circulating inflammatory cells (e.g. neutrophils) (111) and increased plasma levels of inflammatory cytokines in their peripheral circulation. These abnormal systemic inflammatory responses have been shown to be further increased during an AECOPD (110, 112). The origin of the systemic inflammation in people with COPD is still unclear. However, it could be due to the spill-over of inflammatory molecules from the inflamed pulmonary parenchyma through the pulmonary circulation (113). Systemic inflammation has been demonstrated to be associated with several systemic consequences such as nutritional abnormalities, weight loss, skeletal muscle dysfunction, cardiovascular disease, glucose intolerance, osteoporosis and depression (114).

2.2.2.1 Skeletal muscle dysfunction

Although dysfunction of various skeletal muscles has been described in the literature, arguably one of the most important is the dysfunction seen in the quadriceps muscle. Reduced QMF has been identified as a significant predictor for important outcomes such as impaired exercise capacity, number of hospital admissions due to AECOPD (115), number of out-patients visits to pulmonary clinics (115) and survival (116).

2.2.2.1.1 Changes in structure

Changes within the quadriceps muscles of people with COPD include profound muscle atrophy. Relative to data collected in healthy controls, people with COPD have a lower mean ± standard deviation (SD) cross-sectional area of rectus femoris muscle (348 ± 78mm^2 vs. 463 ± 137mm^2; p = 0.001), measured by ultrasound (117). In addition to having smaller quadriceps muscle, there is evidence that the quality of

the muscles is also impaired as several cellular morphological modifications have also been observed in quadriceps muscle of people with COPD (118, 119). For example, following biopsy of the vastus lateralis muscle, people with COPD demonstrated a marked reduction in the proportion of Type I muscle fibres (34 ± 14% vs. 58 ± 16%; $p < 0.0005$) with a corresponding increase in Type IIb muscle fibres (15 ± 12% vs. 5 ± 5%; $p = 0.015$) when compared with healthy controls (119). The cross-sectional area of Type I, IIa and IIb fibres were found to be smaller and the number of capillary contacts across these three fibre types were reduced in people with COPD when compared to healthy controls (119). Mitochondrial function has also been shown to be altered in the quadriceps muscle of people with COPD (120-123). When compared with healthy controls, both the mitochondrial volume density as assessed by mitochondrial enzyme activities (120-122) and expression of key transcription factors for mitochondrial biogenesis (123) have been shown to be reduced in the quadriceps muscle of people with COPD. The activity of citrate synthase in the vastus lateralis muscle fibres of people with COPD was shown to be reduced by approximately 40% when compared with healthy controls (120-122).

The cause of the quadriceps muscle dysfunction is likely to be multi-factorial and includes deconditioning, corticosteroid use, weight loss, gas exchange abnormalities and hormone and electrolyte imbalances (124, 125).

2.2.2.1.2 Impairments in strength

The changes described above result in several impairments in the way the quadriceps muscle functions in people with COPD. Earlier work has demonstrated a reduction in the force-generating capacity of the quadriceps muscle in people with COPD (126-129). This impairment relates to the reduction in the muscle's cross-sectional area (126, 127). A retrospective study involving a large cohort of participants with COPD (n = 591) conducted in the United Kingdom and the Netherlands reported that quadriceps muscle weakness was evident in approximately 30% of participants (127).

The prevalence of quadriceps muscle weakness increases with an increase in disease severity (126-128). In one example, Seymour et al. (127) found that at least 25% of people with mild disease demonstrated with quadriceps muscle weakness and the number increased to 38% in those with very severe disease. Quadriceps muscle force

has been shown to be further compromised during episodes of AECOPDs (46, 47). Spruit et al. (46) found that QMF was the lowest in people hospitalised for an AECOPD when compared with those who were clinically stable as well as with healthy controls (66 ± 22% vs. 86 ± 16% vs. 103 ± 20% predicted). The mean reduction in QMF was reported to be between 5% (46) and 8% (47) within only five days of hospitalisation. More importantly, both of these studies demonstrated that the reduction in QMF during the hospitalisation period took a very long time to recover. Pitta et al. (47) found that QMF did not return to pre-exacerbation values even after a month following hospital discharge. Spruit et al. (46) demonstrated that QMF had improved only by 8% 90 days following hospital discharge. Possible mechanisms for the greater reduction in QMF during hospitalisation for an AECOPD include increased systemic inflammation (46) and oxidative stress (45), the administration of oral corticosteroids (130) and inactivity and bed rest (47). One clear example, when compared to healthy controls, Crul et al. (45) found that the levels of markers that indicate muscle disuse (e.g. MyoD protein and IGF-I) were significantly lower in people hospitalised with an AECOPD, and MyoD protein in particular was shown to have a moderate association with QMF ($r = 0.45$; $p < 0.05$).

Regarding measurement, several methods have been described to assess QMF, such as manual muscle testing (MMT), one-repetition maximum (1-RM), the use of a hand-held dynamometer (HHD) and devices such as an isokinetic dynamometer or a system which allows participants to perform an isometric maximal voluntary contraction against a fixed resistance, with the QMF measured using a force transducer or strain gauge. Devices which allow participants to perform an isometric maximal voluntary contraction against a fixed resistance are considered gold standards. This is because, compared to HHD and MMT, these methods have been shown to provide very sensitive measurements of strength and have the ability to detect small differences in isometric forces (131, 132).

2.2.2.1.3 Impairments in endurance

In addition to a reduction in QMF, several studies have demonstrated lower quadriceps muscle endurance (i.e. increased quadriceps fatigability) in people with COPD when compared to healthy controls (129, 133-136). Muscle fatigue has been defined as the inability of a muscle to maintain a certain force or power output (125). Earlier work has shown that, when compared with healthy controls, the time to task

failure for the quadriceps muscle contracting against a constant submaximal load (i.e. 10% of maximum voluntary contraction) was reduced by 77% in people with COPD (129). The mechanisms that predispose people with COPD to early fatigue, especially in cycle based exercise, can be explained, at least in part, by the relative loss of fatigue-resistant Type I fibres in addition to concurrent structural alterations in capillary density and mitochondrial function (119-122). Similar to the prevalence of quadriceps muscle weakness that has been shown to increase with the increase in disease severity (126-128), quadriceps muscle endurance was also found to be associated with the degree of airflow obstruction ($r = 0.52$; $p < 0.05$) (134). Although data pertaining to the impact of an AECOPD on muscle endurance are not available, earlier work has demonstrated a significant relationship between elevated plasma levels of an inflammatory biomarker (e.g. C-reactive protein [CRP]) and endurance time, measured via a cycle ergometer test in people with severe to very severe COPD (137). The (median [range]) endurance time was significantly lower (8min [2 - 30min] vs. 13min [3 - 30min]) in people with COPD who presented with an elevated CRP compared to those with normal CRP levels (137). Of note, inflammatory markers (e.g. CRP, IL-6, IL-8) have been consistently shown to be elevated during an AECOPD (46).

Regarding measurement, muscle endurance can be assessed as the time to task failure for the quadriceps muscle whilst contracting against a constant submaximal load, usually 10% to 20% of a maximum voluntary contraction (129, 134), the rate of decline in peak torque during a sequence of maximal contractions against an isokinetic dynamometer (135) or a reduction in force generation in response to magnetic femoral nerve stimulation following cycle-based exercise (136).

2.2.3 Clinical characteristics and measurement methods

This section describes the symptoms of dyspnoea and fatigue, impairment in exercise capacity, low levels of PA and poor HRQoL in people with COPD. A summary is provided of the assessment techniques commonly used to measure these outcomes.

2.2.3.1 Dyspnoea and fatigue

2.2.3.1.1 Dyspnoea

Dyspnoea is defined by the ATS as a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity (138). It is the most common symptom especially during activity in people with COPD, and is often the main reason that an individual with this condition seeks medical attention (139). In a large survey (n = 3,265) involving people with COPD in North America and Europe, Rennard et al. (140) found that dyspnoea was associated with a considerable burden of disease, affecting several aspects that are fundamental to daily life. They found that people with COPD reported dyspnoea even when just sitting or lying, and the number of patients who reported dyspnoea increased with an increase in the intensity of activity (140). The mechanisms underpinning dyspnoea in COPD are multifactorial. Primarily, dyspnoea occurs when there is a mismatch between the central neural drive and the incoming afferent information from the peripheral mechanical and chemical receptors (141). The presence of DH has been identified as one of the most important contributors to dyspnoea (44, 142, 143). This is because DH increases the elastic and threshold loads on the inspiratory muscles, thereby increasing the work of breathing. It also shortens and flattens the diaphragm, thereby reducing its mechanical advantage and causing functional inspiratory muscle weakness. These consequences of DH contribute to the alteration of the afferent activity and cause mismatching between the respiratory effort and the mechanical response of the respiratory system (141). The severity of dyspnoea has been demonstrated to increase with an increase in disease severity as well as during an AECOPD (53, 144, 145). This could be explained by the fact that DH is further increased as a result of the increased airflow obstruction during an AECOPD (103). In a 2-year follow-up study of 101 people with moderate to severe COPD, Seemungal et al. (53) reported that 64% of the 504 exacerbations within the 2-year period were associated with an increase in dyspnoea. They also demonstrated that the increase in dyspnoea at the onset of an AECOPD was associated with prolonged recovery time. Specifically, they found that most of the patients who presented with increased dyspnoea at the onset of an exacerbation still reported increased dyspnoea 35 days after the onset of the exacerbation (53).

Regarding measurement, dyspnoea is most often measured using the Borg category ratio scale or in the context of HRQoL (146). The Borg scale has ratio properties with values ranging from zero to 10 together with simple verbal descriptors of intensity such as 'very, very slight' and 'severe' (147). Borg scores are simple to collect, reliable over short periods of times and sensitive to evaluate change in dyspnoea following interventions (e.g. pulmonary rehabilitation program [PRP]) in people with COPD (148, 149). Dyspnoea is also measured as a construct within the assessment of HRQoL using tools such as the Chronic Respiratory Questionnaire (CRQ) (150). In addition to these methods, the other scale commonly reported to assess the impact of dyspnoea during daily life is the modified Medical Research Council (mMRC) scale (151, 152). This scale comprises five statements each of which is assigned a grade that ranges from zero "I only get breathless with strenuous exercise" to four "I am too breathless to leave the house or I am breathless when dressing". The participant selects the statement which best describes their functional limitation resulting from their dyspnoea.

2.2.3.1.2 Fatigue

Another common symptom for people with COPD is general fatigue, defined as a subjective perception of generalised tiredness, exhaustion or lack of energy (146). In a cross-sectional study evaluating the presence of fatigue among people with moderate to severe COPD who had participated in a PRP, Baltzan et al. (153) found that high fatigue was present in 39% of the 251 participants. They also found that those who presented with high fatigue had more depressive symptoms, greater dyspnoea, poorer health status and lower exercise capacity compared to those with low fatigue (153). The mechanism of general fatigue in people with COPD involves the interaction between physiological factors (e.g. hypoxemia and skeletal muscle dysfunction) and psychological factors (e.g. anxiety and depression) (146, 153, 154). For example, in a cross-sectional study of 80 individuals with COPD, depression, QMF and arterial oxygen saturation were identified as being able to explain 62% of the variance in the measurement of general fatigue (154). The severity of general fatigue has also been demonstrated to increase with an increase in disease severity (153-155) as well as during an AECOPD (43). Baghai-Ravary et al. (43) demonstrated that fatigue, measured using the FACIT-Fatigue questionnaire, increased during an AECOPD in as many as 31 (97%) of the 32 patients. The

increased fatigue during an AECOPD is most likely explained by the increase in symptoms of depression, the greater impairment in QMF and worsening of hypoxemia during an exacerbation (43, 46, 108). Increased inflammatory markers (e.g. tumour necrosis factor α) during an AECOPD have also been shown to induce 'sickness behaviour' like lethargy and tiredness (156). With regard to the recovery time for fatigue, Baghai-Ravary et al. (43) found that fatigue had recovered by six weeks following an AECOPD. Recovery time for fatigue within this 6-week period is unknown. Although several scales and questionnaires have been developed to assess general fatigue, in people with COPD general fatigue is commonly assessed as a construct within the assessment of HRQoL using tools such as the CRQ (150).

Other than dyspnoea and general fatigue, people with COPD also report significant leg fatigue, particularly during cycle-based exercise (157-159). For example, when compared to healthy controls, Killian et al. (157) reported a greater proportion of people with COPD stopped their exercise test performed on a cycle ergometer due to intolerable leg fatigue (43% vs. 36%). Among those with COPD, leg fatigue was also more frequently cited (n = 42 [43%]) as symptom limiting exercise than dyspnoea (n = 25 [26%]) (157). Factors contributing to leg fatigue and the impact of AECOPD on muscle fatigue were described in subheading 2.2.2.1.3. Similar to dyspnoea, leg fatigue is often measured using the Borg category ratio scale (147) or a visual analogue scale (160).

2.2.3.2 Decreased exercise capacity

People with COPD have impaired exercise capacity, irrespective of whether exercise capacity is expressed as the maximum work rate achieved during cycle ergometry testing (142, 143), peak rate of oxygen consumption (VO_2 peak) (142, 161), or as the distance walked during a field-based walking test (6, 162, 163). Earlier work has demonstrated that the reasons for terminating exercise tests in people with COPD were either intolerable dyspnoea, leg fatigue or a combination of both dyspnoea and leg fatigue (157-159). In addition to the impairments in lung function, the reduction in exercise capacity is also explained by the reduced oxidative capacity of the quadriceps muscle in this population. Specifically, the reduction in Type I muscle fibres, number of capillary contacts across all muscle fibres as well as the reduction in mitochondrial enzyme activity serve to reduce the oxidative capacity of the muscle and increase its reliance on the anaerobic energy system (161). These changes result

in unusually early increases in arterial lactate, which is a potent respiratory stimulant and increases the ventilatory demand associated with exercise. Consequently, the increased ventilatory demand results in a worsening of lung hyperinflation and contributes to the experience of intolerable dyspnoea and reduced exercise capacity in this population (104).

Exercise capacity has also been shown to be further reduced with an AECOPD (48-50). For example, Carr et al. (50) found that the six-minute walk distance (6MWD) in 29 individuals with COPD was significantly lower two to four weeks following an AECOPD when compared to measurements made during a period of clinical stability (299 ± 99m vs. 359 ± 85m; $p < 0.001$). Of note, the mean reduction of 59 ± 80m reported in this study was greater than the threshold established previously to be considered as the minimal clinically important difference (MCID) for the 6MWD (164). The reduction in exercise capacity during an AECOPD also appears to take a very long time to recover. In another study by the same authors, Carr et al. (165) found that, without any intervention, the 6MWD measured three months following an AECOPD was approximately 30m lower when compared to the pre-exacerbation 6MWD (314 ± 112m vs. 342 ± 87m). The possible mechanisms that explain the reduction in exercise capacity during an AECOPD include an increase in both pulmonary impairments (e.g. DH) and extra-pulmonary impairments (e.g. skeletal muscle dysfunction) during an AECOPD (46, 103).

Regarding measurement, exercise capacity can be assessed using either laboratory-based exercise tests, done on a cycle ergometer or a treadmill, or via field-based exercise tests such as the 6MWT and the incremental shuttle walk test (ISWT) (166-168). Although laboratory-based tests are considered the gold standard for quantifying exercise capacity and provide information which assists in determining the mechanism of limitation, field-based tests are a popular choice as they can be performed at low cost in the clinical setting, require less technical expertise and are more representative of activities of daily living compared to laboratory-based exercise tests (169, 170). Moreover, the measurement properties of field-based tests have been studied extensively (171).

In addition to these laboratory and field-based walking tests, there are emerging data to support the use of other tests of functional performance in people with COPD,

such as the Sit to Stand Test (STST) and the Timed Up and Go (TUG) test. Several variations of the STST protocol are available. These include the original 'timed-stands' test that measures the time taken to perform 10-STS (172), the shorter version of the original 'timed-stands' test (i.e. the 5-STS) (173), and the number of sit to stands (i.e. STST) performed within 30s or one minute (174, 175). Measures obtained during the STST demonstrated a moderate and strong association with the 6MWD ($r = 0.69$ to 0.75; $p < 0.001$) (176, 177)and the ISWT ($r = -0.59$; $p < 0.001$) (178). Measures obtained during the STST have also demonstrated high test-retest repeatability with intraclass correlation coefficient (ICC) values ranging from 0.84 to 0.92 (179) and the STST appears to be responsive to change with several studies demonstrating significant improvements in the test outcome following exercise training in people with stable COPD (175, 180, 181).

Regarding the TUG test, this involves measuring the time required for an individual to get up from a chair, walk to a 3m mark, turn around, walk back to the chair and sit down (182). Two variations of instructions used during this test have been reported in the literature. In the original protocol developed by Podsiadlo and Richardson (182), participants are instructed to perform the task 'at a comfortable and safe pace'. In the second protocol by Shumway-Cook et al. (183), participants are instructed to perform the task 'as quickly as they could' (i.e. at maximum effort). Kamide et al. (184) found that the TUG performed using instruction that asked for a maximum effort resulted in the task being performed at least 2s faster and appeared to be more reliable than the TUG performed at a comfortable pace. In people with COPD, the time required to perform the TUG test has demonstrated a strong association with the 6MWD ($r = -0.74$; $p < 0.001$) (185). The TUG test has good test-retest reliability with the kappa coefficient and the ICC reported for repeated TUG tests in people with COPD being 0.62 and 0.85, respectively (186). The performance in the TUG test has also been shown to be able to detect change following an exercise training program in people with stable COPD (187, 188).

2.2.3.3 Low levels of PA

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (189). There is a considerable amount of evidence showing that people with COPD have a low level of PA compared to their age-matched healthy counterparts (190-193). For example, Pitta et al. (190) found that

people with COPD spent, on average, less time walking (44 ± 26 vs. 81 ± 26 minutes/day) and standing (191 ± 99 vs. 295 ± 109 minutes/day) and walked at a slower speed (1.8 ± 0.3 vs. 2.4 ± 0.5m/s^2) compared to age-matched healthy controls. In another example, Singh et al. (193) found that people with COPD recorded significantly lower counts of PA even on light activity such as slow walking when compared to healthy controls (17 ± 13 counts/min vs. 28 ± 10 counts/min). The reasons underpinning the reduced PA levels in people with COPD can be explained in part by the increased symptoms of dyspnoea on exertion, general fatigue as well as the reduced exercise capacity in this population. People with COPD often adopt a sedentary lifestyle as strategy to minimise their experience of dyspnoea (190, 194). The reduction in daily activity levels from adopting a more sedentary lifestyle in turn results in further deconditioning of muscles, particularly the muscles of locomotion (e.g. quadriceps) which increases the reliance on anaerobic metabolism at lower work rates (195). This leads to the sensation of dyspnoea at lower levels of PA and the dyspnoea-inactivity cycle continues. In addition to dyspnoea, Todt et al. (196) reported that those with severe fatigue, as measured using the Fatigue Impact Scale (197), had nearly a six-fold higher probability of having low levels of PA.

A gradual reduction in several measures of PA, such as average daily steps, total time spent on walking and level of PA (i.e. total daily energy expenditure/whole-night sleeping energy expenditure), has been reported between people grouped according to GOLD grades (198-200) as well following an AECOPD (47, 51, 201-203). When compared to measurements made during periods of clinical stability, Pitta et al. (47) found that those hospitalised for an AECOPD spent less time in weight bearing activities (e.g. standing and walking) and more time sitting and lying. Importantly, they also found that the time these patients spent on weight bearing activities (median, 19% [interquartile range, 10 to 34%]) a month after hospital discharge was lower than those with stable COPD (33 ± 16%) as well as the healthy elderly (52 ± 16%) (47). The mechanisms that most likely explain the decline in PA during an AECOPD are the increase in dyspnoea and fatigue, the greater impairment in QMF as well as the ‘sickness behaviour’ that can be induced from the increase in inflammatory markers during an AECOPD (43, 53, 156).

Regarding measurement of PA, subjective or self-reported methods as well as objective methods have been described (204). Questionnaires and diaries are examples of subjective measures used to quantify the level of PA in daily life (205). Quantifying PA through these methods has the advantage of being inexpensive and easy to administer. However, factors such as recall bias, cognitive ability and interviewer attitudes have been shown to affect the reliability and validity of measures obtained using subjective methods of assessment (206). In order to overcome some of the limitations associated with subjective measures of PA, the use of devices objectively measure PA has increased. Devices available for this purpose include pedometers which are used for measuring steps, accelerometers for detecting body acceleration and metabolic monitors such as the SenseWear armband (BodyMedia Inc., Pittsburgh, Philadelphia, USA). Pedometers are usually small and simple instruments used to measure the number of steps taken by an individual. They are often inexpensive and the output of the device (i.e. steps) is easily understood. However, pedometers can be affected by artefact, in which any vertical movement, such as that associated with car travel, is counted as a step (204). Further, they often lack of sensitivity to detect slow or shuffling gait patterns (207-209). In contrast, accelerometers, which measure movement in one or more planes, have the capacity to detect slow walking, with some providing more varied and detailed information regarding PA undertaken in daily life. There are also hybrid devices, such as the StepWatch^{TM} Activity Monitor (SAM) (Modus Health IIc, Washington, USA) which is a microprocessor-driven pedometer with a multi-level sensor that responds to time, position and acceleration information to record the number of steps in a detailed minute by minute profile. The SAM has shown to be valid, reliable and responsive for measuring steps in people with COPD (210, 211). Two studies that investigated the accuracy of the SAM in people with COPD found that the SAM had more than 90% accuracy in 99% of the participants (210) and there was no significant difference between steps recorded by the device and steps counted via direct observation ($p = 0.63$) (211). The major advantages of the SAM over other devices are that the SAM is easy to use (waterproof and unobtrusive for the wearer), is highly-durable (the battery lasts for 7 years of continuous use) and can continuously record data for up to two months (212). More importantly, the device has been shown to be sensitive in detecting changes in walking speed and accurate in recording steps in people who walk with a walking aid (211).

2.2.3.4 Impaired HRQoL

The term HRQoL refers to the impact of disease on daily life and well-being (213). Compared with healthy individuals, people with COPD have demonstrated lower HRQoL (214-216). For example, Peruzza et al. (214) compared the HRQoL measured using the St George's Respiratory Questionnaire (SGRQ) between 60 people with COPD and 58 healthy controls and found that the score in each domain of the SGRQ was significantly higher (i.e. worse) in people with COPD. The mean differences in the scores for each item were also greater than the threshold established previously as the MCID (i.e. 4 units) for the SGRQ (217). Specifically, the differences in SGRQ were 56.5 vs. 11.8 for the total score, 65.7 vs. 13.6 for the activity domain, 51.1 vs. 10.6 for the impact domain and 56.6 vs. 12.4 for the symptom domain in those with COPD vs. healthy controls (all $p < 0.01$). The low HRQoL in people with COPD can be explained by several clinical characteristics of people with COPD such as disease severity, symptoms of dyspnoea and fatigue, decreased exercise capacity, low levels of PA as well as feelings of anxiety and depression (40, 214, 218, 219). For example, in addition to demonstrating lower HRQoL in people with COPD when compared with healthy controls, Peruzza et al. (214) found that FEV_1, mMRC dyspnoea scale as well as the 6MWD were significantly correlated with the total SGRQ score in people with COPD.

Health-related quality of life has also been shown to be further reduced during an AECOPD (50). When compared to measurements made during a period of clinical stability, Carr et al. (50) found that the presence of an AECOPD was associated with significant reductions in the fatigue, emotional function and mastery domains of the CRQ by a mean of 1.0 ± 1.3 unit, 0.6 ± 1.0 unit and 0.5 ± 1.4 unit, respectively (all $p < 0.05$). Of note, the mean reduction in the score for each domain was also greater than the threshold established previously as the MCID (i.e. 0.5 unit) for the CRQ (220). Factors such as increased severity of airflow obstruction, symptoms of dyspnoea and fatigue, and anxiety and depression during an exacerbation as well as the greater impairment in skeletal muscle, reduction in exercise capacity and PA levels may explain the greater impairment in HRQoL during an AECOPD (43, 47, 50, 53)

Regarding measurement, HRQoL can be measured either using general/generic or disease-specific questionnaires (221). Generic questionnaires such as the 36-item

(SF-36) survey and the Sickness Impact Profile allow comparisons of HRQoL among individuals with a wide range of diseases. On the other hand, disease-specific questionnaires were developed to measure the key impact a specific condition or disease has on HRQoL (221). The SGRQ and CRQ are the two examples of disease-specific HRQoL questionnaires for people with COPD (222, 223). Both questionnaires measure domains considered to be important in determining HRQoL in individuals with COPD. These include dyspnoea, fatigue, emotional function and mastery in CRQ, and symptom, impact and activity in the SGRQ (222, 223). The main advantage of disease-specific HRQoL questionnaires is that they are more responsive to small changes in health status (221).

2.2.4 Summary

Chronic obstructive pulmonary disease is associated with both pulmonary and systemic consequences. Pulmonary pathology in COPD includes changes (i.e. destruction and repair) throughout the central and peripheral airways, lung parenchyma and pulmonary vasculature. One of the most important systemic consequences of COPD is quadriceps muscle dysfunction. When compared to healthy controls, people with COPD demonstrated a reduction in QMF and endurance, lower exercise capacity, and low levels of PA and HRQoL. Hospitalisation for AECOPDs have been shown to further impair the negative consequences associated with COPD. That is, when compared to people with COPD who are clinically stable, those hospitalised for an AECOPD demonstrated a greater impairment in QMF, worse exercise capacity, lower levels of PA and poorer HRQoL. Importantly, the impact of hospitalisation for an AECOPD on some of these outcomes (e.g. QMF, exercise capacity and PA) appears to take a very long time to recover.

2.3 Part 3

Although the 6MWT is a popular assessment of exercise capacity in people with COPD, in some populations, such as those hospitalised for an AECOPD, people are likely to need to rest frequently, or for prolonged periods during the test, due to intolerable dyspnoea. Therefore, the 2MWT may be an appropriate alternative to the 6MWT for measuring functional exercise capacity, particularly in patients characterised by profound dyspnoea on exertion. In contrast to the 6MWT where data pertaining to the measurement properties and interpretation of the test outcome

(i.e. the 6MWD) have been extensively reported, data pertaining to the measurement properties of the 2MWT and the interpretation of the two-minute walk distance (2MWD) are lacking (224). Section 2.3.1 reviews the literature which has reported data pertaining to the measurement properties of the 2MWT. Section 2.3.2 describes the cardiorespiratory responses and levels of symptoms during the 2MWT. Section 2.3.3 reviews the studies that have reported the regression equations to estimate the 2MWD in healthy adults.

2.3.1 Measurement properties of the 2MWT

The measurement properties of an assessment tool are often reported using criteria such as reliability, validity and responsiveness. The following sections review the literature pertaining to the measurement of reliability, validity and responsiveness of the 2MWT in people with COPD. Studies in other populations are reviewed when there are no data pertaining to the measurement of reliability, validity and responsiveness of the 2MWT in people with COPD.

2.3.1.1 Reliability and the effect of test repetition

Estimates of reliability are most often evaluated in terms of inter- and intra-rater reliability (225). Inter-rater reliability relates to the variation in measurements when two or more tests are performed on the same group of individuals but by different investigators. Intra-rater reliability refers to the variation in measurements when two or more tests are performed on the same group of individuals by the same investigator. In other words, inter-rater reliability measures the effect that changing the investigator has on the test outcome, while intra-rater reliability (i.e. also known as repeatability) measures the reliability of the test, in this instance the 2MWT, when all other variables (e.g. participants, environment and investigator) are constant. To date, four studies have evaluated the reliability of the 2MWD in people with COPD (1, 2, 7, 8). Of these four studies, all have reported the reliability of the 2MWDs performed by the same investigator (i.e. intra-rater reliability or repeatability). Two reported a small but significant increase in the 2MWD with test repetition (2, 7), one reported a small difference, which is likely to have been significant (1) and one found no change in the 2MWDs on repeat tests (8) (Table 2.2). Disparities in the results may have been due to the differences in the 2MWT protocol used between the studies. For example, in the only study that did not demonstrate a significant improvement in the 2MWD with test repetition, the participants were given a

practice walk a day prior to the actual testing day (8). Therefore, the effect of test repetition on the 2MWD in this study could have been minimised as the participants were familiar with the test. Although this discrepancy in results may be explained by the inclusion or otherwise of a practice walk, it is also important to note that these four studies were undertaken prior to the publication of standards for performing the filed-based walk test (226), and the protocol they used were either not described (1), provided no encouragement (8), had the investigator walking in front of the patient during the test (7) or included a mixed sample of patients with COPD and chronic heart failure (2). Therefore, the effect of test repetition on the 2MWD in people with COPD performed using a protocol based on the standards for performing field-based walk test is unknown.

Although indices such as ICC, coefficient of variation (CV) and differences in mean 2MWDs analysed using either a paired t-test or analysis of variance are used to report aspects of reliability (Table 2.2), these measures only provide information about group data, not about individual variability. In contrast, indices of reliability such as the standard error of measurement (SEM) and coefficient of repeatability (COR) can be applied to provide an estimate of a range of values within which an individual's true score is likely to lie (227). That is, a difference in the 2MWDs that is greater than the measurement error reported using these indices can be interpreted as a change that is beyond the threshold of error inherent in the test and may represent a true change in this outcome. However, neither the SEM nor the COR for the 2MWD have been reported in people with COPD.

Table 2.2: Reliability measures for the 2MWD in people with COPD

Author/ year	Participants	Test protocols	Inter-rater reliability	Test-retest reliability p-values	ICC	CV
Butland et al. 1982 (1)	n = 13 Age = 51 ± 14 yr FEV_1 = 0.98 ± 0.25L FEV_1% = NR	Practice test: No Test-retest intervals: ≥ 1hr	NT	***Within-day measures*** W1 vs. W2 ↑4m (3%); p value = NR W2 vs. W3 ↑5m (4%); p value = NR W3 vs. W4 ↑1m (1%); p value = NR	NT	NT
Guyatt et al. 1984 (2)	n = 43 Age = 65 ± 8yr FEV_1 = 0.97 ± 0.25L FEV_1% = NR	Practice test: No Test-retest intervals: 2 weeks	NT	***Between-day measures*** p < 0.0001 on repeated 2MWDs	NT	5.4%
Eiser et al. 2003 (7)	n = 57 Age = 69 ± 8yr FEV_1 = 0.92 ± 0.38L FEV_1% = 35±12%	Practice test: No Test-retest intervals: 30 min and 1 week	NT	***Within-day measures*** W1 vs. W2 ↑3m (2%); p < 0.05 W2 vs. W3 ↑2m (1%); p > 0.05 *Between-day measures* D1 vs. D2 ↑4m (3%); p < 0.05 D2 vs. D3 ↑-1m (1%); p > 0.05	NT	NT
Leung et al. 2006 (8)	n = 45 Age = 72 ± 8yr FEV_1 = 0.88 ± 0.27L FEV_1% = 42 ± 13%	Practice test: Yes Test-retest intervals: 20 min	NT	*Within-day measures* W1 vs. W2 ↑0.3m (0.2%); p > 0.05 W2 vs. W3 ↑0.5m (0.4%); p > 0.05	> 0.99	NT

Data are presented as mean ± standard deviation. Abbreviations: 2MWD, two-minute walk distance; CV, coefficient of variation; D1, day 1; D2, day 2; FEV_1, forced expiratory volume in one second; hr, hours; ICC, intraclass correlation coefficient; m, metres; min, minutes; NR, not reported; NT, not tested; SD, standard deviation; W1, walk 1; W2, walk 2; yr, year.

2.3.1.2 Validity

Validity is the extent to which a test measures what it is intended to measure (225). In relation to the 2MWT, validity measures the degree to which the distance walked during the test is a measurement of functional exercise capacity. Although the 2MWT, by virtue of being a walking-based test of exercise tolerance, has inherent face and content validity, this alone is not adequate proof of its validity, as both face and content validity rely on subjective opinions (225). With regard to criterion-related validity, earlier work has demonstrated a moderate association between the 2MWD and measures of VO_2 peak ($r = 0.45$; $p = 0.002$) obtained during a laboratory-based cardiopulmonary exercise test (i.e. the gold standard in measuring exercise capacity) (8). Further, the 2MWD has been shown to be strongly associated with the distance walked during the 6MWT ($r = 0.89$ - 0.94) (1, 8) and the 12MWT ($r = 0.86$) (1). Data pertaining to the construct validity of the 2MWT have been reported in populations other than COPD (228, 229). Rossier et al. (229) demonstrated that the 2MWD in patients with neurological disabilities was significantly lower in those who used a walking aid compared to those who walked independently (38 ± 21m vs. 84 ± 30m; $p < 0.001$). They also reported a lower 2MWD in those who presented with sensory impairment than those who did not present with sensory impairment (49 ± 28m vs. 68 ± 36m; $p = 0.02$). This capacity of the 2MWD to discriminate between patients with or without impairments in mobility supports its validity.

2.3.1.3 Responsiveness

Responsiveness is a measure of the capacity of a test to detect change over time (225). In people with COPD, the 2MWD has been shown to be responsive to changes following bronchodilator therapy and a PRP (7, 8). Specifically, the 2MWD increased by 9 ± 1m ($p < 0.001$) following bronchodilator therapy and 17 ± 14m ($p < 0.01$) following a PRP (7, 8). Leung et al. (8) also reported moderate effect sizes for the change in both the 2MWD and the 6MWD following a PRP (i.e. $f^2 = 0.61$ and 0.53, respectively). However, these earlier studies were both undertaken in people with COPD who were clinically stable and therefore the responsiveness of the 2MWD to change following interventions (e.g. exercise training) during an AECOPD is unknown. Further, although the changes in the 2MWD after bronchodilator therapy and PRP in these two studies were significant, it is not known if they were clinically important. This is because data pertaining to the MCID,

defined as the smallest difference in the 2MWD that is noticeable and considered important for people with COPD, has not been established.

2.3.2 Cardiorespiratory responses and levels of symptoms during the 2MWT

Although the 2MWT is likely to be a less burdensome measure of exercise capacity when compared to the 6MWT and the 12MWT (1, 7, 8), there are few studies comparing responses elicited during these tests. To date, one study has compared the levels of symptoms during the 2MWT with those during the 6MWT (8). In this study, Leung et al. (8) reported a significantly higher rating of perceived exertion (RPE) on completion of the 6MWT compared to the 2MWT in people with moderate to severe COPD (3.0 ± 2.0 vs. 3.3 ± 0.3; $p < 0.05$). However, it is important to note that performance was encouraged during the 6MWT but not during the 2MWT, and this may have contributed to the higher RPE elicited at the end of the 6MWT. No studies have compared the cardiorespiratory responses elicited during the 2MWT and the 6MWT in people with COPD or other clinical populations. Such data are important, especially in people characterised by profound dyspnoea, as they will assist in determining whether or not the 2MWT is better tolerated than the 6MWT.

2.3.3 Regression equations to estimate the 2MWD in a healthy adult population

To date, there are two published regression equations which were developed to estimate the 2MWD in healthy adult populations; one was derived from a sample of Brazilian adults (17) and the other one was derived from a sample of American adults (18). Equations such as these offer clinicians and researchers the opportunity to express the 2MWD measured in patient populations as a percentage of the value estimated in healthy individuals. This section will compare these equations and summarise the factors which are most likely to contribute to the 2MWD in a healthy adult population.

2.3.3.1 Studies that have established regression equations to estimate the 2MWD

Selman et al. (17) derived an equation to estimate the 2MWD from a convenience sample of 390 healthy Brazilian adults. The 2MWT was performed in a 30m corridor and all participants completed two 2MWTs with a 30-minute rest interval between tests. The participants were instructed to walk as fast as possible and a standardised phrase of encouragement was provided only once (i.e. at one minute) during the test.

The better of the two 2MWDs was used in their analysis. The regression equation derived in this study is presented in Table 2.3. Although the 2MWD was significantly different between males and females and associated with age ($r = -0.50$), weight ($r = 0.23$) and height ($r = 0.40$) (all $p < 0.001$), only age and gender were retained in the equation. Together, these variables explained 51% of the variance in the 2MWD in this sample. Selman et al. (17) demonstrated that men walked 12% further than women. The finding that men walked further than women during the 2MWT is most likely explained by gender related differences in aerobic capacity, muscle mass and, of particular importance for walking-based tests, height and stride length. That is, when compared to women, men are generally taller, and taller individuals walk with a longer stride length when compared with shorter individuals. The finding that the 2MWD decreased with advancing age may be explained by the physiological changes that accompany ageing such as the decline in muscle mass (230, 231).

In the other study, Bohannon et al. (18) derived two gender-based equations to estimate the 2MWD from a sample of 1,137 American adults. The 2MWT was performed over a 15m walking course. Similar to the study by Selman et al. (17), the participants were instructed to walk as fast as possible and a standardised phrase of encouragement was provided only once (i.e. at 1 minute) during the test. The regression equation derived in this study is shown in Table 2.3. Although Bohannon et al. (18) demonstrated that the 2MWD was associated with age ($r = -0.41$), body mass index (BMI, $r = -0.32$), height ($r = 0.29$) and weight ($r = -0.16$) (all $p < 0.001$), only BMI and age were retained in the equation for each sample. These equations explained 56% and 57% of the variance in the 2MWD in males and females, respectively. Similar to the study by Selman et al. (17), this study found that age offered the best explanation of the 2MWD in both men and women. However, Bohannon et al. (18) found that BMI also explained a significant proportion of variance in the 2MWD in their sample. The importance of BMI in the regression equation derived in the American study is most likely explained by the higher BMI (mean ± SD, 29 ± 7kg/m^2) and wider range of BMIs (17 – 58kg/m^2) in their study participants when compared to the BMIs in the Brazilian study (median [inter-quartile range], 25kg/m^2 [23 - 28kg/m^2]).

Table 2.3: Regression equations to estimate the 2MWD

Author	Regression equations	R^2
Selman et al. (17)	2MWD, m = 252.583 - (1.165 × age, yr) + (19.987 × gender*)	0.51
Bohannon et al. (18)	♂: 2MWD, m = 279.096 - (0.998 × age, yr) - (1.426 × BMI)	0.56
	♀: 2MWD, m = 257.177 - (0.723 × age, yr) - (1.688 × BMI)	0.57

*male = 1, female = 0
Abbreviations: 2MWD, two-minute walk distance; BMI, body mass index; m, metres; yr, year.

2.3.3.2 Factors likely to influence the 2MWD

2.3.3.2.1 Participant characteristics and effort during the test

Although earlier work has reported that age, gender and BMI are important factors in determining the 2MWD in healthy individuals (17, 18), studies that have established regression equations for the 6MWD have included other variables such as height and leg length (21), weight (21, 39), daily PA (30) and peak heart rate (HR) (19-21). The following section describes factors related to participant characteristics other than age, gender and BMI and markers of participant effort (e.g. peak HR) that are likely to influence the 2MWD.

Both of the studies that developed regression equations to estimate the 2MWD demonstrated that height has a weak to moderate association with the 2MWD (17, 18). This is consistent with most of the studies that have established regression equations to estimate the 6MWD (21, 28, 33-35). Similar to the explanation regarding why men usually walked a greater distance during walking-based tests when compared to women, the influence of height and leg length on walking distance can also be explained by a taller height or longer leg length being associated with a longer stride length and thus resulting in a longer distance walked (32). Weight has been shown to have a weak association with the 2MWD ($r = -0.16$ to 0.23) (17, 18) as well as the 6MWD ($r = 0.21$ to 0.38) (28, 36, 39). This might be related, at least in part, to the narrow range in weight among the participants in the studies in this area. Dependent variables that have a narrow range in values are less likely to be retained in a regression equation.

Although it is possible that the distance achieved during the 2MWT is influenced by a participant's daily PA, most of the studies that have evaluated the influence of daily PA on the 6MWD have demonstrated no significant association between these two variables (20, 22, 23, 33). Being a self-paced walk test, the participant's mood and motivation may also influence the 2MWD. As it is difficult to ascertain whether a participant is performing at their peak during a walking test, it has been suggested that peak HR achieved during the test be used as a surrogate measure of the participant's effort during the test (25). In view of this, several studies that have established a regression equation for the 6MWD have also reported the peak HR measured during the test, expressed as a percentage of the predicted maximum HR

(i.e. [peak HR / 220-age] x 100) (20, 22-26, 31). In some of these studies, the percentage of the predicted maximum HR achieved on test completion was also identified as a predictor of the 6MWD and explained an additional 13% to 21% of the variance in the 6MWD (19, 20, 25). As both of the previously published regression equations to estimate the 2MWD did not include this variable in the analysis, it is unknown whether the addition of peak HR would increase the total variance explained by the regression equations.

2.3.3.2.2 Ethnicity

In addition to differences in the participant characteristics and markers of participant effort, earlier work that has established regression equations to estimate the 6MWD has demonstrated differences in the 6MWD between samples of different ethnicities. Specifically, in two studies (21, 39) where the 6MWT was performed using an identical protocol and by the same team of investigators in an Australian sample and a Singaporean sample, the equations not only retained different predictors for the 6MWD but also different coefficients for the same predictors (Table 2.4). This suggests that factors other than the test protocol may influence walking performance. When the regression equation derived from a sample of Singaporean adults (21) was compared with the regression equation derived from a sample of Australian adults (39), the influence of weight on the 6MWD was greater in Singaporeans than Australians. That is, for every 1kg increase in weight, the 6MWD would decrease by 3.51m using the equation derived from Singaporean adults and decrease by only 1.15m using the equation derived from Australian adults. Differences in the influence body weight has on the 6MWD in these equations may be explained by differences in body composition between the samples. That is, differences in body build (trunk-to-leg-length ratio and slenderness) between Asians and Caucasians result in Asians having a lower percentage of lean body mass (i.e. higher percentage of fat mass) for a given BMI when compared to Caucasians (232). As a result, an increase in weight or BMI in Asian is more likely to reflect an increase in body fat and therefore compromised walking distance. This suggests that the two previously published regression equations to estimate the 2MWD will be of most use for Brazilian (17) and American (18) people, but may be less accurate for people from other countries.

Table 2.4: Regression equations to estimate the 6MWD in Chinese Singaporeans and Caucasian Australians

Author	Ethnicity	Regression equations	R^2
Poh et al. (21)	Chinese Singaporean	6MWD, m = (5.50 × % predicted HRmax) + (6.94 × height, cm) - (4.49 × age, yr) - (3.51 × weight, kg) - 473.27	0.78
Camarri et al. (39)	Caucasian Australian	6MWD, m = 216.90 + (4.12 × height, cm) - (1.75 × age, yr) - (1.15 × weight, kg) - (34.04 × gender*)	0.36

*male = 1, female = 0

Abbreviations: 2MWD, two-minute walk distance; BMI, body mass index; cm, centimetres; HRmax, heart rate maximum; kg, kilograms; m, metres; yr, year.

2.3.3.2.3 Differences in the administration of the test

It appears that the length of the walking track used to conduct the test may influence the 2MWD. For example, the 2MWD in the study by Bohannon et al. (18) was shorter (181 ± 33m) when compared to the study by Selman et al. (17) (median [interquartile range], 211 [191 – 234]) and the study by Bohannon used a walking track which was 15m less than that used by Selman et al. (17) (15.2m vs 30m). Performing the 2MWD over a shorter track length may compromise the distance achieved as it requires participants to slow down to turn and reverse direction more frequently (24, 33, 233). Although the current ERS/ATS technical standard for conducing field-based walking tests does not provide recommendations for the minimal track length for a 2MWT, it states that the 6MWT should be performed on a track ≥ 30m (226). In addition to track length, the shorter 2MWD in the study by Bohannon et al. (18) when compared to the 2MWD in the study by Selman et al. (17) may also be attributable to the fact that the participants in the study by Selman et al. (17) had the opportunity to improve their 2MWD as they undertook two tests and the best test result was used in the regression analysis. Selman et al. (17) reported that majority of the participants (n = 295 [76%]) in their study walked a greater distance in the second 2MWT.

Other components of test protocol that may influence performance during the 2MWT include the shape of the walking track (234, 235) and the use of test instructions (236). Although data are lacking for the 2MWD, earlier work has demonstrated that modifying track layout from a straight to a circular/oval track increased the 6MWD by as much as 28m (234, 235). Further, participants have been shown to walk 53m further on the 6MWT with the instruction to walk ‘as fast as possible’ compared to other instructions such as to walk ‘at your normal pace’ (236). Although factors such as track length and layout, accounting for improvements that result from test familiarisation and differences in instructions are not variables included in regression equations, the impact these factors have on the 6MWD suggests that these factors need to be standardised in future studies that aim to develop a regression equation to estimate the 2MWD in healthy adults.

2.3.4 Summary

In people who experience severe dyspnoea on exertion, such as those with severe stable COPD or those who are hospitalised for an AECOPD, a short test, such as the 2MWT, may be an appropriate alternative to the 6MWT to measure functional exercise capacity. However, data pertaining to the measurement properties of the 2MWT are scarce and no studies to date have compared the cardiorespiratory responses elicited during the 2MWT and the 6MWT in this population. Data pertaining to the interpretation of the 2MWD are also limited. Regression equations to estimate the 2MWD in populations other than Brazilian and American are not available. In order for the uptake of the 2MWT to increase in clinical practice, more data are needed on the measurement properties of the 2MWD. Further regression equations derived in local populations would assist in the interpretation of the 2MWD. These data would also promote the use of the 2MWT as a measurement of exercise capacity to evaluate the effect of interventions particularly in population for whom the 6MWT may be considered too burdensome.

2.4 Part 4

In people with stable COPD, there is strong evidence that a PRP which includes exercise training leads to an improvement in multiple outcomes including dyspnoea and fatigue (60), feelings of anxiety and depression (61), exercise capacity (60), and HRQoL (60, 61). There is also some evidence demonstrating the benefits of exercise training in this population on outcomes such as rate of exacerbation (237) and healthcare utilisation (238). However, data to support the benefits of PRPs or exercise training during a period of hospitalisation for an AECOPD are limited. Although a Cochrane review has reported that exercise training initiated during the period of hospitalisation or immediately following discharge for an AECOPD is safe and effective at improving exercise capacity and HRQoL (239), only one RCT in this review included an exercise program which commenced within two to three days of hospitalisation for an AECOPD (240). However, this study extended the in-patient exercise program to include an eight weeks after discharge out-patient rehabilitation program and only evaluated the effect of the exercise training on completion of the out-patient program (240). Therefore, data included in the Cochrane review do not provide information regarding the safety or effectiveness of an exercise program within the period of hospitalisation for an AECOPD. Since the time of the Cochrane

review, another eight RCTs evaluating the effects of exercise training in people hospitalised for an AECOPD have been published with mixed results. This part of the thesis reviews studies which have reported the effects of exercise training in people hospitalised for an AECOPD (Figure 2.1). Specifically, section 2.4.1 reviews the studies that investigated the effect of exercise training initiated in people admitted to a hospital ward (i.e. not an intensive care unit) for an AECOPD. Section 2.4.2 reviews the studies that investigated the effect of exercise training in people who had been recently discharged from hospital for an AECOPD. Both sections focus on the effect that exercise training has on outcomes of exercise capacity, QMF and PA.

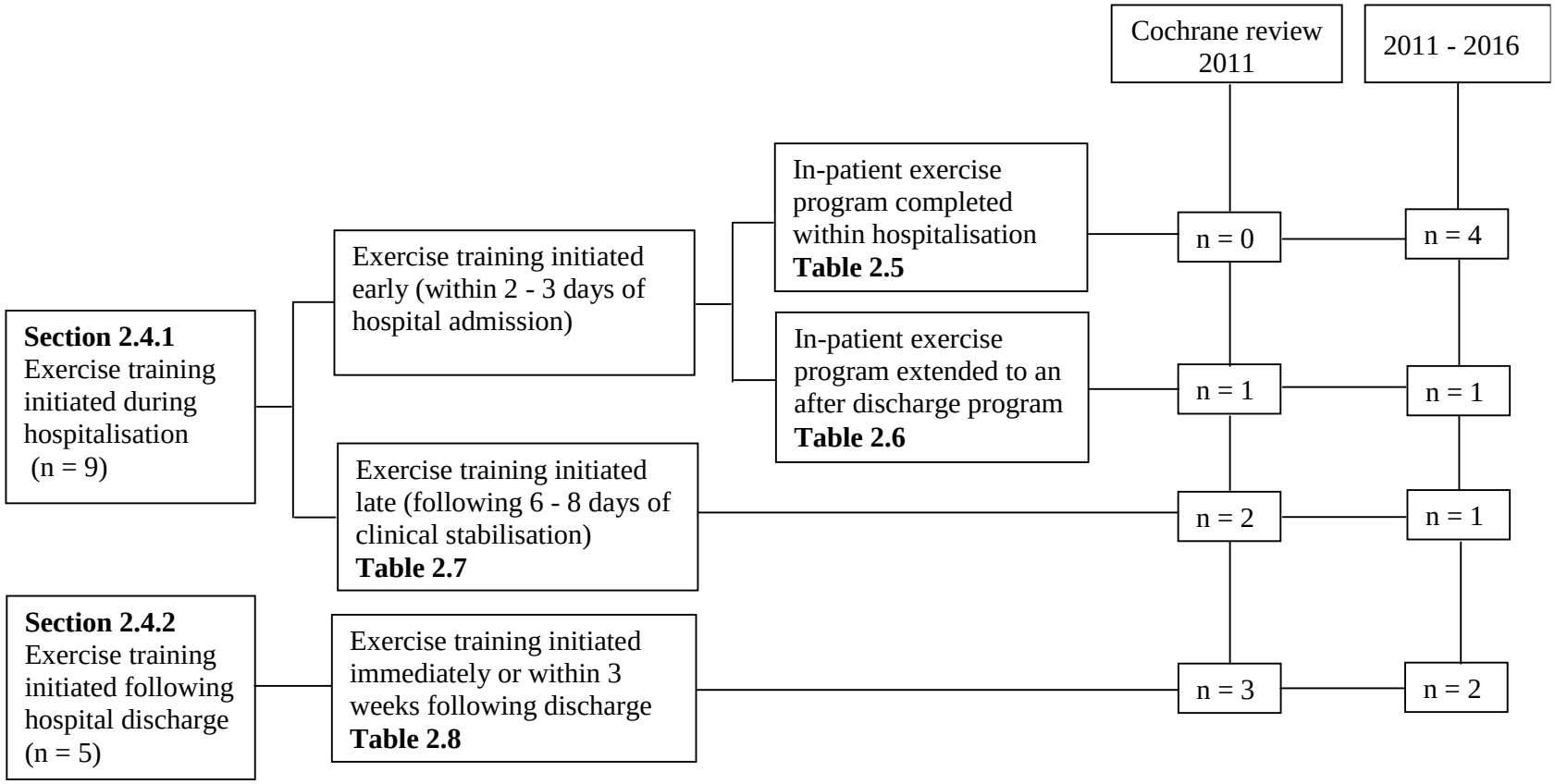

Figure 2.1: Overview of the studies reviewed in part 4 of the literature review**.**
Abbreviation: n, number of studies.

2.4.1 Exercise training initiated during the period of hospitalisation

To date, nine studies, published as full papers, have evaluated the effects of exercise training initiated during the period of hospitalisation for an AECOPD (65-67, 70-72, 240-242). These studies have applied an exercise training intervention in one group and usual care in the control group (CG). The sample sizes ranged from 26 to 389 and the participants had moderate to severe COPD. Of these nine studies, six (67%) initiated exercise training early (i.e. within two to three days of hospital admission) (70-72, 240-242) (Table 2.5 and Table 2.6) and three (33%) initiated exercise training after a period of stabilisation in clinical status (i.e. between 6 and 8 days after hospital admission) (65-67) (Table 2.7). Although all nine studies initiated the exercise program during the period of hospitalisation, five (56%) completed the training program prior to in-patient hospital discharge (65, 70-72, 242) and four (44%) extended the in-patient exercise program with an after discharge program (66, 67, 240, 241). The training protocols applied in these RCTs varied considerably with two (22%) prescribing exclusively resistance training (71, 72), two (22%) prescribing exclusively aerobic training (65, 67), four (44%) prescribing a combination of aerobic and resistance training (66, 70, 240, 242) and one (11%) prescribing neuromuscular electrical stimulation in addition to a combination of both aerobic and resistance training (241). The mean number of training sessions completed during the hospitalisation period ranged from three to 10 sessions (65-67, 70-72, 241).

Of these nine studies, four (44%) reported a robust randomisation process (70, 71, 240, 241), five (56%) reported concealment of the randomisation sequence (70-72, 240, 241) and four (44%) reported blinding of the outcome assessors (70, 71, 240, 241). Information pertaining to the concealment of the randomisation sequence and blinding of the outcome assessor was not provided in three (65, 67, 242) and four (65-67, 242) studies, respectively. The loss to follow-up ranged between 6% and 37% in studies where exercise training was completed within the hospitalisation period (70-72, 242), and 13% (240) and 20% (241) when the in-patient exercise program was extended past hospital discharge.

Table 2.5: Summary of studies where exercise training was initiated within two to three days of hospital admission and completed within the period of hospitalisation

Author/ year	Intervention CG	EG		Significant between-group difference in favour of EG
Troosters et al. 2010 (72)	n = 19, FEV_1 = 50 ± 18%, age = 69 ± 7yr Chest physiotherapy for airway clearance and breathing exercises + no exercise program provided during admission or after discharge	n = 17, FEV_1 = 40 ± 12%, age = 67 ± 8yr Usual care + quadriceps strengthening on knee extension chair at 70% of 1RM for 3 sets of 8 repetitions Duration: 1 session/day for 7 days		*Re-assessment at discharge* ↑QMF
Tang et al. 2012 (70)	n = 11, FEV_1 = 47 ± 20%, age = 78 ± 9yr Chest physiotherapy for airway clearance, mobility assessment and functional training for safe discharge	n = 11, FEV_1 = 45 ± 19%, age = 68 ± 10yr Low intensity EG Usual care + 7.5min walking at 40% of speed during 3MWT + hip abduction, lunges, simulated lifting and chest press at 40% of 1RM for 20-25 repetitions Duration: 2 sessions/day throughout hospitalisation	n = 10, FEV_1 = 46 ± 18%, age = 74 ± 10yr Moderate to high intensity EG Usual care + 7.5min walking at 70% of speed during 3MWT + hip abduction, lunges, simulated lifting and chest press at 70% of 1RM for 8-10 repetitions Duration: 2 sessions/day throughout hospitalisation	*Re-assessment at discharge* No significant between-group differences reported in any outcomes
Borges et al. 2014 (71)	n = 14, FEV_1 = 39 ± 16%, age = 68 ± 9yr Chest physiotherapy for airway clearance, NIV if needed, and verbal instruction to carry on with usual PA + no exercise program provided during admission or after discharge	n = 15, FEV_1 = 42 ± 14%, age = 64 ± 13yr Usual care + WBET 80% of 1RM for sh flexion and abduction, elb flexion, hip flexion kn flexion and extension for 2 sets of 8 repetitions Duration: 1 session/day throughout hospitalisation		*Re-assessment at discharge* ↑6MWD ↑Sh abductors muscle force ↑Elb flexors muscle force ↑Kn flexors muscle force ↑Hip flexors muscle force
He et al. 2015 (242)	n = 28, FEV_1 = 39 ± 5%, age = 74 ± 2yr Not described	n = 66, FEV_1 = 38 ± 3%, age = 69 ± 2yr Treadmill walking at 60% of the peak work rate during treadmill 6MWT for 5-10min increased to 20min + bilateral sh abduction and flexion using light weight for 2min + strength training using free weights/own body weight, begin with 1 set of 10 repetition increased to 3 sets of 10 repetitions Duration: 2 sessions/day throughout hospitalisation		*Re-assessment at discharge* No analysis for between-group differences performed

Data are presented as mean ± standard deviation. n = number included in final analysis. Abbreviations: 1RM, one-repetition maximum; 3MWT, three-minute walk test; 6MWD, six-minute walk distance; 6MWT, six-minute walk test; CG, control group; EG, exercise group; elb, elbow; FEV_1, forced expiratory volume in one second; kn, knee; min, minutes; NIV, non-invasive ventilation; PA, physical activity; QMF, quadriceps muscle force; sh, shoulder; WBET, whole body-body exercise training; yr, years.

Table 2.6: Summary of studies where exercise training was initiated within two to three days of hospital admission and extended to an after discharge program

Author	Intervention CG	EG	Significant between-group difference in favour of EG
Eaton et al. 2009 (240)	**In-patient care** n = 50, FEV_1 = 35 ± 16%, age = 70 ± 9yr Treatment in accordance with the ATS/ERS guidelines (88) and advice on exercise and maintaining daily activities **Follow-up at 3 months** n = 45	**In-patient program** n = 40, FEV_1 = 36 ± 16%, age = 70 ± 10yr Usual care + supervised walking + UL and LL resistance exercise ≥ 30 min/day (no further details are provided) Duration: 1 session/day throughout hospitalisation **Out-patient hospital-based program** n = 39 1hr supervised training (no further details are provided) Duration: 2x/week for 8 weeks	*Re-assessment at 3 months after discharge* ↑CRQ fatigue domain ↑SF-36 physical function ↓HAD anxiety
Greening et al. 2015 (241)	**In-patient care** n = 193, FEV_1 = 57 ± 24%, age = 71 ± 10yr Chest physiotherapy for airway clearance, mobility assessment, and advice on smoking cessation + no exercise program provided during admission or after discharge **Follow-up at 6 weeks** n = 162	**In-patient program** n = 196, FEV_1 = 52 ± 25%, age = 71 ± 9yr Usual care + walking at walking speed at 85% of VO_2 peak during ESWT + resistance training (biceps curls, triceps curls, kn extension, sit to stand, and step ups) + NMES on both quadriceps for 30 min/day Duration: 1 session/day throughout hospitalisation **Home-based program (unsupervised)** n = 148 Progressive walking + NMES Duration: 1 session/day for 6 weeks	*Re-assessment at 6 weeks after discharge* ↑ESWT

Data are presented as mean ± standard deviation. n = number included in final analysis. Abbreviations: 1RM, one-repetition maximum; ATS/ERS, American Thoracic Society/European Respiratory Society; CG, control group; CRQ, Chronic Respiratory Questionnaire; EG, exercise group; elb, elbow; ESWT, endurance shuttle walk test; FEV_1, forced expiratory volume in one second; HAD, hospital anxiety and depression; hr, hours; kn, knee; LL, lower limb; min, minutes; NMES, neuromuscular electrical stimulation; SF-36, 36-item Short Form survey; UL, upper limb; VO_2peak, peak oxygen consumption; yr, years.

Table 2.7: Summary of studies where exercise training was initiated following a period of stabilisation in clinical status

Author	Intervention CG	EG	Significant between-group difference in favour of EG
Kirsten et al. 1998 (65)	**In-patient care** n = 14, FEV_1 = 38 ± 3%, age = 66 ± 12yr Standard physiotherapy (not further details are provided) + no exercise program provided during admission or after discharge	**In-patient program** n = 15, FEV_1 = 34 ± 3%, age = 62 ± 9yr Supervised 5 self-paced walking training/day at ≥ 75% of the daily 6-min treadmill walking test without any time limit Start: 6 to 8 days following hospital admission Duration: 10 consecutive days	*Re-assessment at day 5 and Day 10* ↑6MWD *Changes throughout the training period* ↑% in minute ventilation during 6MWT *Comparison at the same treadmill 6MWT work load as on Day 1* ↓Borg dyspnoea rating ↓$PaCO_2$
Behnke et al. 2003 (67)	**In-patient care** n = 12, FEV_1 = 38 ± 7%, age = 69 ± 7yr Standard physiotherapy (not further details are provided) + no exercise program provided during admission or after discharge **After discharge** No home visits but received monthly phone calls to perform regular exercise	**In-patient program** n = 14, FEV_1 = 35 ± 7%, age = 64 ± 8yr Supervised 5 self-paced walking training/day at ≥ 75% of the daily 6-min treadmill walking test without any time limit Start: 4 to 7 days following hospital admission Duration: 10 consecutive days **Home-based exercise program (unsupervised)** 15min walking at 125% of discharge treadmill 6MWD 3 times/day, visited every 2 weeks at home during the first 3 months, followed with monthly phone calls to perform regular exercise Duration: 18 months	*Re-assessment at 18 months after discharge* ↓re-admission rate ↓bronchodilators use/day *Assessment at 6 vs. 12 vs. 18 month*s ↑CRQ ↓TDI ↑treadmill 6MWD
Ali et al. 2013 (66)	**In-patient care** n = 15, FEV_1 = 45 ± 18%, age = 64 ± 9yr No exercise program provided during admission or after discharge (no further details are provided) **After discharge** No intervention	**In-patient program** n = 15, FEV_1 = 46 ± 21%, age = 63 ± 7yr Supervised 20 min interval training for walking exercise at 75% of the workload achieved during the baseline CPET + UL and LL resistance exercises at 70 % of 1RM for 3 sets of 8 repetitions Start: Not described Duration: 3 to 4 days **Out-patient hospital-based program** (same as in-patient program) Duration: 3 sessions/week for 3 weeks	*Re-assessment at 3 weeks after discharge* ↑FEV_1 % predicted ↑6MWD ↑exercise duration during CPET ↑SF-36 in all domains except pain and general health

Data are presented as mean ± standard deviation. n = number included in final analysis. Abbreviations: 1RM, one repetition maximum; 6MWD, six-minute walk distance; CG, control group; CPET, cardiopulmonary exercise testing; CRQ, Chronic Respiratory Questionnaire; EG, exercise group; FEV_1, forced expiratory volume in one second; LL, lower limb; min, minutes; $PaCO_2$, arterial blood gas pressure of carbon dioxide; SF-36, 35-item short form survey; TDI, transition dyspnoea index; UL, upper limb; yr, years.

2.4.1.1 Results of the studies that investigated the effects of exercise training initiated during the period of hospitalisation

Regarding the results of studies that initiated exercise training during a period of hospitalisation for AECOPD, all nine studies explored the effect of exercise training on exercise capacity. Of these, five (56%) demonstrated a significant between-group difference in this outcome (65-67, 71, 241), of which four (80%) included walking training as the exercise modality (65-67, 241). This finding, at least in part, suggests that walking training is needed to improve exercise capacity in people hospitalised for an AECOPD. However, of these five studies, three (60%) initiated exercise training after four to eight days of hospital admission (65-67) and therefore the results of these studies are unlikely to be relevant for countries such as Australia and Malaysia, in which the hospital length of stay for an AECOPD is often less than one week (68, 69). Of the two studies which initiated exercise training within two to three days of hospitalisation for AECOPD and demonstrated a significant between-group difference in a measure of exercise capacity, the study by Borges et al. (71) reported the use of very long resistance training sessions (i.e. 90 minutes sessions, performed daily), which are unlikely to be feasible in a busy clinical setting. In the other study (241), although exercise training was initiated within two days of hospital admission, on average only 2.7 ± 2.6 sessions of aerobic training and 2.5 ± 1.9 sessions of resistance training were performed during the in-patient program. The majority of the training (i.e. a 6-week exercise program) was home-based following hospital discharge and most importantly, the effect of the in-patient program on exercise capacity was not evaluated. Therefore, to date, there are no studies that have reported the effect of a combined program of both aerobic and resistance training initiated within two to three days of hospitalisation for an AECOPD, on exercise capacity measured at the time of hospital discharge.

Of the other four studies (70, 72, 240, 242), three (75%) (70, 72, 240) did not demonstrate significant between-group difference in exercise capacity and one (25%) (242) did not report whether there was a significant between-group difference in this outcome at the completion of the exercise program. The three studies that did not demonstrate significant between-group difference in exercise capacity were characterised by low levels of program participation (i.e. only 40% of the patients

assigned to the rehabilitation group attended 75% or more of the out-patient exercise sessions) (240), small sample sizes (i.e. n = 10 vs. 11) (70) and the use of exercise that was very specific for the improvement in muscle strength but not exercise capacity (i.e. one session of knee extension exercise each day, without any aerobic exercise) (72).

Regarding the effects on QMF, of the four studies that reported data on this outcome (70-72, 241), only one (72) demonstrated a significant between-group difference in favour of the exercise group (EG). The study which demonstrated a significant between-group difference for QMF evaluated this outcome using an isokinetic dynamometer, reported data on 36 participants, with participants completing an average of 6 ± 1 sessions of training which involved three sets of eight repetitions of knee extension at 70% of 1RM. Although the data by Troosters et al. (72), suggests that specific resistance for the quadriceps muscle during a period of hospitalisation is safe and effective at increasing QMF, the training program in this study necessitated the use of a knee-extension chair (Gymna, Bilzen, Belgium). This equipment may not be readily available, especially in countries with limited healthcare resources, such as Malaysia. In contrast with this study, the lack of effect on QMF in the other three studies appears to be due to the use of a less sensitive outcome measure to evaluate muscle force (i.e. MMT) and a smaller sample size in one study (70), and the prescription of a much lower dose of training that was also not specific to the quadriceps muscle in the other two RCTs (71, 241). It is currently unknown whether or not resistance exercises performed using minimal or no equipment such as half squats, initiated early during a period of hospitalisation for an AECOPD, are effective at increasing QMF.

Regarding the effects on PA, only one study reported data on the average time people hospitalised for an AECOPD spent sitting, lying, standing and walking (71). This study demonstrated that the participants in both EG and CG were mostly inactive and there were no significant between-group differences in the time they spent sitting, lying, standing and walking, not only during the period of hospitalisation but also a month following hospital discharge (71). One possible reason that this study did not demonstrate any significant changes in standing or walking relates to the type of exercises prescribed as part of their training program. That is, this study only

included resistance training exercise. The principle of task specificity is known to influence training-related adaptations and suggests that in order to maximise any increase in standing and walking-based activities, the training program should incorporate standing and walking-based training (243).

Regarding the effects on HRQoL, of the five studies that have reported data on this outcome (66, 67, 71, 240, 241), three (60%) demonstrated a significant between-group difference in favour of the EG (66, 67, 240). These studies assessed HRQoL using the CRQ and/or the SF-36 between three weeks and 18 months following hospital discharge (66, 67, 240). In contrast, the two RCTs that did not demonstrate a significant between-group difference in HRQoL both measured this outcome using the SGRQ (71, 241). One evaluated the effect of exercise training on HRQoL at discharge (71) and the other collected measures at six weeks, three, six and 12 months after randomisation (241). Although it is possible that the lack of effect on HRQoL in these two studies related to the use of a different outcome measure (i.e. the SGRQ), it is perhaps more likely related to the different effect these exercise programs had on exercise capacity. That is, of the three studies that reported significant between-group differences in HRQoL, most also demonstrated significant between-group difference in exercise capacity (66, 67). On the other hand, in those studies that did not report a significant between-group difference in HRQoL, significant between-group differences in exercise capacity were less consistent (71, 241). Therefore, it is possible that improvements in HRQoL are more likely to be achieved by programs which are effective at optimising exercise capacity.

Regarding the effects on healthcare utilisation, of the four studies that reported data on this outcome (67, 72, 240, 241), only one (67) demonstrated a significant between-group difference in re-admission rate over an 18 months period in favour of the EG. This study initiated the exercise program during the period of hospitalisation, and then extended the program for 18 months following discharge. In the period following discharge, the participants were prescribed with an unsupervised home-based exercise program that comprised 15 minutes walking three times per day for 18 months. The participants were visited every two weeks during the first three months and afterwards received monthly phone calls to encourage them to perform regular exercise. This is in contrast to the other three studies which did not

demonstrate any between-group difference in this outcome, where the exercise program and contact with the investigators were completed after four to eight weeks post-discharge but data on healthcare utilisation were collected for three to 12 months (72, 240, 241).

Regarding safety, one study (70) reported one serious adverse event in one (3%) of the 32 participants during the training program. Specifically, the participant in this study developed chest pain during the walking training and it was confirmed by electrocardiogram that the participant was experiencing atrial fibrillation. However, the chest pain resolved within one hour without any medical intervention and the participant resumed participation in the study without further incident. No serious adverse events were reported in other studies.

Regarding adherence to the training program, for the training undertaken during the period of hospitalisation, adherence to the training sessions was reported to be between 85% and 95% (70, 71, 241). When the in-patient exercise program was extended to an after discharge program, it appears that the adherence to the exercise sessions was lower than that seen during the hospitalisation period. For example, Eaton et al. (240) reported that only 40% of those in the EG attended 75% or more of the out-patient exercise program. In another example, Greening et al. (241) found that daily adherence to the unsupervised home-based exercise program was reported by only 54% and 61% of the participants for aerobic and resistance training, respectively.

2.4.2 Exercise training initiated shortly following discharge from hospital for an AECOPD

To date, there are five studies that have evaluated the effects of exercise training initiated shortly following discharge from hospital for an AECOPD (244-248) (Table 2.8). These studies have applied an exercise training intervention in one group and usual care in the CG. The sample sizes ranged from 26 to 60 and the participants had moderate to severe COPD and had been discharged from hospital for an AECOPD. Exercise training was commenced either immediately (248) or within one to three weeks following hospital discharge (244-247). Of these five studies, three (60%) conducted the training programs in an out-patient hospital setting (245-247), one

(20%) as a community-based program (244) and one (20%) provided the training program at home (248). All studies reported that the exercise programs were supervised by physiotherapists, nurses or a doctor from a department of pulmonary medicine. In contrast with the studies that evaluated the benefits of exercise training within the hospitalisation period, where the training protocols varied greatly, all five studies in which exercise training was initiated following discharge included both aerobic and resistance exercises in their exercise program. The frequency of the training sessions was between two and three sessions per week and the duration of the training ranged from six to 12 weeks.

Of these five studies, although group allocation appeared to be randomised, two studies reported concealment of the randomisation sequence (246, 248) and only one reported blinding of the outcome assessor (245). Information pertaining to the concealment of the randomisation sequence and blinding of the outcome assessor was not provided in three (244, 245, 247) and two (247, 248) studies, respectively. The loss to follow-up in these studies ranged between 15% and 19% (244-246, 248).

2.4.2.1 Results of the studies that investigated the effects of exercise training initiated shortly following discharge from hospital for an AECOPD

Regarding the results of studies that initiated exercise training shortly following discharge from hospital for an AECOPD, all five studies explored the effect of exercise training on exercise capacity. Of these, four (80%) demonstrated significant between-group difference in favour of the EG in this outcome (244, 246-248). The lack of training effect in the study by Ko et al. (245) could have been attributed to the fact that although the participants in the EG received an eight weeks hospital-based out-patient exercise program, participants in the CG were instructed to exercise regularly at home (245). Specifically, they were instructed to walk and to perform some stretching exercise on daily basis. Adherence with this advice among those in the CG may have improved their 6MWD.

Regarding the effects on QMF, of the two studies that reported data on this outcome (246, 248), only one (246) demonstrated a significant between-group difference in favour of the EG. The study which demonstrated a significant between-group difference for QMF evaluated this outcome using a strain gauge and reported data on

97 participants. An average of 16 sessions of training were completed which involved twice-weekly aerobic and resistance exercises for eight weeks (246). In contrast with this study, the lack of effect on QMF in the other study appears to be due to the smaller sample size (i.e. 13 in each group) and the prescription of a lower dose of exercise (i.e. 12 vs. 16 exercise sessions) (248). Although it is possible that differences in content of the training program between the two studies also contributed to the different effects on QMF, neither study described the exercise program in sufficient detail to allow such a comparison to be made.

None of the five studies that have evaluated the effects of exercise training initiated shortly following discharge from hospital for an AECOPD measured the effect on PA. Therefore, the effect of exercise training initiated shortly following discharge from hospital for an AECOPD on PA is unknown.

Table 2.8: Summary of studies where exercise training was initiated shortly following discharge from hospital for an AECOPD

Author/ year	Intervention CG	EG	Significant between-group difference in favour of EG
Man et al. 2004 (244)	**Usual care** n = 21, FEV_1 = 37 ± 15%, age = 71 ± 9yr Not described	**Community-based program** n = 21, FEV_1 = 42 ± 19%, age = 70 ± 9yr Supervised 1 hour walking, cycling, strength training for the UL and LL, and 1 hour of educational activities Start: within 10 days of discharge Duration: 2 sessions/week for 8 weeks **Home-based program** (Commenced together with the community-based program) Unsupervised exercise for ≥ 20 min/day (no further details are provided)	*Re-assessment at 3 months after discharge* ↑ISWD ↓SGRQ ↑CRQ (all 4 domains) ↑SF-36 (physical function)
Murphy et al. 2005 (248)	**Usual care** n = 13, FEV_1 = 42 ± 12%, age = 65 ± 11yr Standard medical treatment + no exercise program provided Participants who required PRP were offered out-patient PRP after the completion of the study	**Home-based program** n = 13, FEV_1 = 38 ± 12%, age = 67 ± 10yr Supervised aerobic exercises (step up and down a stair, sit to stand) and light resistance exercises using Thera-Band for 30-40 min Start: immediately following hospital discharge Duration: 2 sessions/week for 6 weeks	*Re-assessment at 3 months after discharge* ↓re-admission rate ↓re-exacerbation rate ↑ISWD ↓SGRQ (total score and activity) ↑CRQ (dyspnoea and emotion)
Seymour et al. 2010 (246)	**Usual care** n = 30, FEV_1 = 52 ± 22%, age = 65 ± 10yr Participants were provided with general information about COPD	**Out-patient hospital-based program** n = 67, FEV_1 = 52 ± 20%, age = 67 ± 10yr Supervised limb strengthening and aerobic exercises Start: within 7 days of discharge Duration: 2 sessions/week for 8 weeks	*Re-assessment at 3 months after discharge* ↓re-admission rate ↓re-exacerbation rate ↑QMF ↑ISWD ↓SGRQ (total score and activity) ↑CRQ (dyspnoea and emotion)

continues next page

Author/ year	Intervention CG	EG	Significant between-group difference in favour of EG
Ko et al. 2011 (245)	**Usual care** n = 26, FEV_1 = 41 ± 18%, age = 74 ± 6yr Participants were given simple instructions to do regular exercise at home that include walking and stretching exercises	**Out-patient hospital-based program** n = 25, FEV_1 = 46 ± 20%, age = 73 ± 8yr Supervised treadmill, arm cycling, arm and leg weight training Start: within 3 weeks after hospital discharge Duration: 2 hr/session, 3 session/week for 8 weeks **Home-based program** Commenced together with the hospital-based program Duration: 20 min/day	*Re-assessment at 3, 6 and 12 months after discharge* ↓SGRQ (total score and impacts)
Deepak et al. 2014 (247)	**Usual care** n = 15, FEV_1 = 47 ± 15%, age = 59 ± 7yr Not described	**Out-patient hospital-based program** n = 15, FEV_1 = 53 ± 18%, age = 58 ± 7yr Supervised limb strengthening and aerobic exercises Start: within 2 weeks of discharge Duration: 2 hr/session for 12 weeks (number of sessions per week was not described)	*Re-assessment at 3 months after discharge* ↑6MWD ↓SGRQ total score

Data are presented as mean ± standard deviation. n = number included in final analysis. Abbreviations: 6MWD, six-minute walk distance; CG, control group; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; EG, exercise group; FEV_1, forced expiratory volume in one second; hr, hours; LL, lower limb; PRP, pulmonary rehabilitation program; QMF, quadriceps muscle force; SF-36, 36-item Short Form survey; SGRQ, St George's Respiratory Questionnaire; ISWD, incremental shuttle walk distance; UL, upper limb; yr, years.

Regarding the effects on HRQoL, all five studies demonstrated significant between-group differences in favour of the EG, measured using the CRQ, SGRQ or the SF-36. With regard to the effect on healthcare utilisation, of the three studies that reported data on this outcome (245, 246, 248), two (67%) demonstrated a significant between-group difference in favour of the EG in the number of hospital re-admissions measured within three months following hospital discharge (246, 248). In these two studies, data on hospital re-admission rate were collected within the period where exercise training was provided (i.e. over a 3 months period) (246, 248). This is in contrast to the only study that did not demonstrate a significant between-group difference in this outcome, where exercise training was provided for eight weeks but data on re-admission rate were collected over a period of one year (245). This suggests that the effect of exercise training on re-admission rate may be greatest during the period that the program is provided.

None of the five studies that have investigated the effect of exercise training initiated shortly following discharge from hospital for an AECOPD evaluated adverse events or reported data pertaining to safety of the exercise training. Regarding adherence to the training program, using a standard cut-off of 50% classes attended, adherence to the training sessions were reported to be between 73% and 77% (244-246).

2.4.3 Summary

To date, there have been 14 studies that have explored the effect of exercise training initiated during or shortly following hospital discharge for an AECOPD. Of these, nine (64%) have initiated exercise training during the hospital admission and five (36%) have initiated exercise training shortly following discharge. Although 10 (71%) studies reported randomising participants to groups and six (43%) reported concealment of the randomisation sequence, studies in this area generally did not report using a blinded outcome assessor and also had large losses to follow-up. These considerations increase the risk of bias in the study results. Regarding the results of those studies that initiated exercise training shortly following hospital discharge, it appears that a combination of aerobic and resistance training is effective at improving exercise capacity and HRQoL. Of those studies that initiated exercise training within the period of hospitalisation, the results of those studies where exercise training was commenced late (i.e. between 4 and 8 days after hospital admission) may not be relevant in the Australian and Malaysian context where

hospital length of stay for an AECOPD is often less than one week. Regarding the results of those studies that initiated the exercise program early (i.e. within 2 to 3 days of hospitalisation), it appears that walking training is needed to improve exercise capacity. However, to date no study which has evaluated the effects of an exercise program, initiated within two to three days of hospitalisation for an AECOPD and, comprising aerobic or a combination of aerobic and resistance exercise, has been powered to detect between-group differences in outcomes such as exercise capacity and QMF.

CHAPTER 3
2MWT: MEASUREMENT PROPERTIES AND COMPARISON OF CARDIORESPIRATORY RESPONSES WITH THE 6MWT IN PEOPLE WITH MODERATE TO SEVERE COPD

This chapter presents the study that examined some of the measurement properties of the two-minute walk test (2MWT) and compared the cardiorespiratory responses and levels of symptoms during the 2MWT and six-minute walk test (6MWT) in people with moderate to severe chronic obstructive pulmonary disease (COPD). The research questions answered in this chapter are:

i. What is the magnitude of change in the two-minute walk distance (2MWD) with test repetition?

ii. What is the coefficient of repeatability (COR) for the 2MWD measured over two days?

iii. Does the 2MWT provide a valid of assessment of functional exercise capacity?

iv. Is the distance walked during the 2MWT different to one third of the six-minute walk distance (6MWD)?

v. Does the 2MWT elicit different cardiorespiratory responses and levels of symptoms when compared with the 6MWT?

The details of the study design are provided, including a description of the study inclusion and exclusion criteria, recruitment strategies and assessment protocol. Details of the measurements and statistical analyses are also described. The results are presented and discussed.

3.1 Study design

A single group cross-sectional study was undertaken between October 2012 and May 2013. Data collection for each participant was completed during two testing sessions, each of two hours duration that were separated by a minimum of 48 hours and a maximum of 14 days. An overview of the study design is provided in Figure 3.1.

3.1.1 Approval from Human Research Ethics Committees

Approval to conduct the study was granted by the Human Research Ethics Committees (HRECs) of Sir Charles Gairdner Hospital (SCGH) (approval number 2012-054) and Curtin University (approval number HR 76/2012). Written, informed consent was obtained from all participants prior to data collection.

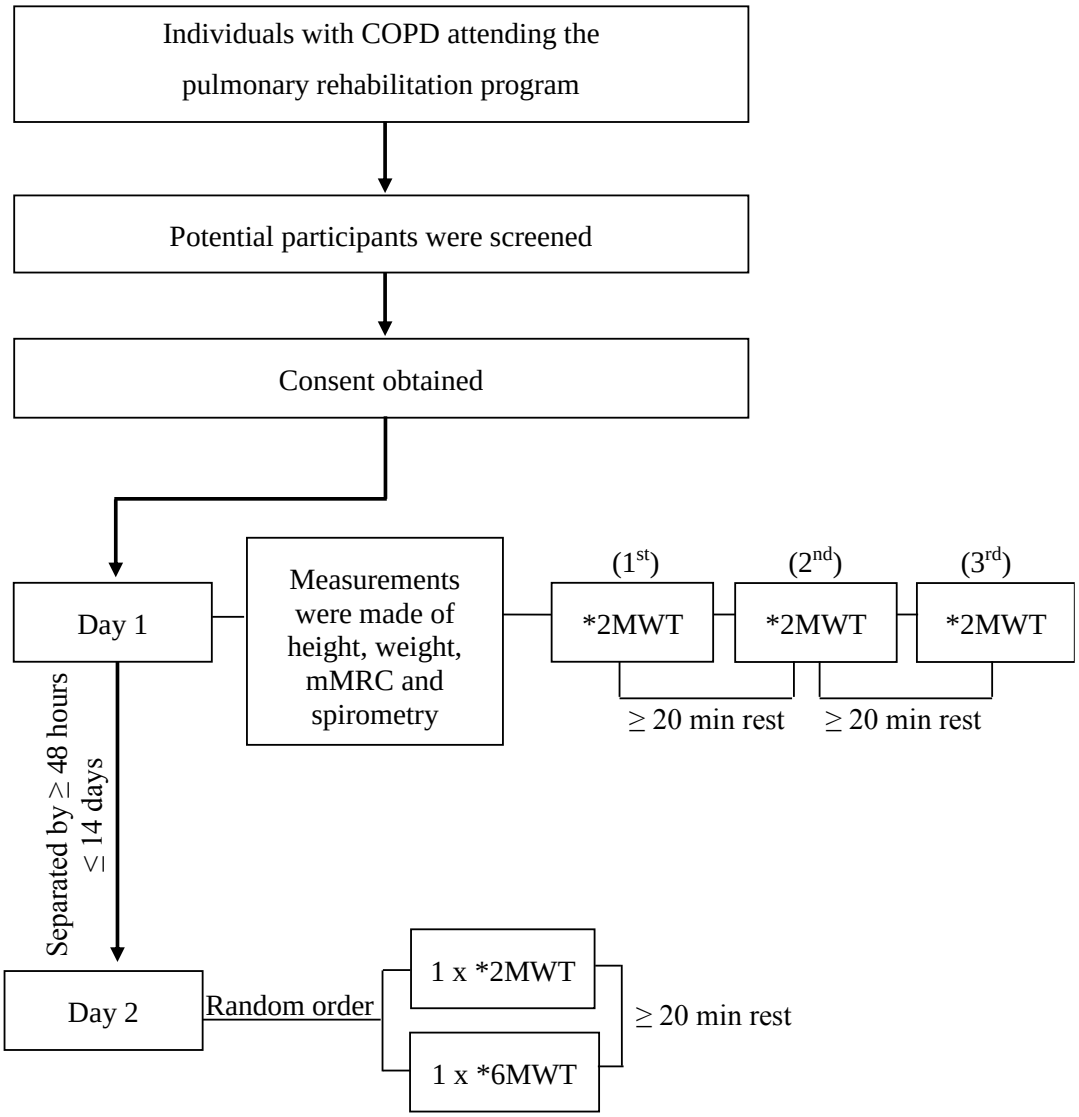

Figure 3.1: Overview of the study design.
* Heart rate, SpO_2 and dyspnoea level were recorded prior to each test.
Abbreviations: 2MWT, two-minute walk test; 6MWT, six-minute walk test; COPD, chronic obstructive pulmonary disease; min, minutes; mMRC, modified Medical Research Council; SpO_2, percutaneous oxygen saturation.

3.1.2 Participants

3.1.2.1 Inclusion criteria

Participants were eligible for inclusion in this study if they had a diagnosis of COPD (249) and were clinically stable, defined as an absence of any change in respiratory symptoms in the previous four weeks that required a change in medication (53), and had at least moderate functional impairment (i.e. 6MWD of ≤ 450m) mainly due to profound dyspnoea. The threshold of ≤ 450m to define moderate functional impairment was based on earlier work by Starobin et al. (250) who demonstrated that a 6MWD of ≤ 450m in people with COPD corresponded to a peak rate of oxygen consumption (VO_2 peak) of 15 to 20ml/kg/min, measured during a cardiopulmonary exercise test, which indicated moderate functional impairment.

People with moderate to severe COPD with at least moderate functional impairment were specifically recruited into this study as they were likely to have similar characteristics as those experiencing an acute exacerbation of COPD (AECOPD), such as profound dyspnoea and oxygen desaturation on exertion and marked impairment in exercise capacity. This was necessary given that the purpose of this study was to propose the use of the 2MWT for the assessment of functional exercise capacity in the acute setting, that is, when patients are hospitalised with an AECOPD. Although it would have been ideal to recruit patients hospitalised with an AECOPD, this was not considered feasible as these patients often change rapidly in response to treatment (251), which would confound the estimate of the repeatability of the 2MWD over two days. Further, it is unlikely that those hospitalised with an AECOPD would be able to complete the study protocol, which comprised five walking tests over two days.

3.1.2.2 Exclusion criteria

Exclusion criteria comprised: (i) presence of condition, other than COPD, which was the primary reason for a limitation in exercise capacity (e.g. neurological disease, severe symptomatic musculoskeletal pain, impaired cognitive function or claudication pain), (ii) a known contraindication to exercise (Appendix 2) (167), (iii) prescribed with beta-blockers (i.e. medications known to affect heart rate response to exercise), and (iv) inability to understand English.

3.1.3 Recruitment

Patients attending out-patient pulmonary rehabilitation programs (PRPs) conducted under the jurisdiction of the SCGH's HREC were screened through the PRP's records. This program does not accept people with severe, limiting cardiac disease. Those who met the selection criteria for the study were asked if they were interested in being told about the study by the physiotherapists responsible for running the PRP. Those who expressed an interest were provided with a verbal explanation about the study and were approached to participate in this study by the investigator (PhD candidate).

3.1.4 Assessment protocol

All participants performed three 2MWTs on day one, and one 2MWT and one 6MWT on day two. The order of the tests on day two was randomly assigned using a computer-generated and concealed randomisation sequence. Participants were given a minimum of 20 minutes rest between consecutive walking tests (75). The rest period was extended when necessary until the HR, percutaneous oxygen saturation (SpO_2) and dyspnoea (Borg category ratio scale) had returned close to the baseline measurements. This was defined as within five beats per minute (bpm), 1% and 1 point of baseline (i.e. pre-test) values for differences in HR, SpO_2 and dyspnoea, respectively (6). All participants were tested at a similar time of the day on both study days. They were also instructed to continue their usual medications on the day of testing.

3.2 Measurements

3.2.1 Walk tests

The 2MWT and the 6MWT were carried out in accordance with a protocol adapted from the European Respiratory Society (ERS)/American Thoracic Society (ATS) Technical Standards for the 6MWT (226) with the following modifications: (i) the inclusion of standardised encouragement every 15s instead of 30s to recommence walking if the participant rested during any of the tests, (ii) standardised encouragement every 30s instead of every minute during the 2MWT and (iii) the instruction 'to walk as fast as you can' instead of 'to walk as far as possible' (see subheading 2.3.3.2.3).

All participants were familiar with the 6MWT but not with the 2MWT prior to participating in this study. Absolute contraindications to performing the exercise tests were taken from published guidelines for cardiopulmonary exercise testing (Appendix 2) (167). Additional relative contraindications comprised: (i) pre-exercise HR of > 125bpm and (ii) resting SpO_2 of < 90%. Those who were using oxygen therapy performed the tests whilst breathing oxygen supplied at their prescribed flow rate for exercise with the oxygen cylinder transported by the participant using a wheeled walker or a trolley.

Both tests were performed over a 30m straight course within a level enclosed corridor and were supervised by the same investigator. Chairs were placed at both ends and at the mid-way point to allow seated rests if required. Standardised instructions were read aloud to the participants before each test. They were informed that they could slow down or rest if necessary. Participants were also told to stop walking and inform the investigator if they experienced any chest pain or dizziness. Participants who demonstrated profound oxygen desaturation, defined as SpO_2 < 80% were instructed to stop walking immediately and to recommence walking if SpO_2 recovered to ≥ 80% (226).

Heart rate (Polar a1, Polar Electro Oy, Kempele, Finland) and SpO_2 (Masimo Rad-5v, Masimo Corporation, California, USA) were measured throughout both tests with the values were recorded before the test, at the end of each minute during the 6MWT and every 30s during the 2MWT, and at test completion. Peak HR was expressed as percentage of predicted HR maximum using the formula, 210 − (0.65 × age) (252). This formula was used because it is the formula recommended by the American College of Sports Medicine (253) and in contrast to the most commonly used formula to estimate the peak HR (i.e. 220 − age) (254), this formula is less likely to underestimate the peak HR in older adults. The investigator walked behind the participant and care was taken to avoid the walking speed of the investigator influencing that of the participant. Upon test completion, participants remained in the testing area and SpO_2 was monitored until it returned to ≥ 90%. In participants who chose to rest, or in whom a rest was imposed because of profound oxygen desaturation (SpO_2 < 80%) (226), the nadir SpO_2 was recorded together with rest duration. The reason for resting was also documented in those who chose to rest.

Dyspnoea was assessed using the Borg category ratio scale (147) at rest, upon test completion, and at the start of any rests taken during the test. The Borg category ratio scale was also used to record leg fatigue at the end of the test (147). The primary outcome measure in both tests was the distance walked.

3.2.2 Descriptive measures

3.2.2.1 Participant details

Details were recorded pertaining to age, gender and ambulatory oxygen use. Weight and height were measured and used to calculate body mass index (BMI [kg/m^2]).

3.2.2.2 Functional limitation

Functional limitation resulting from dyspnoea was assessed using the modified Medical Research Council (mMRC) dyspnoea scale (151, 152). This scale comprises five statements each of which is assigned a grade that ranges from zero "I only get breathless with strenuous exercise" to four "I am too breathless to leave the house or I am breathless when dressing". The participant selects the statement which best describes their level of limitation in daily activities due to breathlessness. The mMRC scale has been shown to be a valid method of categorising people with COPD in terms of their level of functional disability (255).

3.2.2.3 Spirometry

Spirometry was performed according to standard procedures (256) using a portable Spirometer (EasyOne NDD Medical Technologies, Massachusetts, USA). Testing was conducted by the investigator who was trained and certified to standards which aligned with the ATS/ERS standards (256). Participants were required to perform a minimum of three acceptable forced vital capacity (FVC) manoeuvres (256). The largest forced expiratory volume in one second (FEV_1) and FVC from any of the three manoeuvres that met the acceptability and repeatability criteria were selected as the test results. Both FEV_1 and FVC were expressed as a percentage of the predicted normal values (257).

3.2.2.4 BMI, degree of airflow Obstruction, Dyspnoea and Exercise capacity (BODE) index

The BODE index, a multi-dimensional score that comprises measures of BMI, FEV_1, mMRC dyspnea grade and the 6MWD, was calculated to provide a global

description of disease severity that was not only based on the assessment of airflow limitation but also considered the systemic manifestations of COPD (152).

3.3 Statistical analyses

3.3.1 Sample size calculations

Earlier work using the same 6MWT protocol as used in this study, and upon which the 2MWT protocol has been based, demonstrated an increase of 37 ± 37m (mean ± standard deviation [SD]) between repeat 6MWDs in people with moderate to severe COPD (6). As the duration of the 2MWT is one third of the 6MWT, it is most likely that the difference between repeat 2MWDs would be approximately one third of the difference in the repeat 6MWD (i.e. 12 ± 12m). However, as this study was designed to recruit individuals with at least moderate functional limitation (to be more representative of those individuals experiencing an AECOPD), it was anticipated that the difference between repeat 2MWDs would be slightly less than 12m. Therefore, prospective sample size calculations were undertaken to ensure adequate power ($\alpha = 0.05$, $1 - \beta = 0.8$) to detect a difference between repeat 2MWDs of 9 ± 12m. A sample size of 16 participants was required to detect this difference. Assuming a 20% withdrawal rate, the recruitment target for this study was 20 participants.

3.3.2 Statistical analyses

All analyses were performed using the Statistical Package for Social Sciences (SPSS version 19.0; Chicago, IL, USA) with a probability (p) value < 0.05 used to indicate statistical significance. The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test).

To explore the effect of test repetition on the 2MWDs, the three 2MWDs measured on day one were analysed using a repeated measures analysis of variance (RM-ANOVA). Post-hoc analysis using the Bonferroni method was conducted to compare the differences between the repeat 2MWDs. To explore the validity of the 2MWT as a measure of functional exercise capacity in people with COPD, the relationship between the 2MWD and the 6MWD was analysed using Pearson's correlation coefficient. The strength of the correlation was interpreted based on the grading scheme used by Cohen (258).

To determine the coefficient of repeatability of the 2MWDs measured over two different days, the methods described by Bland and Altman were used (259). Specifically, bias was defined as the mean difference between the best of the three 2MWDs measured on day one and the 2MWD measured on day two. The COR was calculated as $1.96 \times \sqrt{2} \times$ within-subject SD of the two 2MWDs (259). The within-subject SD was estimated from the square root of the residual mean square, obtained from the RM-ANOVA. The bias and COR were also calculated separately for those who performed the 6MWT first vs. those who performed the 2MWT first to establish if the order of the test had an influence on COR.

Data collected on day two were used for further analyses. To evaluate whether the distance walked during the 2MWT was interchangeable with one third of the distance walked during the 6MWT, a paired sample t-test was used to compare these distances. The proportion of participants who rested during the 2MWT was compared with those who rested during the 6MWT using Pearson's Chi-square test. With regard to a comparison of the responses during the 2MWT with the 6MWT, paired sample t-tests were used to compare the peak HR, nadir SpO_2, peak dyspnoea and the end-test leg fatigue scores during the 2MWT with those during the 6MWT. All data are expressed as mean ± SD or 95% confidence interval (CI) unless otherwise stated.

3.4 Results

Of the 20 individuals who consented to participate, two (10%) did not attend the second day of the testing session; one (5%) required hospital admission due to an AECOPD and one (5%) was unable to attend the follow-up assessment within the study period. The characteristics of the 20 participants are presented in Table 3.1.

3.4.1 Effect of test repetition

The means (± SD) of the 2MWDs during the three 2MWTs on day one were 135 ± 27m, 141 ± 23m, and 145 ± 24m, respectively and the mean ± SD of the best 2MWD was 146 ± 24m. The distance walked in the 2MWD improved significantly with test repetition ($p < 0.001$). The 2MWD increased by a mean of 6m; 95% CI, 2m to 9m between walk 1 and walk 2, and by a mean of 4m; 95% CI, 2m to 6m between walk 2 and walk 3 (Figure 3.2). When expressed as a percentage of difference from baseline, the 2MWD increased by a mean of 4%; 95% CI, 1% to 7% between walk 1

and walk 2 and a mean of 3%; 95% CI, 1% to 4% between walk 2 and walk 3. Two participants (10%) walked the same distance on all three 2MWTs. A total of two (10%), five (25%) and 13 (65%) participants achieved their best 2MWD on the first, second and third test, respectively.

3.4.2 Repeatability of the 2MWD

The bias and COR for the 2MWD measured over two days were 1m and 14m, respectively (Figure 3.3a). These values were -1m and 11m in participants who were randomly assigned to perform the 2MWT first, and 2m and 16m in participants who performed the 6MWT prior to the 2MWT (Figure 3.3b and 3.3c).

3.4.3 Validity of the 2MWT

There was a strong positive linear association between the 2MWD and the 6MWD ($r = 0.66$; $p = 0.003$).

3.4.4 2MWD vs. one third of the 6MWD

Using data collected on day two, the distance walked during the 2MWT and one third of the distance walked during the 6MWT were 147 ± 24m and 115 ± 29m, respectively. Therefore, the participants walked a mean of 31 ± 22m (27%) further during the 2MWT than one third of the distance walked during the 6MWT ($p < 0.001$).

3.4.5 Cardiorespiratory responses and levels of dyspnoea and leg fatigue during the 2MWT and 6MWT

The mean 2MWD and the 6MWD on day two were 147 ± 24m and 346 ± 88m, respectively. Thirteen (72%) participants rested during the 6MWT, whereas only two (11%) participants rested during the 2MWT ($p < 0.001$). The rest duration ranged from 3s to 167s during the 6MWT and 7s to 13s during the 2MWT.
Cardiorespiratory responses and levels of symptoms during the tests are shown in Table 3.2. The peak HR was greater for the 6MWT than for the 2MWT (mean difference; 95% CI, 6; 4 to 9 bpm), while the nadir SpO_2 was lower during the 6MWT than during the 2MWT (-4; -6 to -2 %). Peak dyspnoea was greater during the 6MWT than during the 2MWT (mean difference; 95% CI, 0.9; 0.4 to 1.4) but there was no difference in end-test leg fatigue (0.3; -0.2 to 0.9) between the two tests.

The pattern of response in HR and SpO_2 during the 2MWT and the 6MWT is illustrated in Figure 3.4. Heart rate increased rapidly throughout the 2MWT and during the first two to three minutes of the 6MWT after which it tended to plateau. Oxygen saturation decreased throughout the 2MWT. During the 6MWT, SpO_2 decreased rapidly during the first two to three minutes and then continued to decrease at a slower rate until the end of the test. For the 2MWT, the nadir SpO_2 occurred at the end of the test in all participants. In contrast, during the 6MWT, the nadir SpO_2 occurred during the test in six participants (33%), all of whom rested at least once.

Table 3.1: Characteristics of the participants (n = 20)

		Mean ± SD
Age, yr		72.5 ± 8.3
Height, m		1.66 ± 0.08
Weight, kg		67.1 ± 19.8
Body mass index, kg/m^2		24.2 ± 6.8
FEV_1, L		0.73 ± 0.33
FEV_1 %pred		28 ± 13
FVC, L		1.72 ± 0.65
FVC %pred		51 ± 15
FEV_1/FVC		0.42 ± 0.07
BODE index		5 ± 2
		n (%)
Gender	Male	9 (45)
	Female	11 (55)
GOLD Grade	Grade I	0
	Grade II	2 (10)
	Grade III	6 (30)
	Grade IV	12 (60)
mMRC	Grade 0	0
	Grade 1	1 (5)
	Grade 2	9 (45)
	Grade 3	9 (45)
	Grade 4	1 (5)
Wheeled walker		16 (80)
LTOT		16 (80)

Data are presented as mean ± standard deviation (SD) or n, number of participants and (%), percentage. Abbreviations: BODE, Body mass index, Airflow Obstruction, Dyspnoea and Exercise capacity; FEV_1, forced expiratory volume in one second; FEV_1 %pred, percentage of predicted FEV_1 (257); FVC, forced vital capacity; FVC %pred, percentage of predicted FVC; GOLD, Global Initiative for Chronic Obstructive Lung Disease; kg, kilograms; L, litres; LTOT, long-term oxygen therapy; m, metres; mMRC, modified Medical Research Council; yr, years.

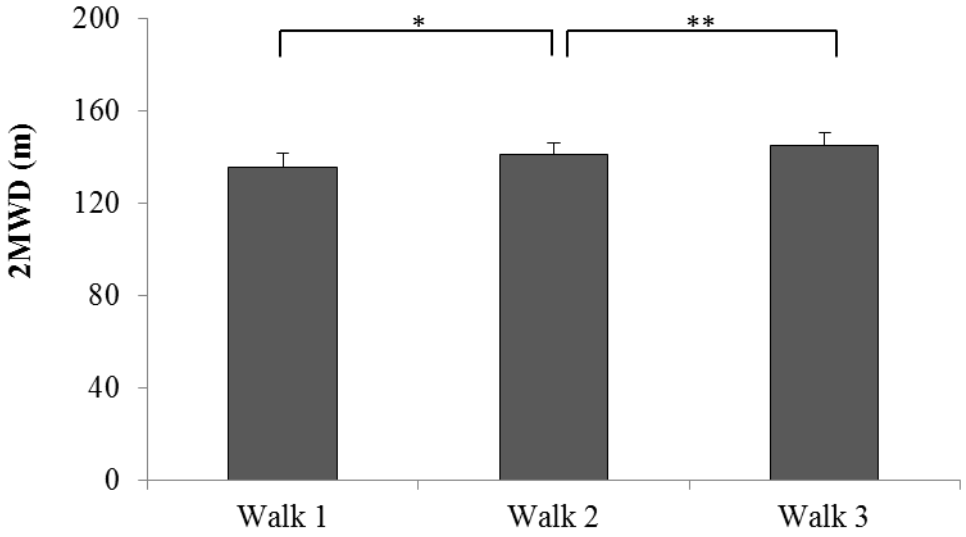

Figure 3.2: The 2MWDs during the three consecutive 2MWTs on day one (n = 20). Data are presented as mean ± standard error (SE).
*p < 0.05 and **p < 0.005. Abbreviations: 2MWD, two-minute walk distance; 2MWT, two-minute walk test.

a)

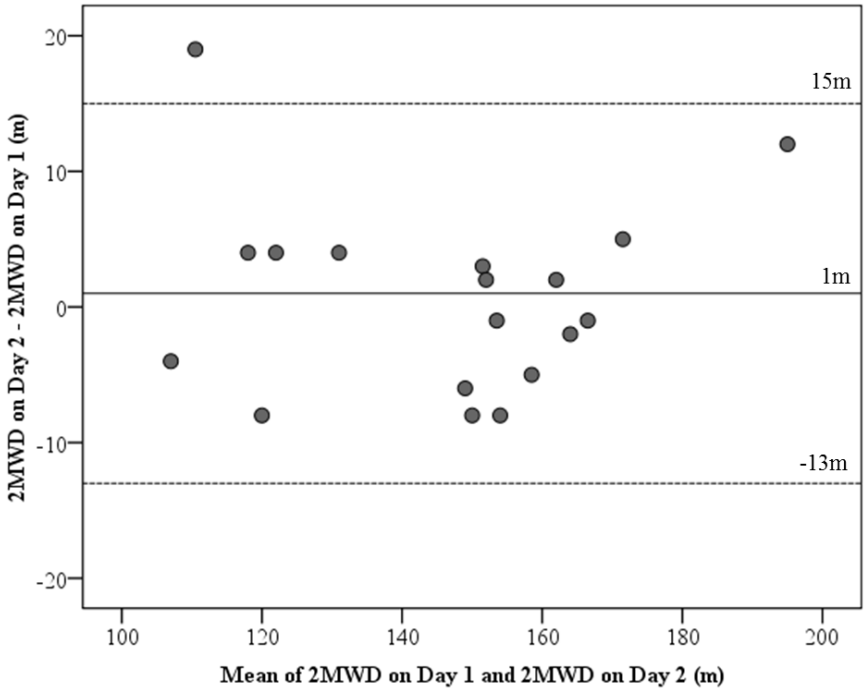

Figure 3.3a: Bland and Altman plot showing the coefficient of repeatability for the 2MWD measured on two different days for all participants (n = 18).
The solid line corresponds to the mean difference (i.e. bias) between the two 2MWDs. The dashed lines indicate the upper and lower limits of the coefficients of repeatability. Abbreviation: 2MWD, two-minute walk distance.

b)

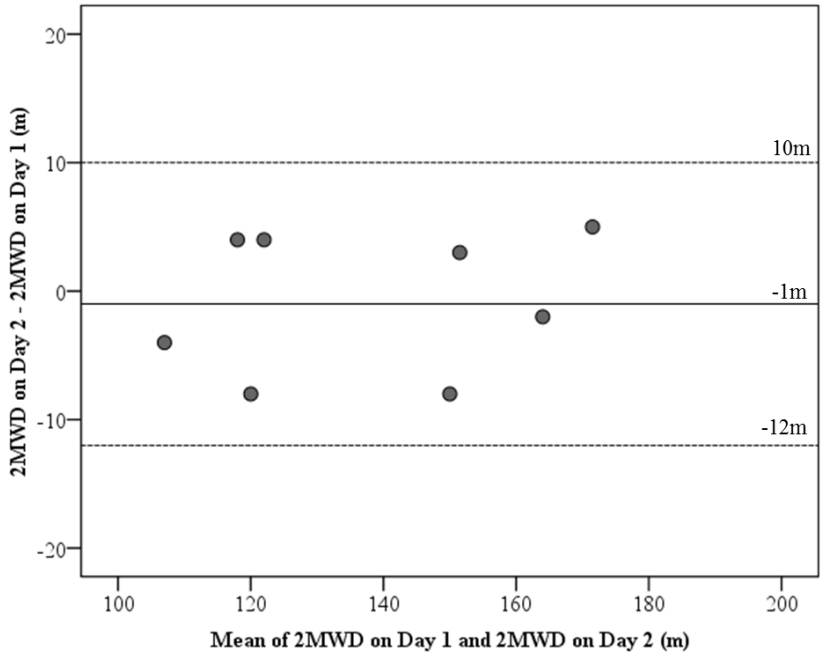

Figure 3.3b: Bland and Altman plot showing the coefficient of repeatability for the 2MWD measured on two different days for participants who were randomly assigned to perform the 2MWT first (n = 8) on the second day of testing. Abbreviations: 2MWD, two-minute walk distance; 2MWT, two-minute walk test.

c)

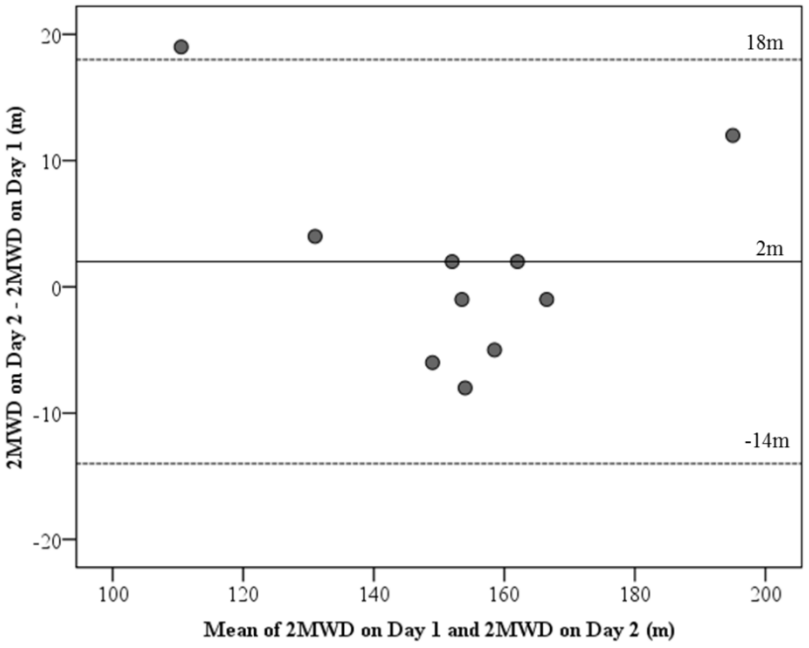

Figure 3.3c: Bland and Altman plot showing the coefficient of repeatability for the 2MWD measured on two different days for participants who were randomly assigned to perform the 6MWT first (n = 10) on the second day of testing. Abbreviations: 2MWD, two-minute walk distance; 6MWT, six-minute walk test.

Table 3.2: Cardiorespiratory responses and levels of dyspnoea and leg fatigue during the 2MWT and the 6MWT (n = 18)

		2MWT	**6MWT**
Distance (m)		147 ± 24	346 ± 88
6MWD %pred		-	57 ± 14
Number of rests, n (%)	1	2 (10)	8 (40)
	2	0	4 (20)
	3	0	1 (5)
Reason for rest, n (%)	Dyspnoea	2 (10)	10 (50)
	SpO_2 < 80%	0	2 (10)
	Leg fatigue	0	1 (5)
Pre-test	HR (bpm)	87 ± 13	86 ± 14
	SpO_2 (%)	96 ± 2	96 ± 2
	Dyspnoea	1.1 ± 1.0	1.2 ± 1.0
During/End-test	Peak HR (bpm)	107 ± 13	112 ± 15**
	Peak HR (%pred HRmax)	67 ± 7	69 ± 9
	Nadir SpO_2 (%)	86 ± 6	82 ± 7**
	Nadir SpO_2 < 85%, n (%)	9 (45)	11 (55)
	Peak dyspnoea	4.1 ± 2.0	5.0 ± 1.8*
	Leg fatigue	2.1 ± 1.9	2.4 ± 2.3

Data are presented as mean ± standard deviation or n, number of participants and (%), percentage. *p < 0.01 and **p < 0.001 compared with 2MWT. Abbreviations: 2MWT, two-minute walk test; 6MWT, six-minute walk test; 6MWD, six-minute walk distance; 6MWD %pred, percentage of predicted 6MWD (20); %pred HRmax, peak HR as % of HRmax (210 – [0.65 × age]) (252); bpm, beats per minute; HR, heart rate; m, metres; SpO_2, percutaneous oxygen saturation.

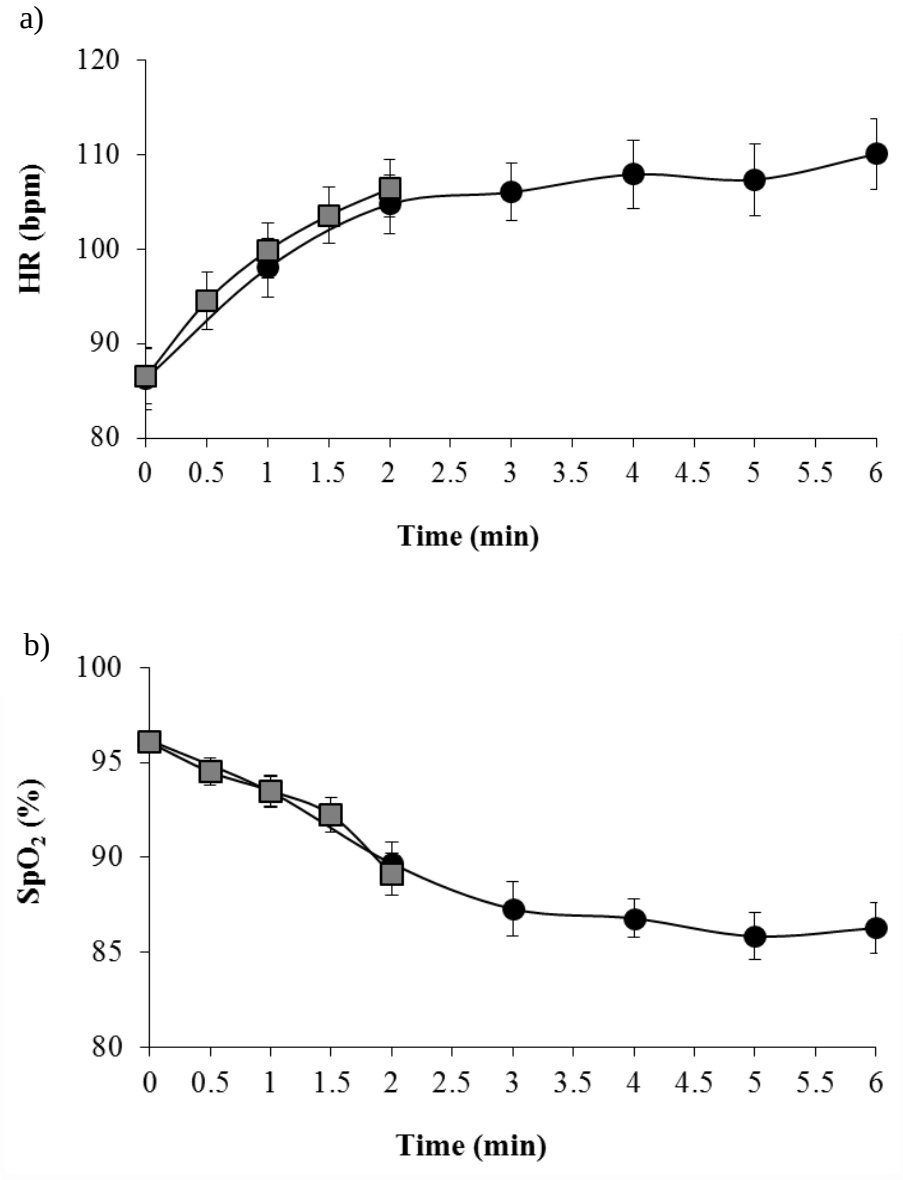

Figure 3.4: Pattern of response in a) HR, b) SpO_2 for each test.
Six-minute walk test, ●; two-minute walk test, ■. Data are presented as mean ± standard deviation. Abbreviations: bpm, beats per minute; HR, heart rate; min, minutes; SpO_2, percutaneous oxygen saturation.

3.5 Discussion

The main findings of this study are, in people with moderate to severe COPD: (i) the 2MWD increased by a small but significant amount with test repetition; (ii) there was a strong correlation between the 2MWD and the 6MWD suggesting that the 2MWT is a valid assessment of functional exercise capacity; (iii) the coefficient of repeatability for the 2MWD repeated over two days was 14m; (iv) participants walked significantly further during the 2MWT compared to one third of the distance walked during the 6MWT and, (v) when compared to the responses during the 2MWT, the 6MWT elicited higher peak HR, greater dyspnoea, lower nadir SpO_2, but no difference in end-test leg fatigue.

3.5.1 Effect of test repetition

The presence of a learning effect in walking tests such as the twelve-minute walk test (260, 261), 6MWT (6, 262-264) and incremental shuttle walk test (ISWT) (265, 266) has been well documented. The ERS/ATS Technical Standard for field-based walking test recommends that two tests should be performed when the 6MWT or the ISWT is used to assess change following an intervention or over time (226). It has been suggested that the mechanisms for the increase in walking distance with test repetition include improvement in the ability of the participant to pace themselves during the repeated tests, increased familiarity with the walking course, increased motivation, and, in those with dyspnoea on exertion such as in individuals with COPD, test repetition also improved their habituation to the sensation of dyspnoea (6, 235).

The present study found that there was a small but significant increase in the 2MWD with test repetition. Although the 2MWD may have increased further on additional tests, Butland et al. (1) found that when a fourth test was performed in a single session, the 2MWD increased by only a mean of 1m. Earlier work that has investigated the effect of test repetition on the 2MWD has reported inconsistent findings (1, 2, 7, 8). Three studies reported a small but significant increase in the 2MWD with test repetition in people with COPD who were naïve to the 2MWT (1, 2, 7), whereas one study found no change in the 2MWD on repeat tests in those with prior experience of the test (8). The finding of the study by Leung et al. (8), where no significant increase in the 2MWD with test repetition was found, may be explained by the inclusion of a practice walk that was undertaken the day before the actual

testing session. Moreover, encouragement was not provided during the test which may have reduced the magnitude of any improvement with test repetition (2). Of note, although the data in the present study demonstrated a significant increase in 2MWD with test repetition, the magnitude of this effect appears to be smaller than the effect of test repetition on the 6MWD in people with COPD. Specifically, in one previous study where the 6MWT was performed using an identical protocol as that used in the present study and carried out by the same team of investigators (6), the 6MWD was found to increase by a mean of 37m; 95% CI, 33m to 41m between walk 1 and walk 2. When expressed as a percentage of difference from baseline, the previous study reported that the 6MWD increased by a mean of 11%; 95% CI, 9% to 12% between walk 1 and walk 2. Therefore, although repeating the 2MWT appears to produce a small increase in the 2MWD, a practice walk for the 2MWT is less important than for the 6MWT and may not be necessary in people who may not be able to complete two 2MWTs within a day.

3.5.2 Repeatability of the 2MWD

The COR for the 2MWD measured over two days in people with moderate to severe COPD was 14m. This suggests that, for an individual patient, a change in the 2MWD of 14m or greater is needed in order to be 95% confident that the difference in the 2MWDs is not due to the natural variability inherent in this test. Factors such as day-to-day variability in respiratory symptoms and severity of airflow obstruction may explain the variation in the 2MWD performed over different days. For example, Espinosa et al. (267) evaluated the variability of the respiratory symptoms in 472 individuals with severe COPD and found that symptoms such as chest tightness and dyspnoea were reported to vary on a daily basis by at least 27% of the individuals. The percentage of individuals who reported variability of these two symptoms over a longer period (i.e. a week) increased to 40% for dyspnoea and 52% for chest tightness. In another example among people with COPD, Kessler et al. (268) found that 45% of 2,258 symptomatic patients perceived variability in at least one symptom over the course of a day and the percentage increased to 54% in those who reported variability in at least one symptom over the course of a week. The participants also reported that their symptoms were worse in the morning compared to the rest of the day (268). However, it is important to note that in the present study all participants were tested at a similar time of the day and therefore the influence of diurnal

variation in symptoms on walking performance is not likely to be the reason for the variability seen in the 2MWDs. If the two tests were performed at different times of the day, the random error in the present study is likely to have been greater and the COR would be larger than 14m.

The order in which the tests were performed on the second day of testing made little difference to the COR. That is, in those who performed the 6MWT first on the second day of testing, the COR for the 2MWD was ± 16m. This was 5m greater than the COR for the 2MWD in those who performed the 2MWT first on the second day of testing (i.e. ± 11m). These data suggest that, in a hospital setting where patients are unlikely to do any activity prior to doing a 2MWT, the COR for the 2MWD may be as low as 11m. However, in an out-patient setting (e.g. out-patient PRP), where patients are likely to have to walk from the car park to the location of the program, the COR for the 2MWD may be somewhat greater (i.e. ±16m).

The COR for the 2MWD in the present study was smaller than that reported in other populations such as in people with poliomyelitis (COR = 22m) (10), and samples of healthy Brazilian (COR = 24m) (17) and American (COR = 43m) adults (18). The reasons for a smaller COR for the 2MWD in the present study are likely to reflect disparities in the administration of the 2MWT between these studies. For example, the COR for the 2MWD in the present study was calculated between the best of three 2MWDs on one day and the fourth 2MWD on another day, whereas, the three other studies calculated the COR for the 2MWD between the first and the second 2MWD conducted either on the same day (17) or on separate days (10, 18). That is, in these earlier studies, the COR may have been inflated by the effect of test repetition. Importantly, the COR for the 2MWD in the present study (i.e. 14m) was smaller than that previously reported for the 6MWD (51m (234) and 63m (269)) in people with moderate to severe COPD. This means that, in people with moderate to severe COPD, clinicians can be confident of a true change with much smaller changes in the 2MWD than the 6MWD.

3.5.3 Validity of the 2MWD

The strong positive linear relationship between the 2MWD and the 6MWD corroborates findings from two previous studies in people with COPD (1, 8). This finding supports the validity of the 2MWD as a measure of exercise capacity in

people with moderate to severe COPD. Although, comparison of the 2MWD with the 'gold standard' measures of exercise capacity (e.g. VO_2 peak) would have strengthened the conclusion that the 2MWD is a valid measure of exercise capacity, collection of such data was not feasible among participants in the present study because of the high proportion of participants who were on ambulatory oxygen.

3.5.4 2MWD vs. one third of the 6MWD

The finding that the mean distance walked during the 2MWT was 31 ± 22m (27%) further than one third of the distance walked during the 6MWT suggests that these two measures are not interchangeable with each other. This finding is important for clinicians who evaluate the effect of an intervention, such as an exercise training program, using the 6MWT. Specifically, in the event that a participant develops an AECOPD during an exercise training program, the clinician may prefer to perform the 2MWT on completion of the program, as this test is less burdensome on the participant than a 6MWT. In this instance, comparing one third of the distance walked during a 6MWT at baseline with the 2MWD measured post-intervention will lead to an over-estimation of the effect of the intervention on this outcome.

3.5.5 Cardiorespiratory responses and levels of dyspnoea and leg fatigue during the 2MWT and 6MWT

This is the first study to compare cardiorespiratory responses during the 6MWT with the 2MWT. In addition to being more time consuming, the 6MWT imposed a greater cardiorespiratory burden on people with moderate to severe COPD as indicated by a greater change in HR and SpO_2 compared to the 2MWT.

With regard to the levels of symptoms during the 2MWT and the 6MWT, there was a difference in peak dyspnoea, but not in the end-test leg fatigue between the two tests. The proportion of participants who rested during the 6MWT due to intolerable dyspnoea was also higher than during the 2MWT. Earlier work has demonstrated that during the 6MWT, dyspnoea increases in a linear fashion, and therefore, it is likely that the greater dyspnoea reported on completion of the 6MWT compared with the 2MWT is largely due to the longer duration of the 6MWT (5, 270).

The low scores for leg fatigue at the end of the 2MWT (2.1 ± 1.9) and 6MWT (2.4 ± 2.3) in the present study are consistent with other studies that also reported low levels of end-test leg fatigue during the 6MWT (6, 158, 234, 265). Earlier work has

demonstrated that, in people with COPD, the symptom, which limits performance during exercise, differs between exercise modalities. Specifically, dyspnoea has been identified as the most common symptom limiting performance during walking-based exercise, while leg fatigue has been identified as the most common symptom limiting performance during cycling-based exercise (157, 158). One possible explanation is that compared to cycling, walking involves a greater number of muscles, especially postural muscles. Therefore, for the same level of oxygen consumption (VO_2), compared to cycling, during walking all of these muscles are working at a lower fraction of their oxidative capacity (271). In contrast, cycling exercise is performed by a smaller muscle mass (i.e. largely the quadriceps muscle), and due to this, the oxidative capacity of the quadriceps muscle is often overwhelmed and there is early reliance on anaerobic energy systems and accumulation of lactic acid in the blood, leading to the sensation of dyspnoea (271).

In contrast to the responses seen during the 6MWT, where both HR and SpO_2 began to plateau after the first two to three minutes of the test, both HR and SpO_2 changed rapidly and did not plateau during the 2MWT. This shows that the 2MWT was of inadequate duration to allow a steady state to be reached. Importantly, it suggests that the responses measured during the 2MWT were somewhat sub-maximal and therefore the 2MWT is less burdensome for the participant than the 6MWT.

3.5.6 Strengths and limitations

There are three main strengths of the present study. First, this study reports data pertaining to the measurement properties of the 2MWT that was carried out using a protocol based on the ERS/ATS technical standard for performing field-based walk test. Second, all tests were performed by the same investigator and the investigator ensure that all participants were tested at a similar time of the day. Third, for most outcome measures collected in this study there was minimal loss to follow up.

The present study also had some limitations. Although being the first study to compare exercise responses between the 2MWT and the 6MWT, the sample size in the present study (n = 18) was relatively modest. A larger sample size would have improved the precision of the estimate of the differences in cardiorespiratory responses and levels of symptoms between the 2MWT and the 6MWT as well as between repeat 2MWDs. A larger sample size would also allowed for subgroup

analyses such as differences in cardiorespiratory responses and levels of symptoms to the 2MWT and the 6MWT with participants grouped according to GOLD grades or between those requiring and not requiring supplemental oxygen. Nonetheless, this sample size was similar to that of previous studies that compared exercise responses during the 6MWT and the incremental exercise test such as incremental shuttle walk test and cycle ergometer test in people with moderate to severe COPD (n = 20) (5, 272). Comparison of more detailed cardiorespiratory responses (e.g. VO_2 peak, ventilation) to the 2MWT and 6MWT would have strengthened the conclusion that the 6MWT elicited a greater burden on the cardiorespiratory system as compared to the 2MWT. However, collection of such data was not feasible in these participants because of the high proportion of the participants in the present study who were on ambulatory oxygen.

3.6 Conclusions

This study has demonstrated that the 2MWT has a very small learning effect which appears to be smaller than the learning effect for the 6MWD reported in previous studies. Therefore, a practice walk for the 2MWT is less important than for the 6MWT and may not be necessary in people with COPD. This study also demonstrated that the 2MWD is repeatable. The COR for the 2MWD was smaller than that previously reported for the 6MWD, and therefore clinicians can be confident of a true change in the 2MWD with much smaller changes in the test result. This study also provides preliminary evidence to support the 2MWT as a valid measure of functional exercise capacity in people with moderate to severe COPD. The finding that participants walked a greater distance during the 2MWT compared to one third of the distance walked during the 6MWT suggests that these two measures are not interchangeable. The 2MWT appears to be better tolerated than the 6MWT in people with moderate to severe COPD. That is, when compared with the 6MWT, the 2MWT elicited a significantly lower peak HR, less oxygen desaturation and less dyspnoea. The proportion of participants who rested due to intolerable dyspnoea was also lower during the 2MWT when compared to the 6MWT. Therefore, in the context of patients who experience severe dyspnoea on exertion, such as in some of those with moderate to severe stable COPD or in those who are hospitalised for an AECOPD, the 2MWT may provide a more appropriate objective measure of functional exercise capacity than the 6MWT. As the 6MWT has several

applications in PRP (e.g. to evaluate change following PRP, prescribe a walking program, identify the presence of exercise induced desaturation) but does not appear to be routinely used in the acute setting, further studies are needed to evaluate other clinical applications of the 2MWT in this group of patients.

The present study provides preliminary evidence pertaining to the potential use of the 2MWT to detect exercise induced desaturation. The 2MWT seems to have a similar capacity to the 6MWT to detect clinically important oxygen desaturation given the fact that a similar proportion of patients in both tests desaturated more than 4% from baseline measures (273). However, the 6MWT may be a more relevant test for assessing the response to supplemental oxygen as the longer test duration is likely to be more representative of walking in daily life. The potential use of the 2MWT in prescribing the intensity of a walking training program and to evaluate change in exercise capacity following exercise training program in people hospitalised with an AECOPD are examined in Chapter 5. The finding that the 2MWT represents only a sub-maximal exercise test while the 6MWT represents a maximal or near maximal exercise test in people with moderate to severe COPD, the method of exercise prescription based on performance during the 2MWT was used not in the same way as a walking training program can be prescribed using the 6MWD.

CHAPTER 4
REGRESSION EQUATIONS TO ESTIMATE THE 2MWD IN MALAYSIAN ADULTS AGED 40 TO 75 YEARS

This chapter presents the study that developed regression equations to estimate the two-minute walk distance (2MWD) in a sample of Malaysians adults. The research questions answered in this chapter are:

i. Can age, gender, height, weight and change in heart rate (ΔHR [i.e. peak HR - resting HR]) measured during the two-minute walk test (2MWT) explain at least 50% of the variance in the 2MWD?
ii. Is the 2MWD measured in Malaysian adults similar to the 2MWDs estimated using the equations derived from Brazilian and American samples?

The details of the study design are provided, including a description of the study inclusion and exclusion criteria, recruitment strategies and assessment protocol. Details of the measurements and statistical analyses are also described. The results are presented and discussed.

4.1 Study design

A prospective, cross-sectional study was undertaken between February 2013 and January 2014. Study participants were volunteers who responded to flyers distributed in four villages located within a 5km radius of each other in the Batu sub-district, Gombak, Malaysia. Data collection for each participant was completed during a single 3-hour session at any of the four villages, depending on the preference of the participant. An overview of the study design is provided in Figure 4.1.

4.1.1 Approval from Human Research Ethics Committees

Approval to conduct the study was granted by the Human Research Ethics Committees of Curtin University (approval number HR127/2012), and Universiti Teknologi MARA (approval number 600-FSK [PT.5/2]). Written, informed consent was obtained from all participants prior to data collection.

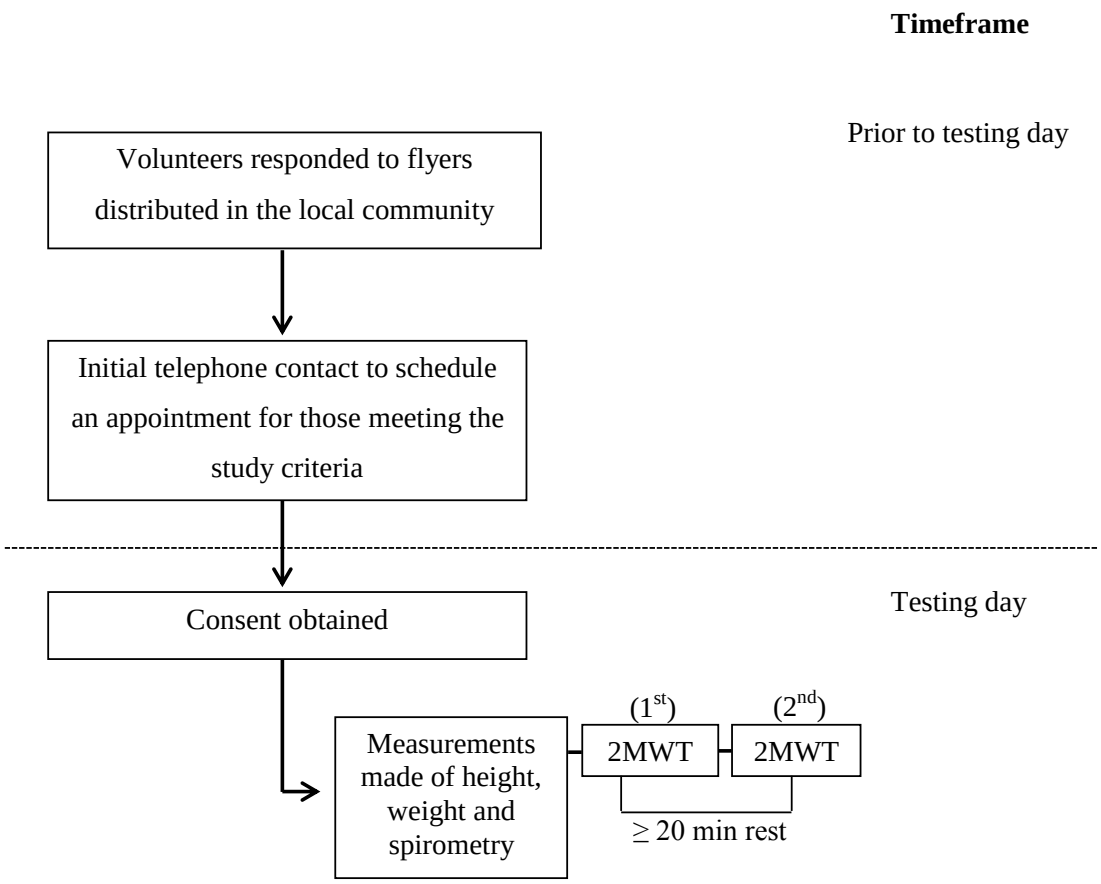

Figure 4.1: Overview of the study design.
Abbreviation: 2MWT, two-minute walk test.

4.1.2 Participants

4.1.2.1 Inclusion criteria

To be eligible to participate, volunteers had to be aged between 40 and 75 years and have no major health issues (defined as no history of cardiopulmonary disease, lung or heart surgery, stroke, and not taking any of the following medications: anti-arrhythmics, short- or long-acting bronchodilators, inhaled corticosteroids, mucolytics or antibiotics) (274). However, those who were prescribed medications for common conditions such as hypertension, hypercholesterolemia and diabetes mellitus were eligible to participate in this study as these medications are widely used among older adults, and the underlying conditions are unlikely to compromise the 2MWD. The age range of 40 to 75 years was selected as it is representative of people with COPD who have been referred to a pulmonary rehabilitation program (PRP) in Malaysia (275). The upper age limit of 75 years was used in this study due to the life expectancy in Malaysia being reported as 75 years in 2014 (276).

4.1.2.2 Exclusion criteria

Exclusion criteria comprised: (i) evidence of airflow obstruction (forced expiratory volume in one second [FEV_1] to forced vital capacity [FVC] < 0.70) (249), (ii) resting blood pressure (BP) > 165/95mmHg (277), (iii) resting HR > 100 beats per minute (bpm), (iv) upper respiratory tract infection within the past four weeks, (v) smoking history > 10 pack-years or currently smoking (as elevated levels of carboxyhaemoglobin has been shown to reduce exercise capacity (278)), (vi) body mass index (BMI) > 40 kg/m^2, (vii) use of a gait aid, (viii) presence of significant musculoskeletal or neurological disease likely to compromise the participant's ability to perform the walking test and (ix) inability to understand either English or Malay.

4.1.3 Recruitment and advice prior to day of testing

Flyers (see Appendix 3) were distributed to the local community by the investigator (PhD candidate). At the time when the flyers were distributed, the investigator ascertained the potential interest of the volunteers. Those who expressed an interest in participating in this study were contacted via telephone to schedule an appointment. Participants were instructed to continue their usual medications on the day of testing. They were also asked to avoid alcohol and the consumption of a

heavy meal for at least two hours prior to the testing session, and strenuous physical exercise in the previous 24 hours.

4.1.4 Assessment protocol

On the testing day, all participants underwent an interview using a standardised health screening form (see Appendix 4) and spirometry testing to confirm that they met the study criteria. Following the interview, all participants performed two 2MWTs that were separated by a rest period of at least 20 minutes (20, 22, 24). This rest period was extended when necessary if HR had not returned to within 10bpm of the resting value measured prior to the first test (20). The same investigator supervised both 2MWTs. Two 2MWTs were performed in this study to account for any improvement resulting from familiarisation with the test protocol (i.e. a learning effect) and the best 2MWD was recorded as the test result.

4.2 Measurements

4.2.1 Primary outcome measure

4.2.1.1 2MWD

The 2MWT was carried out in accordance with the protocol for the six-minute walk test (6MWT) described by the ERS/ATS Technical Standards (226). The protocol was modified to include: (i) standardised encouragement every 30s instead of every minute, (ii) standardised encouragement every 15s instead of 30s to recommence walking if the participant rested during the test (Appendix 5a [English version], 5b [Malay version]) and (iii) the instruction ‘to walk as fast as you can’ instead of ‘to walk as far as possible’ (see subheading 2.3.3.2.3).

An outdoor 30m straight course was used in this study. This was due to the difficulty in finding an indoor track of 30m length in all four villages. It has been shown in a previous study that there was no significant effect of setting (indoor vs. outdoor) on distance walked, rest duration or dyspnoea during the 6MWT in people with COPD (279), for whom variation in weather has been shown to provoke respiratory symptoms (280). Of note, all four testing locations were shaded, and the temperature in Kuala Lumpur is fairly steady throughout the year (i.e. ranges from 28°C to 32°C) (281).

Participants were requested to sit for at least 10 minutes before the test started. During this resting time, measurements were made of HR and BP (Omron M10-IT, Omron Healthcare Europe, Hoofddorp, The Netherlands). Standardised instructions were read aloud to the participants prior to each test. They were informed that they could slow down or rest if necessary. Participants were also told to stop walking and inform the investigator if they experienced any chest pain or dizziness.

4.2.2 Secondary outcome measures

4.2.2.1 HR and symptoms

Heart rate was recorded using a HR monitor (Polar a1, Polar Electro Oy, Kempele, Finland) before the test, every 30s throughout the test and at test completion. Dyspnoea and leg fatigue were assessed at the end of the test using the modified Borg 0-10 scale (147).

4.2.3 Descriptive measures

4.2.3.1 Participant details

Details were recorded pertaining to age and gender. Body weight (kg) and height (m) were measured and used to calculate BMI (kg/m^2).

4.2.3.2 Spirometry

Spirometry was performed in accordance with a standard protocol (256) using a portable spirometer (KoKo Legend II nSpire Health Inc., USA). Testing was done by the investigator who was trained and certified to standards aligned with the ATS/ERS standards (256). Participants were required to perform a minimum of three acceptable FVC manoeuvres (256). The largest FEV_1 and FVC from any of the three manoeuvres that met the acceptability and repeatability criteria were selected as the test results. Both FEV_1 and FVC were expressed as a percentage of the predicted normal values (282).

4.3 Statistical analyses

4.3.1 Sample size calculations

As data on regression equations developed to estimate the 2MWD are limited, sample size calculations were performed using data that were collected to develop a regression equation to estimate the six-minute walk distance (6MWD) (24). In this

earlier study, a sample size of 77 participants was required for five variables, to account for 49% of the variance in 6MWD in a sample of healthy Canadian adults (24). In order to have a similar number of predictor variables (i.e. age, height, weight, gender and ΔHR) to account for a similar proportion of variance in the 2MWD, the target sample size for this study was 77 participants ($\alpha = 0.05$, $1-\beta = 0.8$). This number was inflated by 15% to take into account the fact that some of the participants, especially those aged ≥ 70 years, may not complete the assessments required for this study (e.g. two 2MWTs in a session or spirometry). Therefore, the recruitment target for this study was 91 participants. This sample size was consistent with the sample sizes used in several other studies that developed regression equations to estimate the 6MWD in healthy individuals, even in those with a greater number of predictor variables (19, 33, 39).

4.3.2 Sampling

Stratified sampling was used to ensure an equal number of male and female participants were recruited in each decade of age (i.e. 40 male vs. 40 female participants) and that the sample was representative of the three major ethnicities in Malaysia (i.e. Malay, Chinese and Indian). As data shows that the Malaysian population comprises approximately 50% Malay, 23% Chinese and 7% Indian (43), a sample comprising a 6:3:2 ratio for Malay to Chinese to Indian for each decade from 40 to 69 years was recruited. As the age range for those aged between 70 and 75 years was half of a decade, a sample comprising half the target sample size for that of a full decade (i.e. 3:2:1 ratio) was recruited (Appendix 6).

4.3.3 Statistical analyses

Statistical analyses were performed using SPSS software (Version 19, SPSS Inc., Chicago, IL, USA). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Kolmogorov-Smirnov test).

A paired samples t-test was used to compare the differences between the repeated 2MWDs. The best 2MWD was used for further analyses. Comparison of the 2MWDs between males and females was performed using the independent t-test. If the difference in the 2MWDs between males and females was significant, gender was added as one of the independent variables in the regression analysis. Comparison of

the 2MWDs among the age groups (i.e. 40 to 49 vs. 50 to 59 vs. 60 to 69 vs. 70 to 75 years) was performed using one-way analysis of variance (ANOVA).

Associations between age, height, weight and ΔHR with the 2MWD were examined using Pearson's correlation coefficients. To develop the regression equations, stepwise multiple regression analysis was performed using the variables that were significantly correlated with the 2MWD as the independent variables, with the best 2MWD as the dependent variable. If ΔHR was retained as one of the predictors of the 2MWD in the regression analysis, a second regression equation, without this variable was planned, a priori. The latter equation is important as any equation that includes a measure of cardiac response during the 2MWT may be of limited use when estimating the 2MWD in people with a limited chronotropic response to exercise (e.g. heart failure patients or beta-blocker use).

Assumptions that underpin regression analyses were assessed. Specifically, collinearity was assessed using variance inflation factors (VIF) and condition indices derived from eigenvalues, with values ≤ 5 (283) and ≤ 30 respectively considered to be acceptable. The presence of both univariate and multivariate outliers were identified and were either removed or ignored depending on their impact on the regression model (284). The normality, linearity, and homoscedasticity of the residuals were assessed by examining the normal P-P plot of regression standardised residuals and distribution of the standardised predicted values plotted against the standardised residuals. The standard deviations (SDs) of the residuals from both equation models were reported to allow for the calculation of the lower limit of normal (LLN) for the estimated 2MWD (i.e. estimated 2MWD – 1.64 x residual SD) (285).

The 2MWDs measured in this study were compared with the 2MWDs estimated using the equations derived from a sample of Brazilian (17) and American adults (18) using paired samples t-tests. The method described by Bland and Altman (259) was also used to examine the agreement between the measured and the estimated 2MWDs (17, 18). For all analyses, a p value < 0.05 was regarded as statistically significant. All data are expressed as either mean ± SD or mean difference (MD) with 95% confidence interval (CI) unless otherwise stated.

4.4 Results

Of the 91 participants who were screened, four did not meet the study criteria (2 had a $FEV_1/FVC < 0.7$, 1 walked with a marked limp and reported a swollen ankle, and 1 was unable to complete the spirometry). Almost half (n = 43 [49%]) of the participants were on regular medications for common conditions (i.e. n = 37 [43%] for hypertension, n = 19 [22%] for hypercholesterolemia and n = 18 [21%] for diabetes mellitus). The characteristics of the 87 participants (males = 43 [49%]) and the results of the 2MWTs are summarised in Table 4.1.

4.4.1 2MWD

None of the participants required a rest during either of the 2MWTs. The mean 2MWDs recorded during the two consecutive 2MWTs were 193 ± 33m and 199 ± 34m respectively, and the best 2MWD was 200 ± 34m. The 2MWD increased by a mean of 6m (3%); 95% CI, 4m (2%) to 8m (4%) with test repetition. Four participants (5%) walked the same distance on both 2MWTs, whereas 21 (24%) and 62 (71%) participants achieved their best 2MWD on the first and second tests, respectively. The 2MWDs for the males and females were 217 ± 31m and 184 ± 28m, respectively. Males walked 33m (18%) further than females ($p < 0.001$) (Figure 4.2). There was a reduction in the 2MWD with increasing age ($p < 0.001$) (Figure 4.3).

Table 4.1: Characteristics of the participants and results of the 2MWT

	Total group (n = 87)	**Male** (n = 43)	**Female** (n = 44)
Age, yr	57.1 ± 9.6	58.0 ± 9.7	56.2 ± 9.5
Height, m	1.59 ± 0.77	1.65 ± 0.53	1.54 ± 0.57**
Weight, kg	67.8 ± 13.0	73.1 ± 13.4	63.1 ± 11.1**
BMI, kg/m^2	26.8 ± 4.4	26.7 ± 4.2	26.8 ± 4.6
Spirometry			
FEV_1, L	2.22 ± 0.58	2.61 ± 0.45	1.83 ± 0.41**
FEV_1 %pred	90 ± 15	90 ± 13	91 ± 17
FVC, L	2.77 ± 0.73	3.30 ± 0.51	2.25 ± 0.49**
FVC %pred	92 ± 15	92 ± 13	92 ± 16
FEV_1/FVC	0.80 ± 0.05	0.79 ± 0.05	0.82 ± 0.05*
Smoking history			
Smoker, n (%)	0 (0)	0 (0)	0 (0)
Ex-smoker, n (%)	15 (17)	15 (35)	0 (0)
Non-smoker, n (%)	72 (83)	28 (65)	44 (100)
2MWT data			
2MWD, m (test 1)	193 ± 33 (112-261)	210 ± 30 (112-239)	177 ± 28 (118-261)**
2MWD, m (test 2)	199 ± 34 (117-260)	216 ± 31 (117-237)	183 ± 29 (126-260)**
Best 2MWD, m	200 ± 34 (117-261)	217 ± 31 (117-239)	184 ± 28 (126-261)**
Resting HR, bpm	83 ± 10	82 ± 10	84 ± 10
Peak HR, bpm	133 ± 20	134 ± 19	132 ± 20
ΔHR, bpm	51 ± 22	53 ± 22	50 ± 23
%pred HRmax	80 ± 11	83 ± 11	80 ± 11
End-test dyspnoea	2.0 ± 1.2	2.1 ± 1.2	1.9 ± 1.2
End-test leg fatigue	1.4 ± 1.3	1.4 ± 1.3	1.3 ± 1.2

Data are presented as mean ± SD (range) or number (percentage).
*$p < 0.05$ and **$p < 0.001$ for comparisons between males and females.
Abbreviations: ΔHR, peak measured HR during the 2MWT – resting HR; 2MWT, two-minute walk test; 2MWD, two-minute walk distance; %pred HRmax, peak HR as a % HRmax (220-age); bpm, beats per minute; BMI, body mass index; FEV_1, forced expiratory volume in one second; FEV_1 %pred, percentage of predicted FEV_1 (282); FVC, forced vital capacity; FVC %pred; percentage of predicted FVC; HR, heart rate; kg, kilograms; L, litres; m, metres; yr, years.

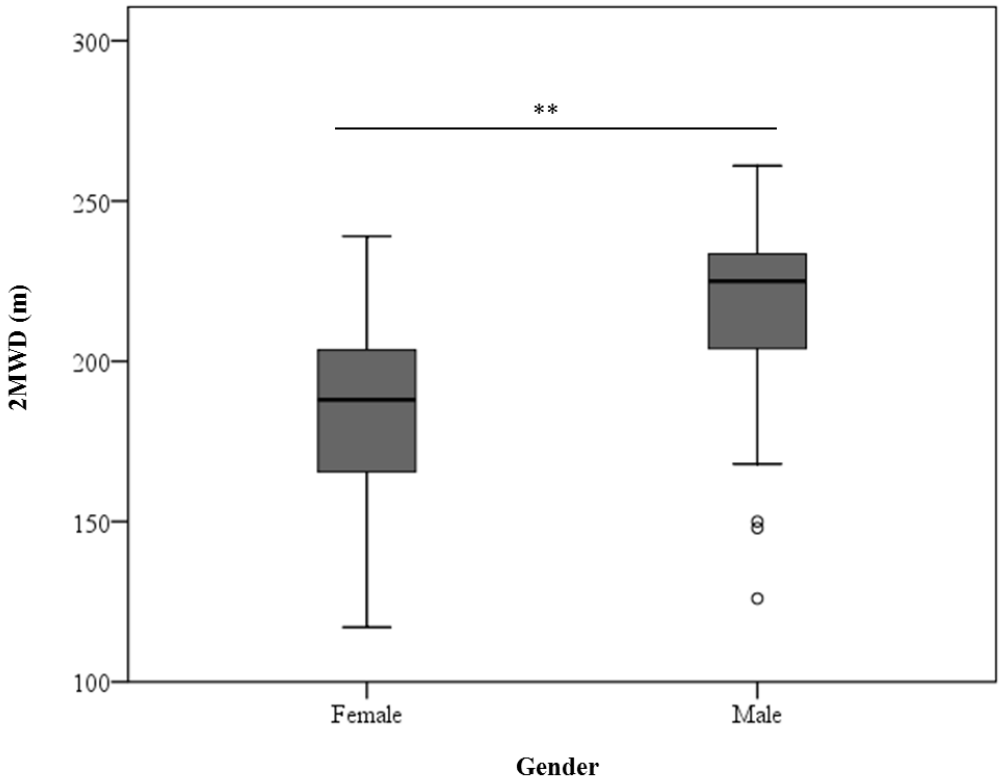

Figure 4.2: Differences in 2MWD between genders.
Data are shown as box plots. The horizontal line in the box indicates the median value of the data. The upper edge of the box indicates the 75th percentile while the lower edge of the box indicates the 25th percentile of the data set. The upper limit represented by the whisker lines is Q3 + 1.5 × IQR. The lower limit represented by the whisker line is Q1 – 1.5 × IQR. Circles correspond to outliers.
**$p < 0.001$
Abbreviations: 2MWD, two-minute walk distance; IQR, interquartile range; m, metres.

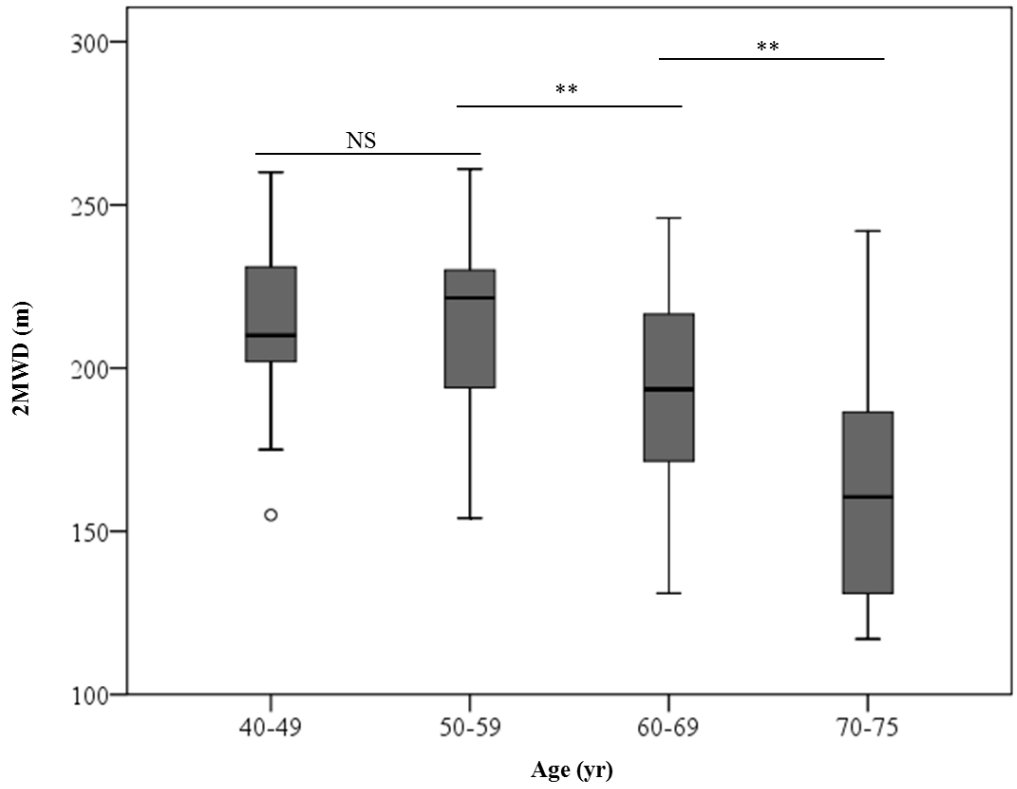

Figure 4.3: Influence of age on 2MWD.
Data are shown as box plots. The horizontal line in the box indicates the median value of the data. The upper edge of the box indicates the 75th percentile (Q3) while the lower edge of the box indicates the 25th percentile (Q1) of the data set. The upper limit represented by the whisker lines is Q3 + 1.5 × IQR. The lower limit represented by the whisker line is Q1 – 1.5 × IQR. Circle corresponds to outliers.
**p < 0.001
Abbreviations: 2MWD, two-minute walk distance; IQR, interquartile range; m, metres; NS, non-significant; yr, years.

4.4.2 Regression equations

Correlation coefficients between age, height, weight and ΔHR with the 2MWD are shown in Table 4.2. The predictor variables that explained the largest proportion of variance in the 2MWD were gender, age and ΔHR (Table 4.3). The model that explained the greatest proportion of the variance in the 2MWD, without violating the assumption of collinearity was:

2MWD = 196 - (1.1 × age) + (1.0 × ΔHR) + (31.2 × gender)

with the 2MWD measured in metres, age in years, ΔHR in bpm, females = 0, and males = 1. Together, these variables accounted for 73% of the variance in the measurement of the 2MWD. The SD of the residuals from this equation model was 17m. Therefore, the LLN = predicted 2MWD – (1.64 × 17m). The normal P-P plot of the regression standardised residuals and the scatterplot of standardised residuals against the standardised predicted values for this regression model are provided in Figure 4.4a and Figure 4.4b, respectively. Given that ΔHR was retained in the first model, a second model that excluded ΔHR was also derived from this sample. This equation was:

2MWD = 279 - (1.7 × age) + (35.9 × gender)

with 2MWD in metres, age in years, females = 0, and males = 1. These variables accounted for 47% of the variance in the measurement of the 2MWD. The SD of the residuals from this equation model was 24m. Therefore, the LLN = predicted 2MWD – (1.64 × 24m). The normal P-P plot of the regression standardised residuals and the scatterplot of standardised residuals against standardised predicted values for this regression model are given in Figure 4.5a and Figure 4.5b, respectively.

4.4.2.1 Additional analyses

Predictors for the 2MWD were gender, age and ΔHR. However, exploration of the data set revealed a strong correlation between height and the 2MWD in females (r = 0.50; p = 0.001) but not in males (r = 0.001, p = 0.996). Due to this, further analyses were conducted to determine whether adding an interaction term to the model for gender with height, weight or a combination of height and weight (i.e. BMI) improved its performance. That is, an interaction term would allow the association between anthropometrics in females only to be considered in the final model. When

an interaction term between gender and height was included as one of the independent variables in the regression analysis, the regression equation explained an additional 0.2% of the variance in the 2MWD. When two interaction terms were included in the regression analysis (height × gender and weight × gender), the regression equation explained an additional 2.3% of the variance in the 2MWD. When BMI (i.e. weight adjusted for height) was included in the regression analysis, the regression equation explained an additional 1.4% of the variance in the 2MWD (Figure 4.6). Given that these interaction terms explained only a small proportion of the variance in the 2MWD, they were not included in the final model. In other words, it can be concluded that the strong association between height and the 2MWD in females did not have an important impact on the regression model to estimate the 2MWD among females.

Table 4.2: Correlation coefficients between participant characteristics and the 2MWD

	Total group (n = 87)	**Male (n = 43)**	**Female (n = 44)**
Age, yr	-0.43**	-0.55**	-0.55**
Height, m	0.50**	0.001	0.50*
Weight, kg	0.12	-0.001	-0.16
ΔHR, bpm	0.62**	0.66**	0.68**

*p < 0.005, and **p < 0.001
Abbreviations: 2MWD, two-minute walk distance; ΔHR, change in heart rate (i.e. peak – resting); bpm, beats per minute; kg, kilograms; m, metres; n, number; yr, years.

Table 4.3: Predictor variables for the 2MWD obtained from multiple linear regression analyses

Model 1 ($R^2 = 0.73$)

	Unstandardised coefficient (B)	**Standard error**	**p value**	**Partial R^2**
Constant	196.38	14.63	< 0.001	-
Age (yr)	-1.07	0.21	< 0.001	0.08
Gender	31.22	3.83	< 0.001	0.18
ΔHR (bpm)	0.996	0.11	< 0.001	0.47

Model 1 ($R^2 = 0.47$)

	Unstandardised coefficient (B)	**Standard error**	**p value**	**Partial R^2**
Constant	278.61	16.03	< 0.001	-
Age (yr)	-1.68	0.28	< 0.001	0.23
Gender	35.94	5.31	< 0.001	0.24

Abbreviation: ΔHR: change in heart rate; 2MWD, two-minute walk distance; bpm, beats per minute; yr, year

a)

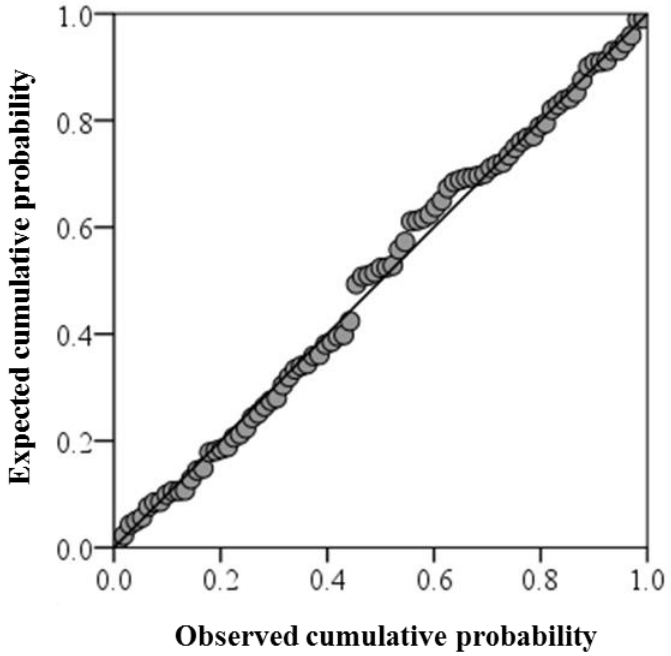

Figure 4.4a: Normal P-P plot of regression standardised residuals for Model 1: 2MWD = 196 – (1.1 x age) + (1.0 x ΔHR) + (31.2 x gender).
The points were clustered tightly along the diagonal line (i.e. line of identity) indicating that the residuals were normally distributed.

b)

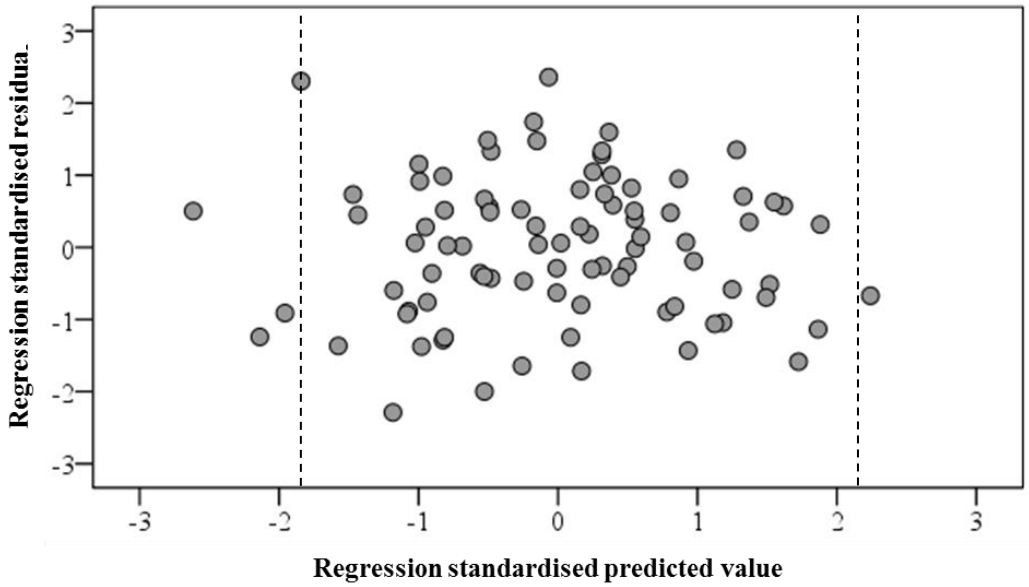

Figure 4.4b: Scatterplot of standardised predicted value (x-axis) vs. standardised residual value (y-axis) for Model 1: 2MWD = 196 – (1.1 x age) + (1.0 x ΔHR) + (31.2 x gender).
Mean values equal to zero and few data points extended beyond a standardised residual value of 2 indicating that the model was a good fit.
Abbreviations: 2MWD, two-minute walk distance; ΔHR, change in HR.

a)

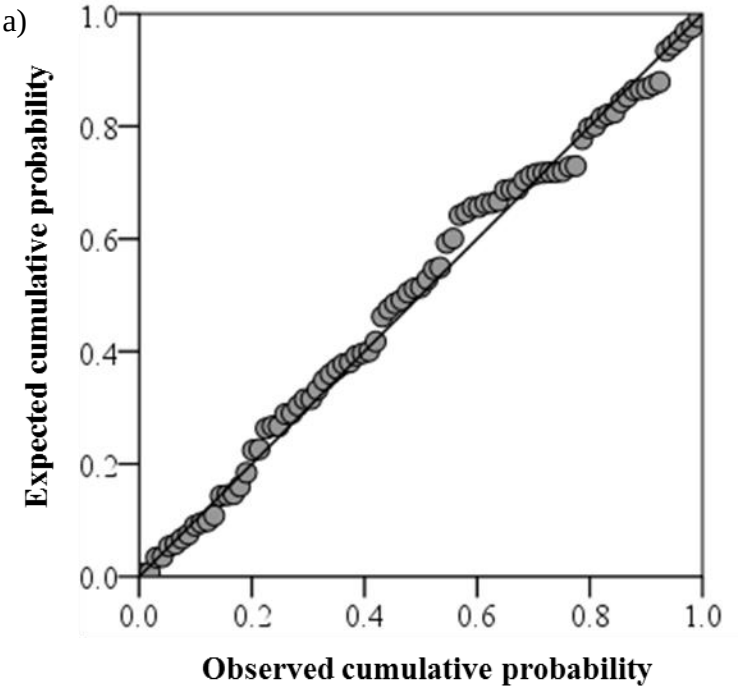

Figure 4.5a: Normal P-P plot of regression standardised residuals for Model 2: 2MWD = 279 - (1.7 x age) + (35.9 x gender).
The points were clustered tightly along the diagonal line (i.e. line of identity) indicating that the residuals were normally distributed.

b)

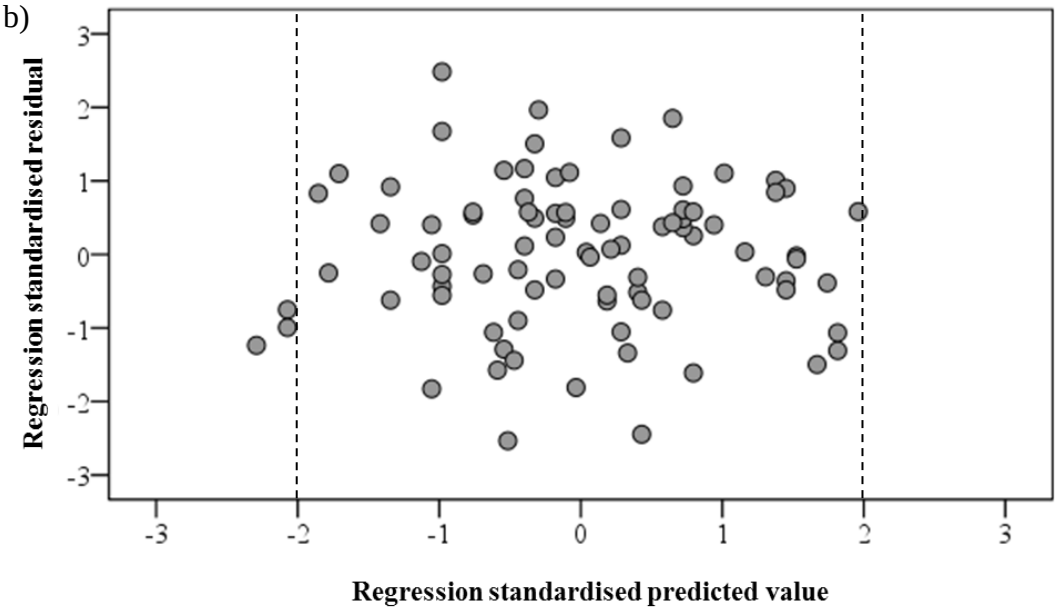

Figure 4.5b: Scatterplot of standardised predicted value (x-axis) vs. standardised residual value (y-axis) for Model 2: 2MWD = 279 - (1.7 x age) + (35.9 x gender). Mean values equal to zero and few data points extended beyond a standardised residual value of 2 indicating that the model was a good fit. Abbreviations: 2MWD, two-minute walk distance.

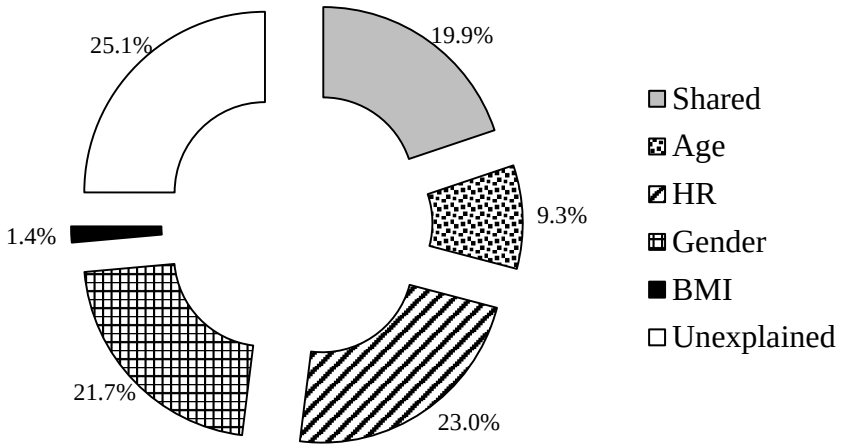

Figure 4.6: Contribution of each predictor variable to the 2MWD. Abbreviations: BMI, body mass index; HR, heart rate.

4.4.3 Comparison with the 2MWD estimated using a previously published equation

Figure 4.7a and Figure 4.7b illustrate the comparisons between the 2MWD measured in this study with the 2MWD estimated using the equations derived from both the Brazilian and American samples (17, 18). The MD; 95% CI between the 2MWD measured in the current study and that estimated using the equation derived from a sample of Brazilian and American adults were 4; -1 to 10m (17) and 23; 18 to 29m (18), respectively. In the Bland and Altman plots (Figure 4.8a and Figure 4.8b), the upper and the lower limits of agreement were not calculated. This was due to the presence of proportional bias in the differences between the measured and estimated 2MWDs in both plots (286).

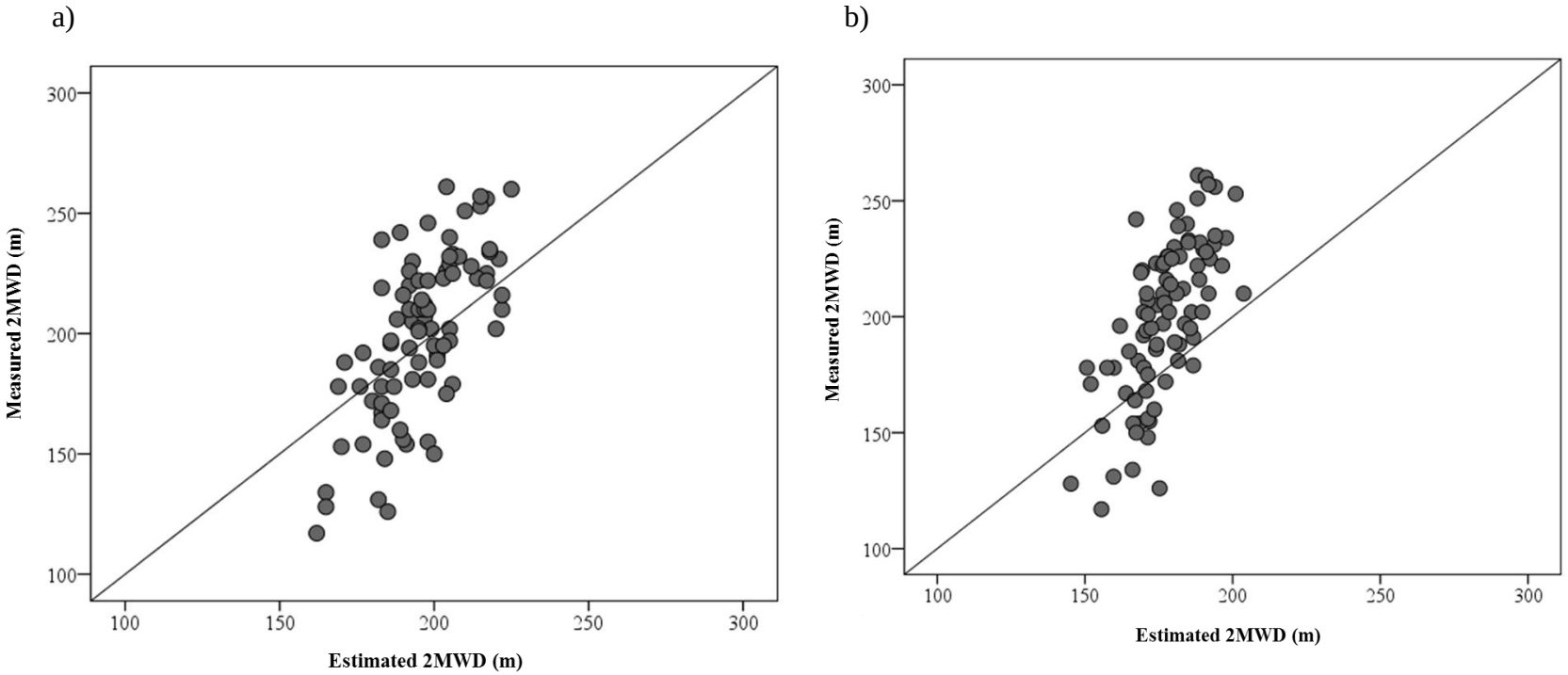

Figure 4.7a: Scatterplot of the 2MWD measured in a Malaysian sample (y-axis) vs. the 2MWD estimated using equation derived in a Brazilian sample (x-axis).
Figure 4.7b: Scatterplot of the 2MWD measured in a Malaysian sample (y-axis) vs. the 2MWD estimated using equation derived in an American sample (x-axis). Lines of identity for both plots are shown.
Abbreviations: 2MWD, two-minute walk distance; m, metres.

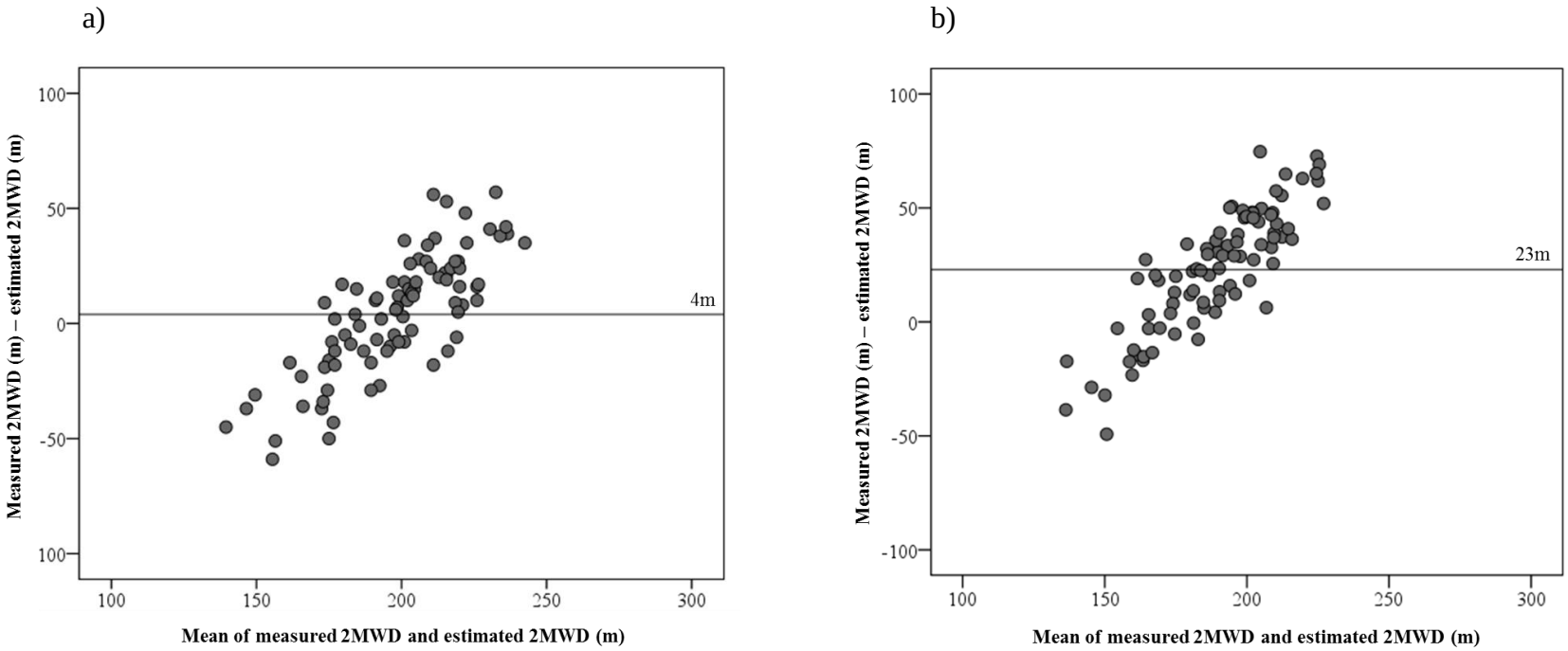

Figure 4.8a: Bland and Altman plots showing agreement between the 2MWD measured in a Malaysian sample and the 2MWD estimated using equation derived in a Brazilian sample.
Figure 4.8b: Bland and Altman plots showing agreement between the 2MWD measured in a Malaysian sample and the 2MWD estimated using equation derived in an American sample**.**
The solid line corresponds to the mean difference (i.e. bias) between the two 2MWDs. Due to the presence of proportional bias in the measurement error, the limits of agreement between the measured and the estimated 2MWD were not calculated in both plots.
Abbreviations: 2MWD, two-minute walk distance; m, metres.

4.5 Discussion

This is the first study to derive equations to estimate the 2MWD in Malaysians adults without significant disease. This study found that 73% of the variance in the 2MWD was explained by gender, age and ΔHR during the test, and when ΔHR was excluded from the regression equation, the combination of gender and age explained 47% of the variance in the 2MWD. The values for the SD of the residuals for the estimated 2MWD were presented for both equations, which allowed calculation of the LLN for the estimated 2MWD.

4.5.1 The influence of gender, age and cardiac response on the 2MWD

On average, male participants walked 18% further than the females. The difference in the 2MWD between genders in the present study is of a similar magnitude to that found in previous studies on the 2MWD (17) and the 6MWD (20, 22-24, 27, 33, 36) in healthy adults. The finding that male participants walked a greater distance than females can be best explained by the fact that males are generally taller than females (Table 4.1) and taller individuals walk with a longer stride length as opposed to shorter individuals (287). Other than the difference in height, males also have greater muscle mass and strength than females. Both, height and muscle strength have been identified in a previous study as two of the most important predictors of gait speed in healthy individuals (288).

The present study also demonstrated that the 2MWD decreased with increasing age. This finding is consistent with that of most studies that measured the 2MWD (17) or 6MWD (17, 20-24, 27, 28, 34-36) in healthy adults. This can be explained by the decline of muscle mass (230, 231) and the increase in sedentary behaviour with an increase in age (289). Only two studies have reported non-significant associations between age and the 6MWD in healthy adults (30, 39). This negative finding probably relates to the relatively narrow age range in the study samples in these two studies (i.e. 55 to 75 years (39) and 45 to 65 years (30)) which may have reduced the influence of age on this outcome. As shown in Figure 4.3, the influence of age on the 2MWD seen in the current study was not statistically significant between the age ranges of 40 to 49 and 50 to 59 years. This suggests that the influence of age on the

2MWD is likely to be seen in samples which have a larger range in age, possibly more than two decades.

The mean peak HR achieved during the better of the two 2MWTs was 81% of the predicted HRmax. This finding confirms that the 2MWT is a sub-maximal test for healthy adults, and is consistent with a previous study that reported a peak HR of 70% predicted HRmax during the 2MWT (17). A similar HR response had also been reported during the 6MWT in healthy adults (20, 22, 25, 39).

4.5.2 Effect of test repetition

The small but significant increase in the 2MWD with test repetition documented in this study (i.e. 3%; 95% CI, 2% to 4%) is consistent with the finding of the study described in Chapter 3 among people with moderate to severe stable COPD (i.e. 4%; 95% CI, 1% to 7%). The fact that the 2MWT in both studies was conducted using a similar test protocol and by the same investigator suggests that the magnitude of learning on the 2MWD with test repetition is small regardless of health status. Earlier work that has investigated the effect of test repetition on the 2MWD in other populations, such as in healthy Brazilian adults (17), or in other diseases such as in those with poliomyelitis (10) and heart failure (2), also reported a learning effect for the 2MWD of a similar magnitude. In contrast, the change in the 6MWD with test repetition has been reported to be lower in healthy individuals compared to those patients for whom dyspnoea plays a major role in exercise limitation, such as people with COPD (i.e. ranged from a mean of 9m to 24m [2% to 4%] in healthy individuals (20, 21, 24, 31, 36) vs. 27m to 37m [6% to 11% in people with COPD) (6, 262, 263, 290). Therefore, it appears that, learning effect to some extent is influenced by the duration of the test.

4.5.3 Regression equations

In the present study, the inclusion of ΔHR in equation model 1 explained an additional 26% of the variance in the 2MWD. This finding corroborates the results of previous studies that have demonstrated a measure of cardiac response during the 6MWT explains between 13% (19) and 27% (20) of the variance in the 6MWD. In contrast with earlier work which included the peak HR expressed as a % predicted HR maximum (HRmax) (19-22), this study included the measure of ΔHR during the 2MWT in the regression analysis. This was done because the % predicted HRmax is

calculated based on age (291), and age was identified as an independent variable in both prediction equations. Therefore, it is likely that the inclusion of % predicted HRmax may violate the assumption of collinearity and consequently result in over-fitting of the regression model.

4.5.3.1 Regression model 1

Approximately 73% of the variance in the 2MWD could be explained by age, ΔHR and gender. Hence, it can be concluded that the data fits the model very well. Referring to the unstandardised beta (B) values in Table 4.3, this model shows that, for every 1 unit (year) of increase in age, the 2MWD would be decreased by 1m. In contrast, the 2MWD increases by 1m with an increase of 1bpm in ΔHR. Being male was also identified as having a positive influence on the 2MWD. Specifically, the model indicates that the 2MWD will increase by 31m in males. From the analysis undertaken to determine the overall fit of the model, it can be seen in Figure 4.4b that the highest standardised residual of 2.361 is smaller than ±3 and only 2% of the sample had standardised residual values greater than ±2. Therefore, it can be concluded that the sample appeared to conform to what was expected for a fairly accurate and reliable model. The model derived also generalises very well as shown by the close proximity between the adjusted $R^2 = 0.725$ vs. observed $R^2 = 0.734$.

4.5.3.2 Regression model 2

Regression model 2 shows that approximately 47% of the variances in the 2MWD could be explained by age and gender. Referring to the unstandardised beta (B) values for this model, as shown in Table 4.3, an increase in age reduced the 2MWD; every one unit (year) of increase in age led to a decrease in the 2MWD of approximately 2m. Similar to Model 1, the 2MWD increased, by 36m, in males. From the analysis undertaken to determine the overall fit of the model, it can be seen in Figure 4.5b that the highest standardised residual of 2.486 is smaller than ±3 and only 1% of the sample had standardised residual values greater than ±2. Therefore, it can be concluded that the sample appeared to conform to what was expected for a fairly accurate and reliable model. The model also generalises very well as shown by the close proximity between the adjusted $R^2 = 0.461$ vs. observed $R^2 = 0.473$. Neither the study by Selman et al. (17) nor the study by Bohannon et al. (18) reported data pertaining to the highest standardised residual values in their participants or the

differences between the adjusted and observed R^2 of their regression models and therefore comparison with existing literature is not possible.

4.5.4 Comparison with the 2MWD estimated using previously published equations

Both of the previously published equations were expected to over-estimate the 2MWD in Malaysians adults. This is because Asians have been reported to have a lower percentage of lean body mass for a given BMI when compared to other ethnicities (232, 292-294), and lean body mass is positively associated with muscle strength (295), a known determinant of maximal walking speed in healthy individuals (288). However, the 2MWD estimated using both of the previously published regression equations did not over-estimate the measured 2MWD in Malaysian adults. There was no significant difference between the 2MWD measured in a sample of Malaysian adults and the 2MWD estimated for them using the regression equation derived from a Brazilian sample (17). This was despite the participants in the present study being comparatively older (age 57 ± 10 years vs. median [interquartile range] 52 [36 to 68] years), and shorter (height 1.59 ± 0.77m vs. 1.66 [1.58 to 1.72m]) than the Brazilian sample (17). On the other hand, the 2MWD estimated using the equation derived from an American sample significantly under-estimated the 2MWD measured in the sample of Malaysian adults by 23 ± 27m ($p < 0.001$) (18). This was also despite the fact that the American participants were younger (age 46 ± 18 years vs. 57 ± 10 years) and taller (height 1.68 ± 0.10m vs. 1.59 ± 0.77m) than the participants in the present study (18). Factors such as discrepancies in the 2MWT protocol used between these three studies and cultural differences among Malaysian, Brazilian and American may be able to explain this unexpected finding.

4.5.4.1 Discrepancies in the 2MWT protocol used between the studies

A factor related to the 2MWT protocol that could account for the lack of difference seen between the measured and estimated 2MWD (17) is that more frequent encouragement was given during the 2MWT in the present study compared to the Brazilian study (every 30s vs. 60s (17)). This may have resulted in a greater effort level during the test in the current study, as suggested by a greater magnitude in ΔHR (49 [36 to 68] bpm vs. 39 [25 to 55] bpm (17)). Encouragement has been shown to have a positive effect on walking test performance (2). Similar to the Brazilian study

(17), encouragement was also given only once throughout the 2MWT in the study among Americans adults (18). Cardiac response during the test was not reported in the American study hence a comparison of effort level cannot be made. Other than the 2MWT protocol in the American study being conducted with a lower frequency of encouragement, the fact that their equation was derived from only one test compared to the best of two 2MWDs as was used in the present study, may also have led to an under-estimation of their 2MWD (18). As reported earlier (see subheading 4.4.1), the 2MWD in the present study increased significantly by a mean of 6m; 95% CI, 4m to 8m on repeated tests. It is also possible that the use of a shorter walking track (15.2m) in the American study (18) may have compromised the 2MWD achieved in their study (see subheading 2.3.3.2.3).

4.5.4.2 Cultural differences among Malaysian, Brazilian and Americans

To date, there are no studies that have explored the potential influence cultural factors may have on the 2MWD. However, studies that have established prediction equations for the 6MWD across different cultures have shown that culture-specific factors such as parity, lifestyle, socioeconomic status and educational level significantly influence the 6MWD (36, 296). For example, Ben Saad et al. (36) in a study among 229 healthy North African adults demonstrated that issues of developing countries such as high parity and low socioeconomic status and educational level significantly influenced the 6MWD. Specifically, they found that the 6MWD was lower in high parity (≥ 6) vs. low parity (≤ 5) women and in people with low vs. high income and educational status (36). Although there are likely to be some cultural differences between Malaysian, Brazilian and American adults, it was beyond the scope of this study to examine the influence of any of the cultural-specific factors on the 2MWD. Of note, given that all three studies would have recruited people who potentially have an interest in exercise (i.e. the walk test), perhaps cultural-specific factors would have less influence on the test result.

4.5.5 Agreement between the measured and the estimated 2MWD

The Bland and Altman plots for the agreement between the 2MWD measured in the present study and the 2MWDs estimated from both previously published regression equations showed the presence of proportional bias in the distribution of the error between the measurements (Figure 4.8). As explained in Portney and Watkins (225), the pattern of proportional bias indicates that the two measurements do not agree

equally through the range of measurements. In the present case, the error was influenced by the size of the measurement whereby a greater estimated 2MWD was seen in cases of a low measured 2MWD, and a lower estimated 2MWD was seen in cases of a high measured 2MWD. Therefore, the two measurements could not be considered interchangeable with each other. Similar finding has also been reported in a previous study that compared the 6MWD measured in a sample of North Africans adults with the 6MWD estimated using regression equations derived from other populations (36).

4.5.6 Strengths and limitations

There are two main strengths of the present study. First, stratified sampling was used to ensure the sample was representative of the Malaysian population. Second, this was the first study in the Asian region to derive equations to estimate the 2MWD, which will be important not only to interpret the 2MWD in clinical populations in Malaysia but also in other Asian countries with similar cultural backgrounds and anthropometric characteristics to Malaysia, such as Indonesia, Singapore and Southern Thailand.

The present study had some limitations. First, the participants in the present study were volunteers who responded to flyers distributed in their community, thus the results may be influenced by a possible selection bias (e.g. volunteers for research are usually healthier and better educated) (297). Second, the selection of participants within the age range of 40 to 75 years in the present study may limit the generalisability of the equations to estimate the 2MWD in all adults in Malaysia, especially in individuals younger than 40 years. However, the age range of 40 to 75 years was selected as it is representative of people with COPD who have been referred to a PRP in Malaysia (275). Future studies should consider broadening the age range to allow for prediction of the 2MWD in people with diseases other than COPD. Third, this study aimed to produce equations to estimate the 2MWD in a general Malaysian population, not for specific ethnic groups in Malaysia. However, in the absence of regression equations for specific ethnic groups, the regression equation developed in this study included representation from the three main ethnic groups that reside in Malaysia and so is likely to provide the best estimate of the 2MWD for the ‘average’ Malay.

4.6 Conclusions

The equations produced in this study allows the main outcome of the 2MWT (i.e. the 2MWD) in clinical populations in Malaysia to be interpreted as a percentage of the value estimated in a person with the absence of significant disease. Even though the inclusion of ΔHR in the regression model explained an additional 26% of the variance in the 2MWD, it is important to report both equations. This is particularly important when assessing exercise capacity in individuals who require medications that have the potential to influence the HR response to exercise. Furthermore, the inclusion of the ΔHR in the regression equation requires the measurement of HR during the test. This may also be a limitation in a busy healthcare setting when it necessitates an extra measure to use the regression equation. Therefore, in most clinical settings, the equation that does not include the ΔHR will be more appropriate to estimate the 2MWD. Future studies should examine the accuracy of the regression equations reported in this study.

CHAPTER 5
A RANDOMISED CONTROLLED TRIAL OF EXERCISE TRAINING IN PEOPLE HOSPITALISED WITH AN AECOPD

This chapter presents the randomised controlled trial (RCT) which evaluated the effectiveness of an exercise program initiated early during the hospitalisation of people with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The research questions answered in this chapter are:

i. does an exercise program, initiated within two days of hospital admission, that comprises walking and resistance exercise, produce additional benefits in exercise capacity, quadriceps muscle force (QMF), functional performance and physical activity (PA), over and above any changes seen with usual care?
ii. is there a difference in the level of adherence between supervised and unsupervised exercise training sessions?

The details of the study design are provided, including a description of the inclusion and exclusion criteria, recruitment strategies, assessment protocol, and randomisation process and blinding procedures. The assessments made at baseline and prior to discharge as well as the details of the data management and statistical analyses are described. The results are presented and discussed.

5.1 Study design

This study was a single blind randomised controlled parallel-group trial. Data collection was performed between July 2013 and August 2014. An overview of the study design is provided in Figure 5.1. Baseline (i.e. pre-intervention) assessments commenced after participants gave written, informed consent and were completed within two days of hospital admission. Participants then were randomised to either an exercise group (EG) or a control group (CG). Participants in both groups received the usual medical and physiotherapy care given to patients admitted with an AECOPD. Those in the EG also received one supervised and one unsupervised training session each day throughout their hospitalisation. Spirometry and re-assessment measurements were performed on the day of discharge.

5.1.1 Approval from Human Research Ethics Committees and trial registration

Approval to conduct the study was granted by the Human Research Ethics Committees of Malaysia Ministry of Health (approval number NMRR-12-12-971-12644), Universiti Teknologi MARA (approval number 600-RMI [5/1/6]), and Curtin University (approval number HR 13/2013). The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR [registration number ACTRN12612000745842]). Written, informed consent was obtained from all participants prior to data collection.

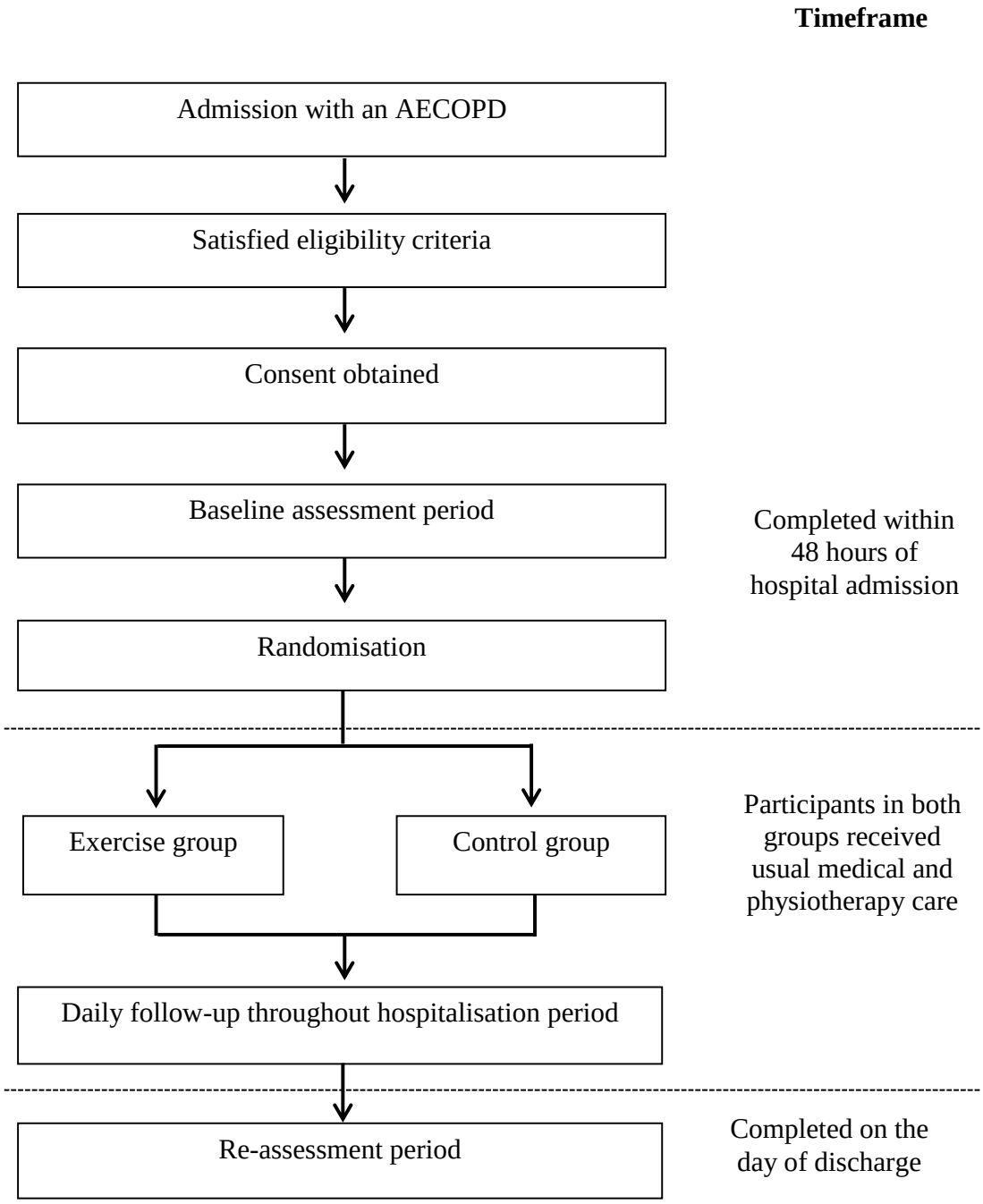

Figure 5.1: Overview of the study design
Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

5.1.2 Participants

5.1.2.1 Inclusion criteria

Patients who were admitted to hospital with an AECOPD as their primary diagnosis were eligible to participate in this study.

5.1.2.2 Exclusion criteria

Exclusion criteria comprised: (i) admission to the intensive care unit, (ii) contraindications to exercise testing (Appendix 7) (167), (iii) presence of any comorbid condition thought to compromise safety during the assessments and exercise sessions, (iv) severe musculoskeletal/ neurological condition thought to adversely influence performance during the assessments and exercise sessions, (v) hospitalisation within the previous 14 days, (vi) any requirement for non-invasive ventilation (NIV) during waking hours, (vii) unlikely to be admitted for at least five days and (viii) inability to understand English or Malay.

5.1.3 Recruitment

Patients admitted to two general hospitals: Hospital Selayang (HS) and Institute of Respiratory Medicine (IRM), Kuala Lumpur, Malaysia were screened daily through the hospital database. Those who were admitted with an AECOPD as the primary diagnosis were told about the study by the medical professionals' in-charge of the patients (i.e. nurses or medical doctors). They were asked if they would like to hear more about the study from the investigator. Those who expressed an interest to hear more about the study were approached by the primary investigator (PhD candidate) who provided a verbal explanation about the study and sought written informed consent from each participant to participate in this study. Information about the study was provided to participants prior to randomisation and therefore, all participants received identical information regardless of group allocation.

5.1.4 Assessment protocol

During the baseline assessment, measurements were collected of exercise capacity (two-minute walk test [2MWT]), QMF and functional performance (i.e. Sit to Stand Test [STST] and Timed Up and Go [TUG] test). The participants also completed questionnaires pertaining to health status (chronic obstructive pulmonary disease [COPD] assessment test [CAT]) (298) and the magnitude of their functional

limitation resulting from dyspnoea (modified Medical Research Council Scale [mMRC]) (151, 152). These tests were performed in the following order: CAT, mMRC, 2MWT, STST, TUG and QMF. The 2MWT was performed along the ward corridor, while the other three tests (i.e. STST, TUG and QMF) were performed in the ward's meeting room. Participants were given a PA monitor (StepWatch™ Activity Monitor [SAM]; OrthoCare Innovations, Seattle, Washington, USA) to be worn continuously throughout the hospitalisation period. Re-assessment measurements comprised spirometric measures of lung function, followed by the 2MWT, STST, TUG and QMF.

5.1.5 Randomisation

On the same day that all baseline assessments were completed, participants were randomly assigned to either the EG or CG. The randomisation sequence was generated using a computer-based program (http://www.random.org/) and concealed using sequentially numbered opaque envelopes. The sequence was stratified according to the hospital from which the participants were recruited (i.e. HS or IRM), and participants' baseline two-minute walk distance (2MWD [i.e. < 100 m or ≥ 100 m]). The sequence was also blocked so that for every two participants randomised, one was allocated to the EG and one to the CG.

5.1.6 Blinding

Complete blinding of all study personnel and participants was not feasible. The primary investigator, who was responsible for the collection of baseline measurements and training of the participants in the EG, was aware of each participant's group allocation. However, re-assessment measurements were performed by a qualified physiotherapist who was unaware of the participant's group allocation. All participants were aware of the existence of the two study groups, but they were not informed about what treatment the other group was receiving.

5.2 Measurements

5.2.1 Primary outcome measures

5.2.1.1 2MWD

Exercise capacity was measured using a 2MWT. Absolute contraindications to performing the test were taken from published guidelines for cardiopulmonary

exercise testing (Appendix 7) (167). Additional relative contraindications comprised: (i) pre-exercise heart rate (HR) of > 125 beats per minute (bpm) and, (ii) resting percutaneous oxygen saturation (SpO_2) of < 90%. Participants who required supplemental oxygen performed the test breathing oxygen supplied at their prescribed flow rate for exercise, delivered through nasal prongs with the oxygen cylinder transported by the participant using a trolley. As supplemental oxygen has been demonstrated to increase exercise capacity and reduce dyspnoea on exertion (299-301), for each participant, any use of supplemental oxygen during the baseline 2MWT was kept identical during the re-assessment 2MWT.

The 2MWT was carried out in accordance with a protocol adapted from the European Respiratory Society (ERS)/American Thoracic Society (ATS) Technical Standards for the 6MWT (226) with the following modifications: (i) standardised encouragement every 15s instead of 30s to recommence walking if the participant rested during the test, (ii) standardised phrases of encouragement every 30s instead of every minute and (iii) the instruction 'to walk as fast as you can' instead of 'to walk as far as possible' (see subheading 2.3.3.2.3).

The test was performed over a 30m straight course within the ward corridor. The course was marked with a cone at either end. Chairs were placed at both ends and at the mid-way point to allow seated rests if required. Standardised instructions were read aloud to the participants in either English or Malay before the test. They were informed that they could slow down or rest if necessary. Participants were also told to stop walking and inform the investigator if they experienced any chest pain or dizziness. Participants who demonstrated profound oxygen desaturation, defined as $SpO_2 < 80\%$, were instructed to stop walking immediately and to recommence walking if SpO_2 recovered to $\geq 80\%$ (226).

Percutaneous oxygen saturation (Masimo Rad-5v, Masimo Corporation, Irvine, California, USA) and HR (Polar a1, Polar Electro Oy, Kempele, Finland) were monitored throughout the 2MWT with the values recorded before the test, every 30s during the test, and at test completion. The investigator walked behind the participant and care was taken to avoid influencing the walking speed of the participant. Following test completion, participants remained in the testing area, and SpO_2 was

monitored until it returned to ≥ 90%. In participants who needed to rest during the 2MWT, the frequency, duration and reason for resting were recorded. In participants for whom a rest was imposed because of profound oxygen desaturation (SpO_2 < 80%) (302), the nadir SpO_2 was also recorded. Dyspnoea was assessed using the Borg category ratio scale (0-10) (147) at rest, upon test completion, and at the start of any rests taken during the test, with the highest dyspnoea score used in the analyses. Leg fatigue was recorded on test completion (147). The main outcome of the 2MWT (i.e. 2MWD) was expressed in meters and as a percentage of the predicted value for a healthy Malaysian sample, using the regression equation presented in Chapter 4 of this thesis.

5.2.1.2 QMF

The strength of the quadriceps muscles of the dominant leg was assessed during an isometric maximum voluntary contraction (MVC) using a force transducer (digital force gauge [BFG1000, Mecmesin Limited, Slinfold, West Sussex, UK]). The device (Figure 5.2a) contains a highly accurate load cell (± 0.2% of full scale [1000 Newton, N]) that converts tension/compression force into an electrical signal. The built-in software in the device converts this electrical signal into a force value (N) that is displayed on the screen of the device. The force transducer has been shown to provide a very sensitive measurement of strength and has the ability to detect even small differences in isometric forces (131, 132) when compared to the two most commonly used method of assessing muscle strength in the clinical setting (i.e. manual muscle testing [MMT] and hand-held dynamometer [HHD]). The force transducer and accompanying apparatus is also lighter and can be transported more easily than the isokinetic machines (i.e. the gold standard in measuring muscle force). The force transducer was mounted on a steel support affixed to a purpose-built chair (Figure 5.2b). The position of the participant was standardised (i.e. seated with hips and knees flexed to 90^o and feet not touching the floor). External stabilisation was provided at the pelvis, trunk and the lower extremities of the leg not being tested (non-dominant side) (Figure 5.2c). A force plate was attached to the force gauge and was held perpendicular to the distal third of the tibia (Figure 5.2d). A high-density foam pad was placed at the front part of the force plate to protect the participant's skin. The device was factory calibrated, and zeroed before each measurement in accordance with the manufacturer's recommendations.

With the arms folded across the chest, participants were instructed to gradually increase the force exerted against the force plate to produce a MVC that was maintained for 5s. This duration (5s) has been shown to be adequate to generate a maximum force in older adults (303, 304). The participants were also reminded to avoid a rapid and explosive type of contraction. The protocol included a familiarisation period, and followed with three to five trials with a minimum of 30s rest between each contraction (305). Standardised verbal encouragement was given during the test. The highest value that was within 10% of at least one other measure was used in the analyses (72). Outcomes were expressed in kilograms (kg) and as a percentage of the predicted value in a healthy population (306).

a)

b)

c)

d)

Figure 5.2a: Force gauge
Figure 5.2b: Force gauge chair
Figure 5.2c: Position of the participant during the test
Figure 5.2d: Position of the force gauge

5.2.2 Secondary outcome measures

5.2.2.1 STST

The STST was used to measure functional performance in this study as it: (i) reflects many common activities of daily living such as rising from a chair/bed or getting out of a car and (ii) requires little instrumentation (i.e. a stopwatch and a standard chair). The protocol used for the STST was based on the 30s chair raise protocol described by Rikli and Jones (174). Specifically, the test was performed using a standard height chair (45cm) without arm rests. With the arms folded across the chest, participants were instructed to move between sitting and standing upright as many times as possible within a 30s period. Prior to commencing the test, the investigator demonstrated the task and the participant was asked to complete a practice trial of two repetitions. During the test, participants were permitted to rest and no encouragement was given. A position that was more than halfway up from sitting to standing at the end of the 30s was counted as a full stand. The number of stands performed within 30s was counted as the test result. The score was also expressed as a percentage of the predicted value in a healthy population (307).

In people with stable COPD, the number of repetitions achieved during the STST has demonstrated moderate to strong associations with measures such as QMF ($r = 0.46$, $p = 0.01$) (308) and six-minute walk distance ($r = 0.75$, $p < 0.001$) (177). The test has demonstrated the ability to detect change following a pulmonary rehabilitation program (PRP) in people with stable COPD (175).

5.2.2.2 TUG test

The TUG test was used to measure functional performance in this study as it is a measure of basic mobility (309) that has been shown to be safe even in people aged > 70 years (173). The TUG test protocol was based on the protocol described by Podsiadlo and Richardson (182) with modification of the test instruction ‘to walk as quickly as you can’ instead of ‘to walk at a comfortable and safe pace’ (see subheading 2.2.3.2). The test was performed using a standard straight-backed chair with arm rests. The test required the participant to stand up from the chair, walk a distance of 3m as quickly and as safely as possible, turn around at the cone, and return to the sitting position. Participants were permitted to push up with their arms

to get into the standing position. No encouragement was given during the test. The time (s) taken to complete the task was measured as the test result. As earlier work has suggested that the performance during the TUG test differs between individuals of different ethnicities (184), the test result (i.e. time) in this RCT was interpreted based on the reference values developed in elderly Thai (310) rather than Caucasians.

The time taken to complete the TUG test has demonstrated moderate to strong associations with measures of balance (e.g. Berg Balance Scale [r = -0.72]), gait speed (r = -0.55) and functional capacity (e.g. Barthel Index [r = -0.51]) (182) in older adults. In people with COPD, the TUG test has been shown to have high test-retest repeatability (186) and is responsive to change following a PRP (187).

5.2.2.3 PA

Physical activity was measured in terms of the number of steps taken each day throughout the duration of hospitalisation and was recorded using the SAM. Prior to data collection, the SAM (Figure 5.3a) was initialised for each participant by entering their (i) height (cm), (ii) selecting the range of walking speed (moderate), (iii) leg motion (normal), (iv) time zone (Malaysia), and (v) number of days over which measurements were to be made (15 days). This small (75 x 50 x 20 mm) and light-weight (38g) device was attached to the participant's right ankle using a Velcro® strap (Figure 5.3b). The device was set to flash a red light for the first 40 steps taken by the participants to indicate that it had started detecting steps. During this time (i.e. the first 40 steps taken by the participant), the investigator monitored that the red flashing light blinked one time for every step taken by the participant to ensure that the device was working (212). Participants in both groups were instructed to wear the device continuously, day and night, and were told not to remove the device even when showering and during sleeping. The SAM was only removed from the participant's ankle on the day they were discharged from hospital.

Data from the SAM were downloaded using the accompanying software (StepWatch^{TM} 3.1; OrthoCare Innovations, Seattle, Washington, USA) via a docking station (Figure 5.3c). The device detected the total number of steps taken by only one leg (i.e. right leg). Therefore, this value was doubled to calculate the total number of steps taken by the participant. The device also provided data pertaining to the total

time which the participant spent being sedentary (i.e. 0 steps/min), walking at low (≤ 60 steps /min) and moderate (> 60 steps/min) intensities (311). The SAM has been shown to be accurate in recording steps in people with COPD, including those who walk very slow or use a walking aid (211). The step rate derived from the SAM has shown excellent agreement with the step rate derived via direct observation in people with COPD (211).

a)

b)

c)

Figure 5.3a: Stepwatch™ Activity Monitor
Figure 5.3b: Stepwatch™ Activity Monitor attached to the right leg
Figure 5.3c: Docking station

5.2.3 Descriptive measures

5.2.3.1 Participant's details

Body weight (kg) and height (m) were measured and used to calculate body mass index (BMI [kg/m^2]). The participant's medical history (e.g. current medication use, comorbidities and smoking history) was recorded. The number of smoking pack-years was calculated by dividing the average number of cigarettes smoked per day by 20 (i.e. the number of cigarettes in a pack), then multiplying by the number of years that the participant had smoked (84).

5.2.3.2 Health status

The impact of COPD on each participant's health status was assessed using the 8-item CAT in either English or Malay (298). The CAT score has demonstrated a strong association ($r = 0.80$, $p < 0.001$) with the COPD-specific version of the St George's Respiratory Questionnaire (SGRQ) (298).

5.2.3.3 Functional limitation

Participants were asked to rate their functional limitation resulting from dyspnoea using the modified mMRC dyspnoea scale (151, 152). This scale comprises five statements each of which is assigned a grade that ranges from zero "I only get breathless with strenuous exercise" to four "I am too breathless to leave the house or I am breathless when dressing". The participant selects the statement which best describes their level of limitation in daily activities due to breathlessness. The mMRC scale has been shown to be a valid method of categorising people with COPD in terms of their level of functional disability (255).

5.2.3.4 Spirometry

Spirometry was performed at hospital discharge according to standard procedures (256) using a portable Microloop II (Micro Medical Ltd, Rochester, Kent, UK) device, which was calibrated every six months. Testing was conducted by the primary investigator who was trained and certified to standards which aligned with those of the ATS/ERS standards. Participants were required to perform a minimum of three acceptable forced vital capacity (FVC) manoeuvres (256). The largest forced expiratory volume in one second (FEV_1) and FVC from any of the three manoeuvres that met the acceptability and repeatability criteria were selected as the test results.

Both FEV_1 and FVC were expressed as a percentage of the predicted normal values (282).

5.2.3.5 Adverse events

Adverse events (Table 5.1) were recorded during both assessment and training sessions. If an adverse event occurred, the investigator immediately ceased the session and sought appropriate help as per hospital protocols.

5.3 Interventions

Participants in both groups who required supplemental oxygen during activity were provided with portable oxygen to use during their hospitalisation.

5.3.1 Control group

Participants in the CG received the usual medical and physiotherapy care given to patients admitted with an AECOPD according to the Malaysian Clinical Practice Guideline (CPG) (89). Usual physiotherapy care comprised airway clearance techniques (e.g. active cycle of breathing techniques, percussion and vibrations, gravity assisted drainage positions [if required]), strategies to minimise dyspnoea (e.g. pursed lip breathing and positioning [if required]), and encouragement to mobilise in the ward. Participants in the CG did not receive any exercise program but were not restricted in their physical activities throughout the period of hospitalisation. The primary investigator also visited all participants in the CG on a daily basis. They were asked about their condition and were free to ask any questions related to their health. This daily meeting was a strategy to minimise the difference in attention from the primary investigator between the EG and the CG (312).

5.3.2 Exercise group

The participants in the EG received usual medical and physiotherapy care given to patients admitted with an AECOPD according to the Malaysian CPG (89). In addition, they performed two individual training sessions (one supervised and one unsupervised) each day throughout their hospitalisation period. The duration of the exercise training was 30min per session, and the supervised training was conducted by the primary investigator. The training commenced on the day following randomisation and continued until the participant was discharged. At the beginning of each supervised exercise session, measurements were made of BP (Omron M10-IT, Omron Healthcare Europe, Hoofddorp, The Netherlands), pulse rate and SpO_2

(Masimo Rad-5v, Masimo Corporation, California, USA). Criteria for postponing an exercise program were a pre-exercise (i) systolic BP > or < 20% of resting value, (ii) pulse rate > 125bpm and /or (iii) SpO_2 < 90%. Prior to commencing the training, participants were familiarised with both the Borg scale (0-10) (147) to rate dyspnoea and leg fatigue, and the visual analogue scale (VAS) (313) to rate any symptoms of delayed onset muscle soreness (DOMS). The VAS consisted of a 10cm horizontal line with one descriptor at each end (i.e. no pain – worst possible pain) (313). Dyspnoea and leg fatigue were measured at the end of each supervised training session, whereas any symptoms of DOMS were measured prior to the exercise session on the following day. During each supervised session, pulse rate and SpO_2 were monitored intermittently. Criteria for ceasing an exercise session were defined as an adverse event, and have been summarised in Table 5.1.

The intensity and progression of the exercises were titrated based on the participants' levels of dyspnoea and leg fatigue. As such, if the participant could complete the designated exercise intensity with reported dyspnoea and leg fatigue of ≤ 5 on the Borg scale, progression was made on every second day of training session. If the participants reported a Borg score of ≥ 6, progression was delayed until the next exercise session. During exercise training, supplemental oxygen was administered, as required, to maintain SpO_2 of > 88%. Each training session comprised walking and functional resistance exercises. For all participants, training took place on their ward.

5.3.2.1 Walking training

The initial prescription for the walking exercise was based on the baseline 2MWD. Specifically, if a participant could walk 100m on the baseline 2MWT, he/she was instructed to walk 100m twice a day (once supervised, once unsupervised). Progression was then made on every second day of training (symptoms permitting) by increasing the distance walked by 20%. For example:

Baseline 2MWD	=	100m
Prescription on the first exercise session	=	100m
Prescription on the third exercise session (if symptoms permitted)	=	100m + (20% × 100m) = 120m
Prescription on the fifth exercise session (if symptoms permit)	=	120m + (20% × 120m) = 144m

5.3.2.2 Resistance training

The resistance component of the training program comprised three exercises, namely sit to stands, step ups, and half squats. Detailed descriptions of these exercises are given in Table 5.2. For all three exercises, the initial prescription was based on the baseline measurement of the STST. Specifically, if the participant achieved 10 sit to stands during the baseline STST, he/she was instructed to perform one set of 10 sit to stands, 10 step ups, and 10 half squats exercise twice a day (one supervised and one unsupervised). Progression was then made on every second day of training (symptoms permitting) by increasing the repetition of each exercise type by one set. The achievement of three sets of number of repetitions of the STST completed at baseline indicated that the participants had completed the target progression for the training program. For example:

Baseline STST	=	10 repetitions
Prescription on the first exercise session	=	one set of 10 repetitions of each exercise
Prescription on the third exercise session (if symptoms permitted)	=	two sets of 10 repetitions of each exercise
Prescription on the fifth exercise session (if symptoms permitted)	=	three sets of 10 repetitions of each exercise

5.3.2.3 Adherence to the training session

Each day, the participants in the EG were given a diary card to monitor their adherence to the unsupervised training sessions (Appendix 8). Adherence was measured as the percentage of scheduled sessions that were completed. Reasons for not participating in the training sessions were documented.

Table 5.1: Parameters used to define adverse events

Signs	Adverse events
Heart rate	> 85% of estimated maximum HR (i.e. > 85% of 210 – [0.65 × age]) (252)
Angina pectoris	Chest discomfort (i.e. pressure, heaviness, tightness, squeezing, burning or choking sensation)
Oxygen desaturation	SpO_2 < 80%
Blood pressure	Change in systolic blood pressure (BP) > or < 20% of resting value
Fall/ collapse	Fall or collapse during the assessment or exercise session

Abbreviations: HR, heart rate; SpO_2, percutaneous oxygen saturation.

Table 5.2: Description of the resistance exercises

Type of exercise	Description
Sit to stands	The exercise was performed with the participant seated in the centre of a straight-backed chair; feet were flat on the floor and slightly apart. Participants were instructed to stand upright and return back to a fully seated position with their arms folded across their chest.
Step ups	A step measuring 40cm × 25cm × 25cm was used. Participants were instructed to climb up and down the step following the sequence up-up-down-down leading with alternate leg for each set of repetitions. A chair was placed in front of the participant as a safety measure for them to hold onto if they felt they were going to fall (participants were not allowed to hold onto the chair during the exercise).
Half squats	In a standing position, participants were instructed to squat down until their thighs were parallel to the floor (or as far as they could), hold the position for one second, and return to the standing position slowly. Participants were reminded to keep their back straight during the exercise. A chair was placed in front of the participant as a safety measure for them to hold onto if they felt they were going to fall (participants were not allowed to hold onto the chair during the exercise).

5.4 Statistical analyses

5.4.1 Sample size calculations

As data on the change in 2MWD following exercise training in people hospitalised with an AECOPD were not available, sample size calculations were performed using data from a previous RCT of exercise training in people hospitalised with an AECOPD that reported change in QMF (72). In this earlier study, participants were allocated either to an EG that received resistance training for the quadriceps once per day or a CG that received usual care. Over the course of hospitalisation, participants in the EG demonstrated a mean change in QMF of +10 ± 16% from baseline measures while those in the CG demonstrated a mean change in QMF of -1 ± 13% from baseline measures (between-group difference of 11%). However, in the present study, participants allocated to the EG received training twice daily and therefore it was anticipated that the between-group difference in QMF would be greater than 11%. Assuming a between-group difference of 15% ± 14% ($\alpha = 0.05$, $1 - \beta = 0.8$), a sample size of 15 participants per group was needed (30 in total). This number was increased from 30 to 38 to allow for a 20% attrition rate (314). This sample size also provided sufficient power to detect a between-group difference of 17 ± 14m in the 2MWD, which was a change reported by people with stable COPD on completion of a five-week PRP (8).

5.4.2 Statistical analyses

Statistical analyses were performed using SPSS software (Version 19, SPSS Inc., Chicago, IL, USA). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Kolmogorov-Smirnov test). At baseline, between-group comparisons of continuous data were undertaken using independent t-tests. For data that were skewed from normal distribution, analyses were undertaken using a Mann-Whitney *U* test. Pearson's Chi-square tests were used for between-group comparison of categorical data (e.g. comorbidities and medications).

Progression in the training load for walking and resistance exercise were assessed using paired t-test and Wilcoxon Singed Ranked Test, respectively. Specifically, for the walking training, the distance walked at the initial supervised exercise was

compared with the distance walked at the final supervised exercise session. For the resistance training, the number of repetitions at the initial supervised exercise session was compared with the number of repetitions at the final supervised exercise session. Within- and between-group differences were analysed using a two-way repeated measures analysis of variance (two-way RM-ANOVA). Differences were expressed as mean difference (MD) and 95% confidence interval (CI). In the EG, adherence to the supervised and unsupervised training sessions was compared using the paired t-test. Analyses were undertaken according to an intention-to-treat basis (315). That is, analyses were conducted using follow-up data from all participants irrespective of whether or not they completed the prescribed number of exercise sessions. There was no attempt to impute missing data or to account for participants without follow-up data. For all analyses, a p value < 0.05 was regarded as statistically significant. All data are expressed as either mean ± standard deviation (SD) or median (interquartile range [IQR]), unless otherwise stated.

5.4.3 Management of PA data

In people hospitalised with an AECOPD, no studies have investigated the minimum wear time needed to reliably measure PA. In people with stable COPD, Watz et al. (198) showed that two days of measurement was sufficient for a reliable measurement of PA in people with very severe disease. Similarly, the study by Pitta et al. (190) concluded that, in people with moderate to severe COPD, two days of PA measurement were necessary for the data to have acceptable reliability (i.e. intraclass correlation coefficient between 0.70 and 0.88). Therefore, the minimum requirement for a participant's data to be included in the analyses of PA in this study was the availability of PA data over two days, with 100% wear time in each 24-hour period. Days in which less than 24 hours of PA data were available (i.e. the days when the SAM was applied and removed by a participant) were discarded. For participants who were included in these analyses, the total number of steps taken per day, time spent being sedentary and the time spent walking at low and moderate intensities (see subheading 5.2.2.3) were averaged over the number of assessment days (i.e. days with 100% wear time in each 24-hour period). Between-groups differences were compared using independent-samples t-tests. For data that were skewed from normal distribution, Mann-Whitney *U* tests were used.

5.5 Results

During the period of recruitment, a total of 120 patients were screened across the two hospitals. Seventy-three (61%) patients did not meet the study criteria and 47 (39%) were invited to participate in the study. Of the 47 patients who were approached, nine (19%) declined participation: six (67%) refused to exercise during hospital stay, two (22%) were concerned that participation in this RCT would lead to a longer hospital stay, and one (11%) refused to participate in any kind of research study. Thirty-eight participants completed the baseline measurements and were randomised to either the EG (n = 20) or the CG (n = 18). At baseline, there were no significant differences between the EG and the CG in anthropometric or clinical characteristics (Table 5.3). Recruitment was similar at both sites (HS [n = 19], IRM [n = 19]). Four (20%) participants in the EG and two (11%) in the CG did not complete the re-assessment measurements. Figure 5.4 shows the flow of screening, randomisation, and follow-up in the study.

Table 5.3: Baseline characteristics of the study participants (n = 38)

Variable		**Total (n = 38)** mean ± SD	**EG (n = 20)** mean ± SD	**CG (n = 18)** mean ± SD	p value
Age, yr		63.8 ± 7.5	62.3 ± 6.6	65.5 ± 8.2	0.18
Weight, kg		55.6 ± 15.3	52.9 ± 13.9	58.6 ± 16.7	0.26
Height, m		1.63 ± 0.07	1.63 ± 0.08	1.62 ± 0.07	0.56
Body mass index, kg/m^2		21.0 ± 6.1	19.7 ± 4.5	22.4 ± 7.4	0.17
FEV_1, L		0.87 ± 0.40	0.88 ± 0.36	0.87 ± 0.45	0.96
FEV_1 %pred		33 ± 14	33 ± 14	34 ± 14	0.89
FVC, L		1.96 ± 0.60	2.01 ± 0.49	1.89 ± 0.72	0.54
FVC %pred		58 ± 17	59 ± 15	57 ± 19	0.75
FEV_1/FVC		0.45 ± 0.14	0.44 ± 0.15	0.46 ± 0.13	0.64
Smoking pack-years		47 ± 25	51 ± 27	45 ± 23	0.49
CAT score		20 ± 5	21 ± 4	20 ± 6	0.45
			n (%)	n (%)	p value
Gender	Male		20 (100)	17 (94)	0.29
	Female		0	1 (6)	0.29
Site	HS		10 (50)	10 (56)	0.73
	IRM		10 (50)	8 (44)	0.73
GOLD	Grade I		1 (5)	2 (11)	0.49
	Grade II		4 (20)	4 (22)	0.87
	Grade III		10 (50)	8 (45)	0.73
	Grade IV		5 (25)	4 (22)	0.84
mMRC	Grade 0		0	0	-
	Grade 1		7 (35)	3 (17)	0.20
	Grade 2		5 (25)	6 (33)	0.57
	Grade 3		6 (30)	7 (39)	0.56
	Grade 4		2 (10)	2 (11)	0.91
Wheeled walker			0	0	-
Supplemental oxygen[#]			14 (70)	11 (61)	0.56
LTOT[≠]			3 (15)	4 (22)	0.57
Portable oxygen at home			0	0	-
Smoking status	Ex-smoker		12 (60)	17 (94)	0.01*
	Current-smoker		6 (30)	1 (6)	0.05
	Non- smoker		2 (10)	0	0.17

*$p < 0.05$, [≠]home oxygen, [#]oxygen therapy administered during the hospitalisation.
Abbreviations: CAT, COPD assessment test; CG, control group; EG, exercise group; FEV_1, forced expiratory volume in one second; FEV_1 %pred, percentage of predicted FEV_1 (282); FVC, forced vital capacity; FVC %pred, percentage of predicted FVC; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HS, Hospital Selayang; IRM, Institute of Respiratory Medicine; kg, kilograms; L, litres; LTOT, long-term oxygen therapy; m, metres; mMRC, modified Medical Research Council; SD, standard deviation; yr, years.

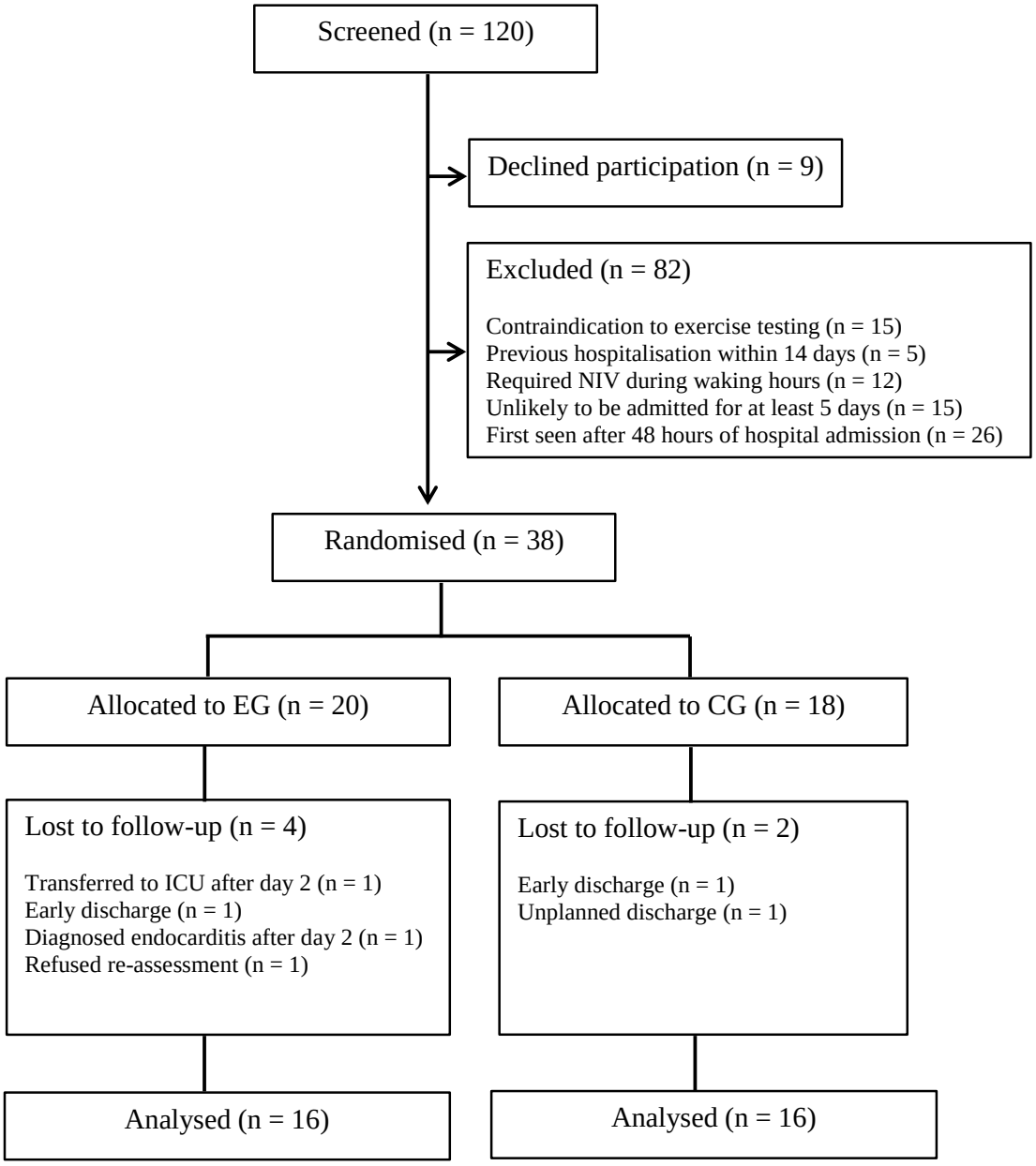

Figure 5.4: Flowchart of randomised participants
Abbreviations: CG, control group; EG, exercise group; ICU, intensive care unit; n, number; NIV, non-invasive ventilation.

5.5.1 Medical treatment and co-morbidities

During the period of hospitalisation, 31 (82%) of the 38 participants received oral corticosteroids (80% in EG vs. 83% in CG; p = 0.79) and 27 (71%) received antibiotics (80% in EG vs. 61% in CG; p = 0.20). A similar number of participants in the EG and the CG were on inhaled steroids before admission to hospital (25% vs. 22%; p = 0.84). The participants were being treated for other common conditions such as hypertension (35% in EG vs. 44% in CG; p = 0.55), diabetes mellitus (25% in EG vs. 33% in CG; p = 0.57) and hypercholesterolemia (20% in EG vs. 22% in CG; p = 0.87).

5.5.1.1 Safety and feasibility of the baseline and re-assessment measurements

During baseline assessments, one participant demonstrated a decrease in SpO_2 from 92% at the end of the 2MWT to 69% within three minutes following the completion of the test. The participant was immediately given a short burst of 4L/min supplemental oxygen and the SpO_2 recovered to ≥ 90% within half an hour. During baseline assessments, 13 (34%) participants required one or two rest(s) during the 2MWT due to intolerable dyspnoea. No adverse events were observed during or following the QMF, STST and TUG tests.

During the re-assessments, four participants (two from each group) rested during the 2MWT due to intolerable dyspnoea. The two participants in the EG required between one and two rest(s), while the other two participants in the CG required only one rest during the test. No adverse events were observed during or following the 2MWT, QMF, STST and TUG tests.

5.5.2 Exercise training program

5.5.2.1 Adherence to the training sessions

The 16 participants allocated to the EG performed 4 ± 1 (range 2 to 6) sessions of supervised exercise and 4 ± 1 (2 to 7) sessions of unsupervised exercise. On average, they completed 96 ± 9% of their scheduled supervised training sessions and 92 ± 13% of their scheduled unsupervised training sessions. There was no difference between the level of adherence to supervised and unsupervised sessions (p = 0.22). Table 5.4 reports the number of missed sessions in both supervised and unsupervised training as well as the reasons given by the participants for not adhering to the

training session. No training sessions were missed because of unacceptable BP, pulse rate or SpO_2 (see subheading 5.3.2).

5.5.2.2 Safety and feasibility of the exercise program

No adverse events were observed during the supervised training sessions and therefore no session was terminated by the investigator. Figure 5.5a-d displays the cardiorespiratory responses and level of symptoms recorded during the supervised exercise sessions. The mean levels of peak dyspnoea, leg fatigue and nadir SpO_2 across all training sessions were 2.6 ± 1.0, 0.5 ± 0.7 and 93 ± 3% during walking training and 2.5 ± 0.7, 1.0 ± 0.6 and 94 ± 3% during resistance training, respectively. The participants also reported a median (IQR) score of zero (0 to 2) for the intensity of DOMS symptoms following 24 hours of exercise sessions across the entire training period.

5.5.2.3 Progression of the exercise program

There was a significant increase in the distance walked during the first and final supervised training sessions (129 ± 30 vs. 160 ± 44; $p < 0.001$). Figure 5.5e presents the progression in the training load for walking exercise during the training period. There was a significant increase in the total numbers of repetitions of resistance exercise completed during the first and final supervised training sessions (12 ± 3 vs. 20 ± 5; $p = 0.001$). Figure 5.5f presents the progression in the training load for each of the resistance exercises (i.e. sit to stands, half squats and step ups) during the training period. Figure 5.6a and 5.6b illustrate the highest distance and greatest number of repetitions achieved for both walking and resistance exercises compared to the final prescription in each participant. One (6%) participant did not achieve the final targeted prescription for walking exercise. For the resistance exercise, seven (44%) participants did not achieve the final targeted prescription. The reasons related to general fatigue and fear of over-exertion.

Table 5.4: Missed training sessions and reasons for not participating in training sessions

(n = 16)	**Supervised**		**Unsupervised**	
	WT	RT	WT	RT
Total number of possible training sessions	61	59	67	67
Total number of missed training sessions	3	3	6	7
Reasons for not participating in the training sessions				
Dyspnoea	-	-	1	1
Leg fatigue	-	-	2	3
Visitors interruption	-	-	1	1
Feeling unwell	1	1	1	1
Advised by covering doctor not to exercise	1	1	1	1
Refused	1	1	0	0

Abbreviations: n, number; RT, resistance training; WT, walking training

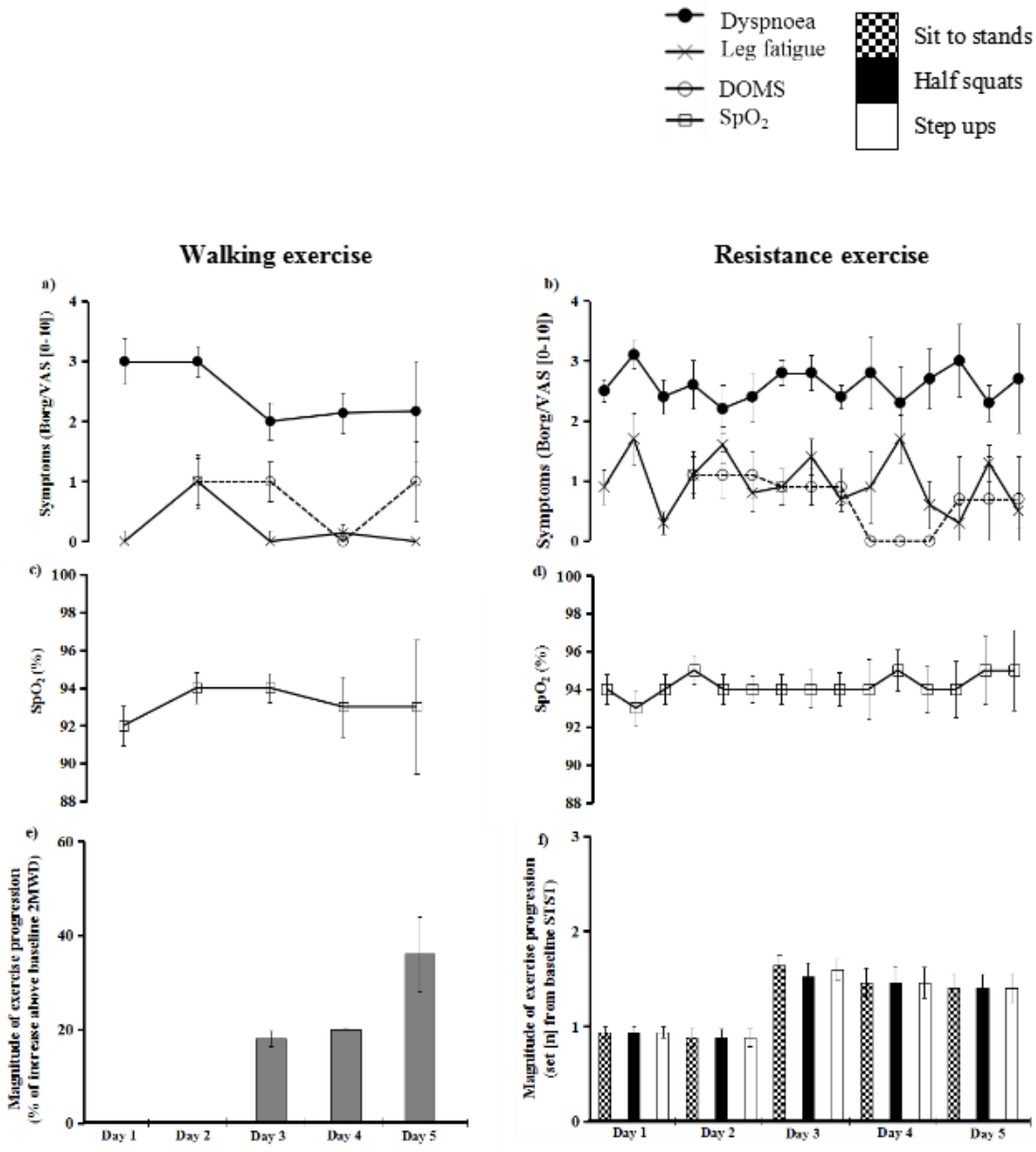

Figure 5.5: Cardiorespiratory responses, levels of symptoms and progression in walking and resistance exercises.
Peak dyspnoea (●) and leg fatigue (×) measured using the Borg scale at the end of each exercise session and DOMS (o) measured using the VAS 24 hours following the training session during a) walking and b) resistance exercise. Nadir SpO_2 (□) recorded during c) walking and d) resistance exercise. Progression in the training load for e) walking and f) each of the resistance exercises. Data are mean ± SE. Abbreviations: 2MWD, two-minute walk distance; DOMS, delayed onset muscle soreness; SpO_2, percutaneous oxygen saturation; VAS, visual analogue scale; STST, Sit to Stand Test.

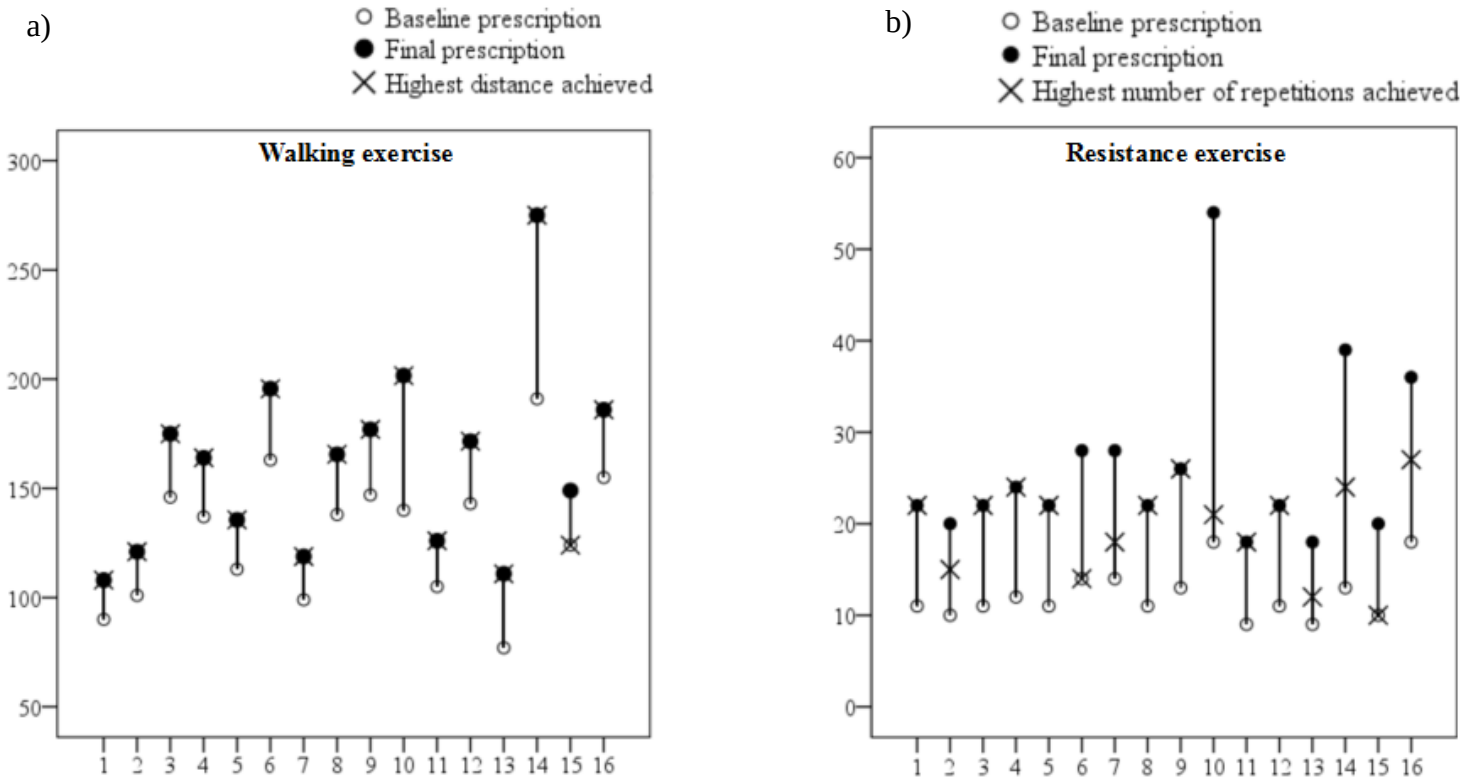

Figure 5.6: The progression in the prescription of a) walking exercise and b) resistance exercise (n = 16). Participant number 15 exercised at the baseline prescription throughout hospitalisation due to one missed session (feeling unwell) and the participant was discharged after the third exercise session while participant 2, 6, 7, 10, 13 and 16 declined to exercise at the targeted final prescription for the resistance exercises. In Figure 5.6b, it can be seen that participant 10 had a comparatively high final prescription and this was due to this participant having the longest length of hospital stay. Abbreviations: m, metres; n, number.

5.5.3 Measurements

The number of participants in the EG and the CG who completed each of the baseline and re-assessment measurements is presented in Figure 5.7.

5.5.3.1 Anthropometric and clinical characteristics

At baseline, there were no significant differences between the EG and the CG in anthropometric or clinical characteristics (Table 5.5). The median [interquartile range] hospital length of stay were 8 [6 to 9] days in the EG and 7 [6 to 8] days in the CG ($p = 0.64$).

5.5.3.2 2MWD

With the EG and CG considered together, participants walked a mean of 129 ± 38m (62 ± 18%) during the baseline 2MWT. At baseline, there were no differences in any of the variables collected during the 2MWT between the EG and CG.

Within-group differences:

In the EG, the magnitude of change in the 2MWD between baseline and re-assessment measurement was 33 ± 15m ($p < 0.001$). In the CG, the magnitude of change in the 2MWD between baseline and re-assessment measurement was 20 ± 13m ($p < 0.001$). When compared with the coefficient of repeatability (COR) for the 2MWD as estimated in Chapter 3 (see subheading 3.4.2), 14 (88%) and nine (56%) participants had an improvement of ≥ 14m in the EG and CG, respectively (Figure 5.8).

Between-group differences:

Compared with the CG, the EG demonstrated a greater change in the 2MWD (MD; 95% CI, 13m; 3m to 23m) (Figure 5.9a). Table 5.6 presents the baseline and re-assessment measurements for measures collected during the 2MWT. There were no between-group differences in the change in peak HR, nadir SpO_2, peak dyspnoea, end-test leg fatigue or the proportion of participants who rested during the test.

5.5.3.3 QMF

With the EG and CG considered together, the QMF of the participants at baseline was 20.3 ± 5.7kg (64 ± 14% predicted) (306). At baseline, there was no difference in QMF between the EG and CG.

Within-group differences:

In the EG, the magnitude of change in QMF between baseline and re-assessment measurement was 5.9 ± 3.4kg ($p < 0.001$). In the CG, the magnitude of change in the QMF between baseline and re-assessment measurement was 3.1 ± 3.6kg ($p < 0.01$).

Between-group differences:

Compared with the CG, the EG demonstrated a greater change in QMF (MD; 95% CI, 2.8; 0.3 to 5.3kg) (Figure 5.9b).

5.5.3.4 STST

With the EG and CG considered together, the number of repetitions in the STST at baseline was 12 ± 3 (46 ± 14%) (307). At baseline, there was no difference in the STST results between the EG and the CG.

Within-group differences:

In the EG, the magnitude of change in the STST between baseline and re-assessment measurement was 3 ± 3 repetitions ($p < 0.01$). In the CG, the magnitude of change in the STST between baseline and re-assessment measurement was 2 ± 2 repetitions ($p < 0.001$).

Between-group differences:

The magnitude of change in STST repetitions was similar between the two groups (MD; 95% CI, 1; -1 to 2 repetitions) (Figure 5.10a).

5.5.3.5 TUG test

With the EG and CG considered together, the time needed by the participants to perform the TUG test at baseline was 8.5 ± 2.8s. At baseline, there was no difference in the TUG test results between the EG and CG.

Within-group differences:

In the EG, the magnitude of change in TUG between baseline and re-assessment measurement was -1.5 ± 1.3s ($p < 0.01$). In the CG, the magnitude of change in the TUG between baseline and re-assessment measurement was -0.6 ± 1.9s ($p = 0.21$).

Between-group differences:

The magnitude of change in TUG was similar between the two groups (MD; 95% CI, -0.8; -2.0 to 0.4s) (Figure 5.10b).

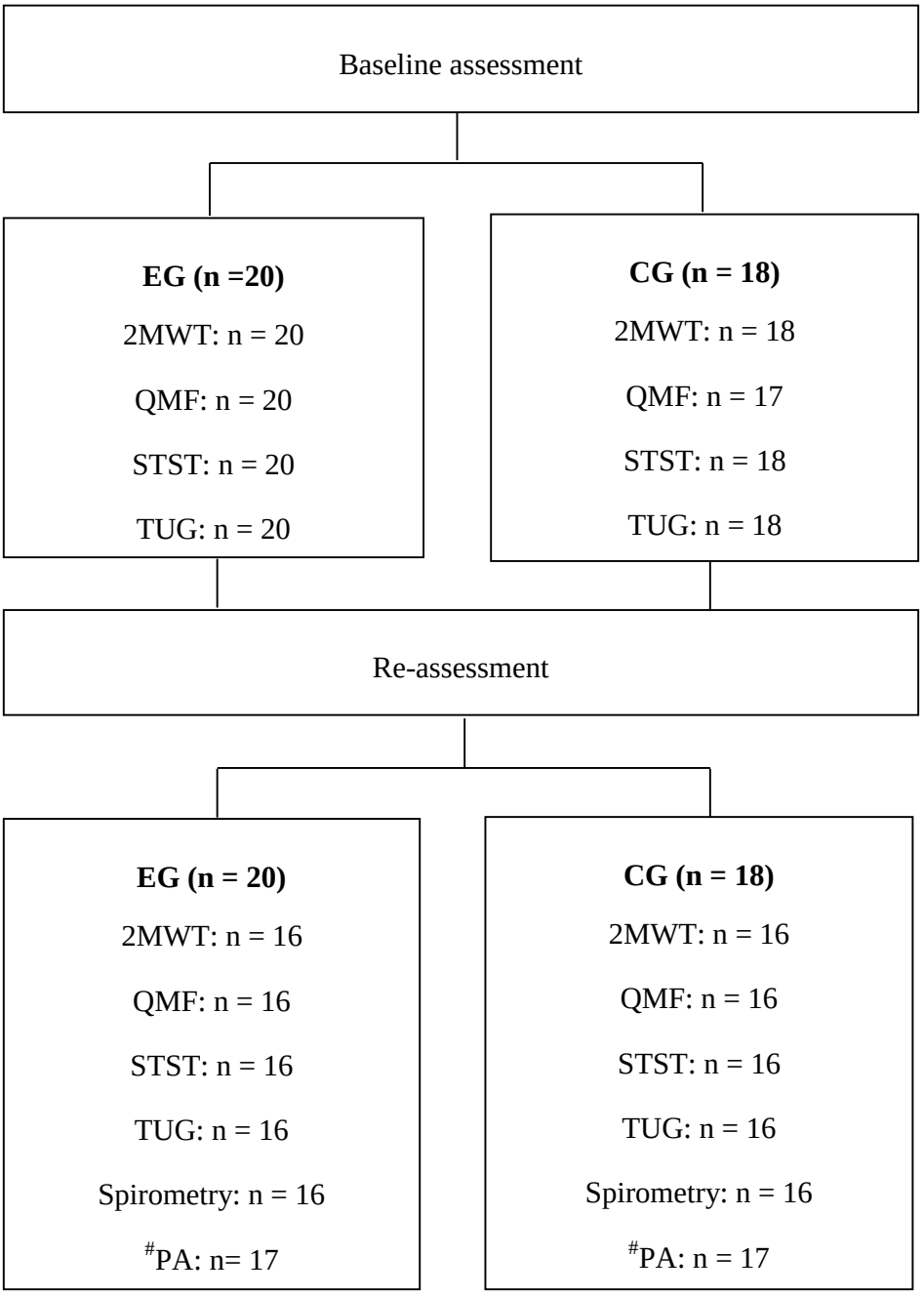

Figure 5.7: Number of participants who completed each of the baseline and post-intervention assessments.
#PA: n = 17 in each group including two participants (one in each group) with full SAM data but refusing all other re-assessment measurements.
Abbreviations: 2MWT, two-minute walk test; n, number; CG, control group; EG, exercise group; QMF, quadriceps muscle force; STST, Sit to Stand Test; TUG, Timed Up and Go; PA, physical activity.

Table 5.5: Baseline characteristics of the study participants (n = 32)

Variable		**Total (n = 32)** mean ± SD	**EG (n = 16)** mean ± SD	**CG (n = 16)** mean ± SD	p value
Age, yr		64.2 ± 7.8	62.4 ± 7.2	65.9 ± 8.2	0.21
Weight, kg		54.1 ± 14.9	50.8 ± 11.8	57.4 ± 17.3	0.22
Height, m		1.62 ± 0.07	1.62 ± 0.07	1.62 ± 0.07	0.78
Body mass index, kg/m^2		20.7 ± 6.3	19.3 ± 4.1	22.1 ± 7.8	0.20
FEV_1, L		0.83 ± 0.33	0.87 ± 0.33	0.79 ± 0.34	0.47
FEV_1 %pred		32 ± 13	34 ± 14	31 ± 12	0.61
FVC, L		1.88 ± 0.58	1.99 ± 0.49	1.77 ± 0.66	0.28
FVC %pred		57 ± 17	60 ± 16	55 ± 18	0.39
FEV_1/FVC		0.45 ± 0.13	0.45 ± 0.15	0.46 ± 0.13	0.88
Smoking pack-years		48 ± 22	49 ± 24	48 ± 21	0.93
CAT score		21 ± 5	21 ± 4	21 ± 6	0.94
			n (%)	n (%)	p value
Gender	Male		16 (100)	15 (94)	0.31
	Female		0	1 (6)	0.31
Site	HS		9 (56)	9 (56)	1.00
	IRM		7 (44)	7 (44)	1.00
GOLD	Grade I		1 (6)	1 (6)	1.00
	Grade II		3 (19)	3 (19)	1.00
	Grade III		9 (56)	8 (50)	0.72
	Grade IV		3 (19)	4 (25)	0.67
mMRC	Grade 0		0	0	-
	Grade 1		6 (38)	2 (13)	0.10
	Grade 2		3 (19)	5 (31)	0.41
	Grade 3		5 (31)	7 (43)	0.47
	Grade 4		2 (12)	2 (13)	1.00
Wheeled walker			0	0	-
Supplemental oxygen[#]			11 (69)	10 (63)	0.71
LTOT[≠]			2 (13)	4 (25)	0.37
Portable oxygen at home			0	0	-
Smoking status	Ex-smoker		10 (63)	15 (94)	0.03*
	Current-smoker		5 (31)	1 (6)	0.07
	Non- smoker		1 (6)	0	0.31

*$p < 0.05$, [≠]home oxygen, [#]oxygen therapy administered during the hospitalisation.
Abbreviations: CAT, COPD assessment test; CG, control group; EG, exercise group; FEV_1, forced expiratory volume in one second; FEV_1 %pred, percentage of predicted FEV_1 (282); FVC, forced vital capacity; FVC %pred, percentage of predicted FVC; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HS, Hospital Selayang; IRM, Institute of Respiratory Medicine; kg, kilograms; L, litres; LTOT, long-term oxygen therapy; m, metres; mMRC, modified Medical Research Council; SD, standard deviation; yr, years.

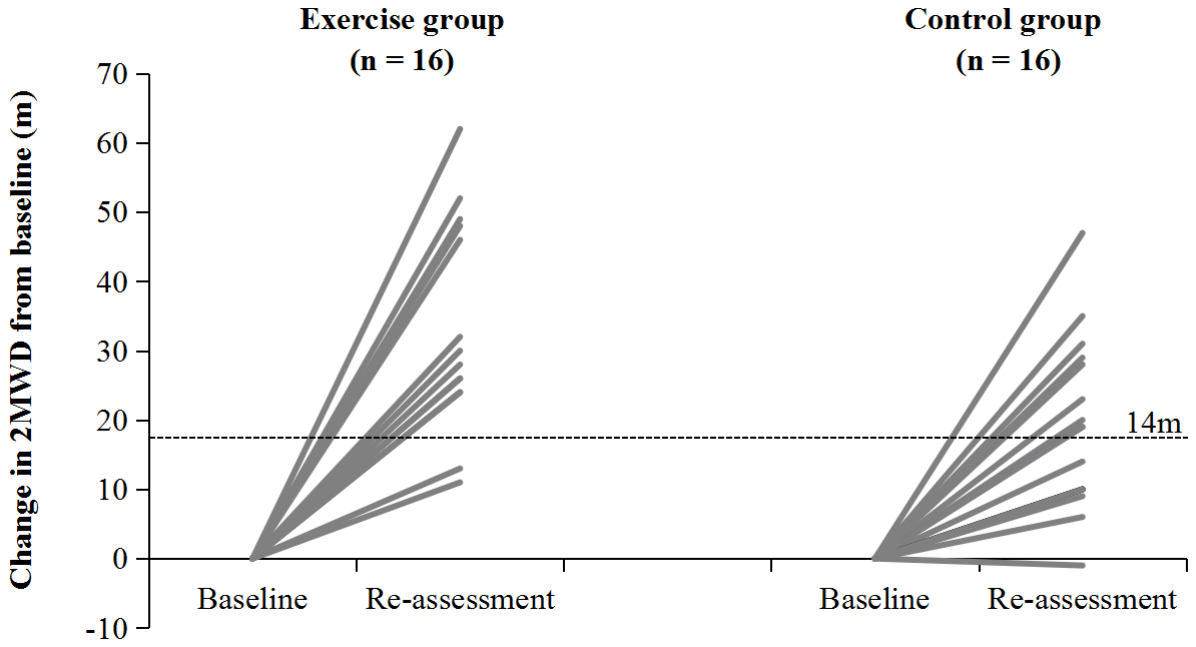

Figure 5.8: Change in the 2MWD from baseline. Dashed horizontal line represents the COR of 14m for the 2MWD. Abbreviations: 2MWD, two-minute walk distance; COR, coefficient of repeatability; m, metres.

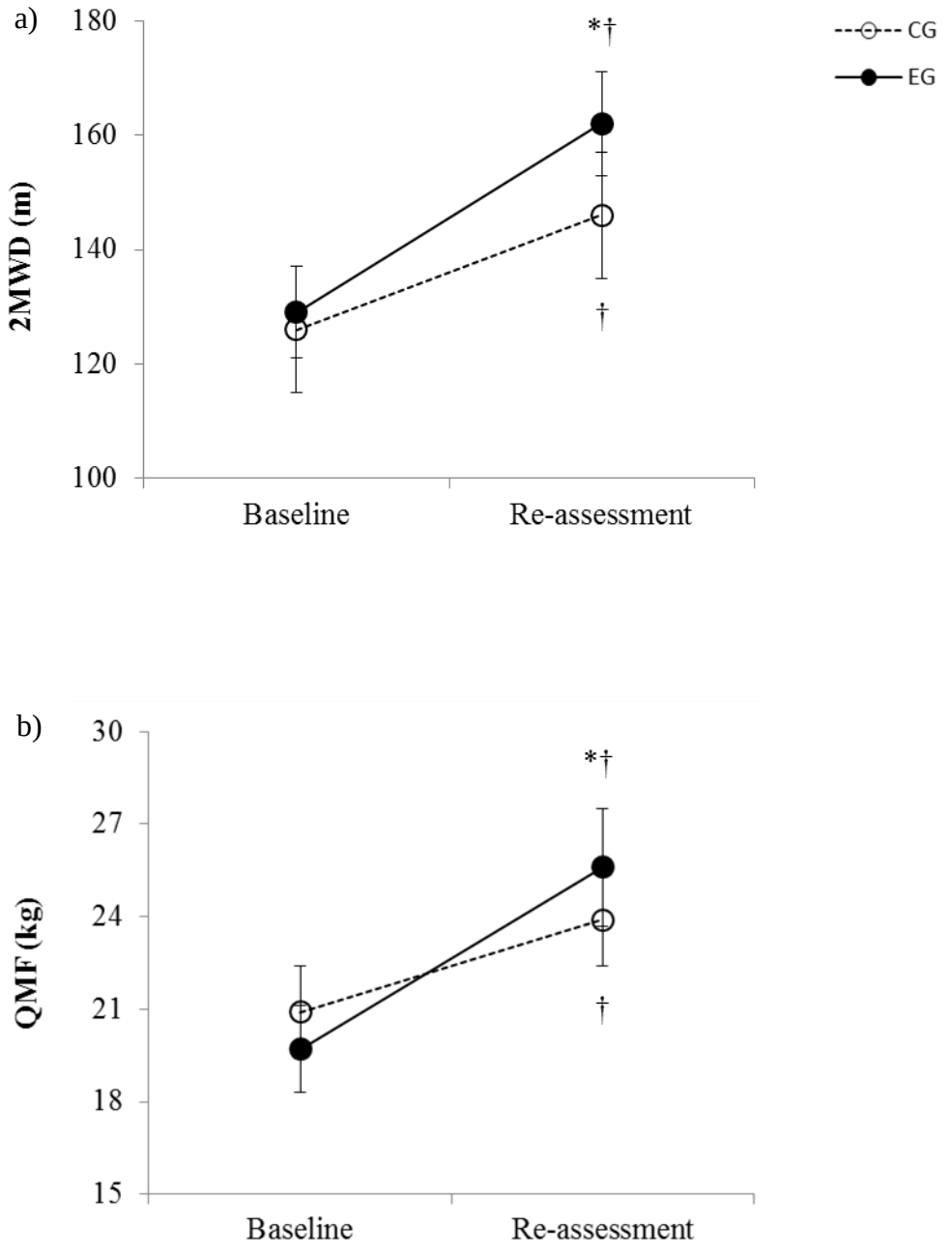

Figure 5.9: Baseline and re-assessment measures for a) 2MWD and b) QMF between the EG and CG.
Data are expressed as mean ± standard error. *$p < 0.05$ indicates a significant between-group difference, †$p < 0.05$ indicates a significant within-group difference.
Abbreviations: CG, control group; EG, exercise group; 2MWD, two-minute walk distance; kg, kilograms; m, metres; QMF, quadriceps muscle force.

Table 5.6: Within- and between-group differences for measures collected during the 2MWT

Variable		EG (n = 16) mean ± SD			CG (n = 16) mean ± SD			Between-group difference	
		Baseline	Re-assessment	p value	Baseline	Re-assessment	p value	MD;	95% CI
2MWD (%pred)		62 ± 16	77 ± 19	< 0.01	62 ± 20	72 ± 21	< 0.01	5;	0.4 to 10.3
Peak HR (bpm)		121 ± 17	120 ± 20	0.72	123 ± 12	124 ± 17	0.90	-2;	-11 to 8
Peak HR (%pred HRmax)		72 ± 9	71 ± 11	0.73	74 ± 7	74 ± 10	0.96	-1;	-6 to 5
Nadir SpO_2 (%)		91 ± 5	94 ± 4	0.03	88 ± 6	91 ± 5	0.14	-0.2;	-4.5 to 4.1
Peak dyspnoea		4.9 ± 2.3	2.6 ± 1.7	0.01	4.3 ± 2.3	3.5 ± 2.0	0.32	-1.5;	-3.4 to 0.4
End-test leg fatigue		0.5 ± 1.0	0.6 ± 1.4	0.65	0.4 ± 0.8	1.0 ± 1.4	0.10	-0.4;	-1.3 to 0.4
Rest duration (s)		8 ± 16	4 ± 11	0.12	10 ± 18	3 ± 8	0.04	4;	-16 to 25
		n (%)	n (%)		n (%)	n (%)		p value	
Number of rests	0	11 (69)	14 (88)	0.08	11 (69)	14 (88)	0.18	0.94	
	1	4 (25)	1 (6)	0.56	5 (31)	2 (12)	0.18	0.46	
	2	1 (6)	1 (6)	1.00	0	0	1.00	1.00	

Between-group differences were calculated by comparing the change in the EG between baseline and re-assessment measures with the change in the CG between baseline and re-assessment measures.

Abbreviations: 2MWD, two-minute walk distance; 2MWD (%pred), percentage of 2MWD estimated using the equation derived in Chapter 4; 95% CI, 95% confidence interval; bpm, beats per minute; CG, control group; EG, exercise group; HR, heart rate; %pred HRmax, peak HR as % of HRmax (210 – [0.65 × age]) (252); MD, mean difference; n, number; s, seconds; SD, standard deviation; SpO_2, percutaneous oxygen saturation.

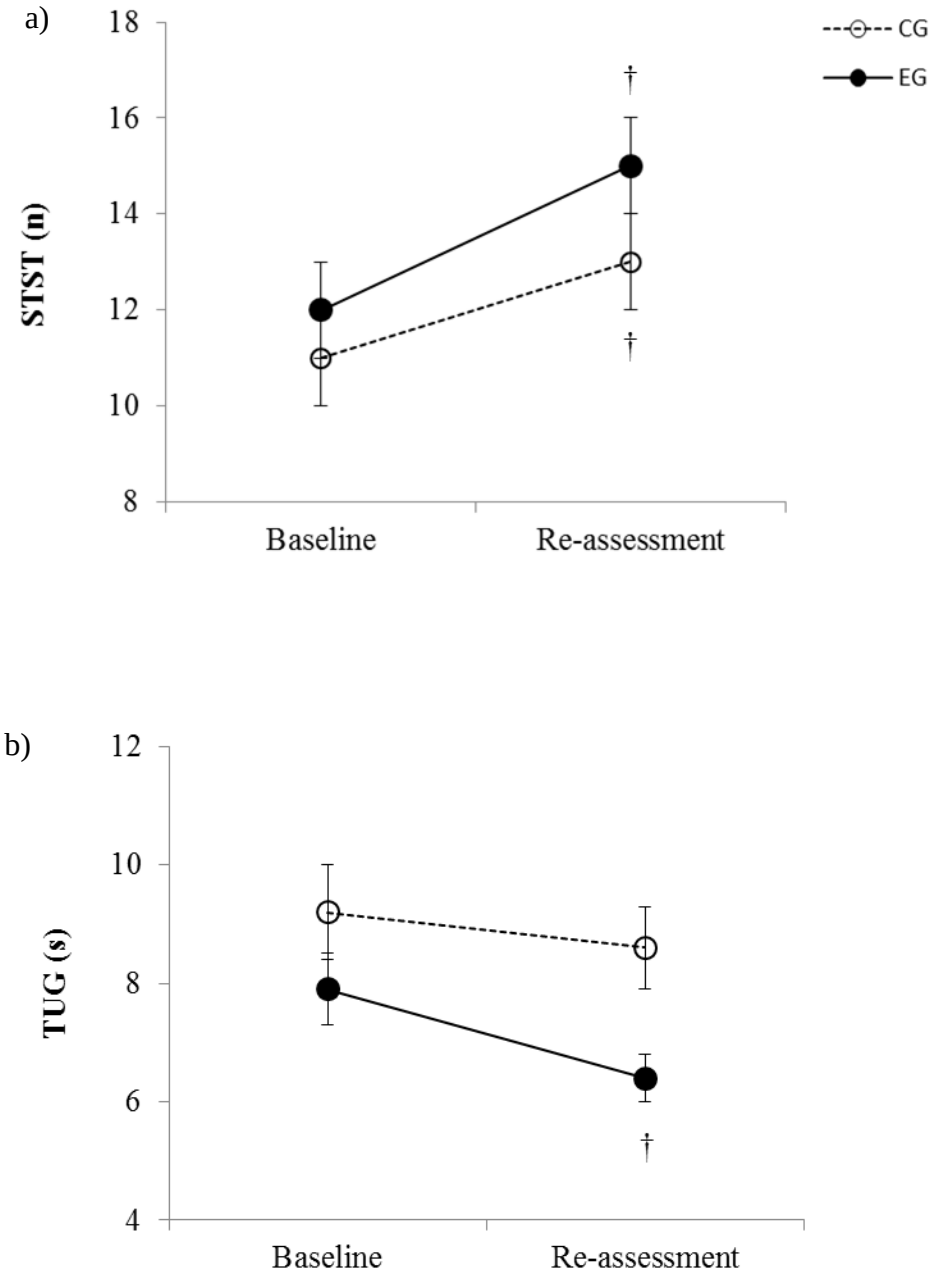

Figure 5.10: Baseline and re-assessment measures for a) STST and b) TUG between the EG and CG.
Data are expressed as mean ± standard error. *p < 0.05 indicates a significant between-group difference, †p < 0.05 indicates a significant within-group difference. Abbreviations: CG, control group; EG, exercise group; n, number; s, seconds; STST, Sit to Stand Test; TUG, Timed Up and Go.

5.5.3.6 PA

The total days of wearing the SAM were similar between the EG and the CG. Compared with the CG, the EG demonstrated less time spent being sedentary and more time spent walking at low intensity PA. Time spent walking at moderate/high intensity PA and the average number of steps taken per day were similar between the EG and the CG (Table 5.7).

Table 5.7: Between-group differences for measures of PA

Variable	Total (n = 34)		EG (n = 17)		CG (n = 17)		Between-group difference
	Median [IQR]		Median [IQR]		Median [IQR]		p value
Total wear time (day)	4	[3 to 5]	4	[3 to 5]	4	[2 to 5]	0.45
Steps/day	3497	[1666 to 6134]	4215	[2133 to 6693]	2198	[1242 to 4857]	0.07
Time being sedentary (min/day) [#]	1226	[1116 to 1311]	1154	[1082 to 1275]	1261	[1177 to 1342]	0.04
Time walking at low intensity (min/day) [#]	169	[97 to 256]	248	[143 to 307]	126	[84 to 221]	0.03
Time walking at moderate intensity (min/day) [#]	37	[17 to 69]	42	[30 to 77]	26	[11 to 53]	0.11

Data are presented as median [interquartile range] and therefore [#]the sum of the time spent in each domain does not equal exactly 24 hours or 1440 min.

Abbreviations: CG, control group; EG, exercise group; IQR, interquartile range; min, minutes; n, number; PA, physical activity.

5.6 Discussion

This is the first study in Malaysia to evaluate the effects of an exercise program initiated within two days of hospitalisation for AECOPD. This study found that individuals in the EG demonstrated greater gains in exercise capacity and QMF compared to the changes observed in the CG. No differences were detected between the EG and CG for the magnitude of change in functional measures (i.e. STST and TUG test). With regard to the measures of PA, individuals in the EG spent less time being sedentary and more time walking at low intensity PA when compared to the CG. Although there was no difference between the groups in average number of steps taken per day, this is most likely to reflect the large variability in this measure and a possible Type II error.

5.6.1 Effects of an exercise program in people hospitalised with an AECOPD

5.6.1.1 2MWD

This is the first RCT of an exercise program initiated early during hospitalisation for an AECOPD that investigated changes in exercise capacity using the 2MWT. This study showed that in people hospitalised for an AECOPD, an exercise program that included both walking and resistance exercises improved functional exercise capacity over and above any change seen in the CG. Improvements in functional exercise capacity may be important in this population as previous cross-sectional studies have shown that low exercise capacity is one of the strongest predictors for outcomes such as greater disability (316), increased healthcare utilisation (317) and worse survival in people with COPD (318, 319). Nevertheless, data from RCTs that initiated exercise training during or shortly following hospitalisation for an AECOPD are inconsistent regarding the influence of this intervention on survival. To date, four of the RCTs that initiated exercise training during or shortly following hospitalisation for an AECOPD have reported data on both exercise capacity and mortality (67, 162, 241, 244). With regard to exercise capacity, all four studies demonstrated significant between-group difference in favour of EG following exercise intervention. With regard to mortality, three (75%) of the four studies that reported survival data did not undertake any statistical analysis on this outcome (67, 162, 244). However, when data from these three studies were combined in a meta-analysis, there was a significant effect on mortality in favour of the EG (odds ratio [OR] 0.28; 95% CI

0.10 to 0.84) (239). In contrast to this finding, a large recent RCT demonstrated a difference in mortality between the EG and the CG, such that those in the CG had better 12 month survival (OR 1.74; 1.05 to 2.88) (241). The exact reason for this discrepancy in findings is unclear. Therefore, although cross-sectional studies have demonstrated that exercise capacity is related to survival, it is uncertain whether an exercise intervention, initiated during or shortly following hospitalisation from an AECOPD, which is effective at increasing exercise capacity, will influence survival.

Although the overall dose of the exercise (i.e. 4 ± 1 supervised and 4 ± 1 unsupervised sessions) in this study seems to be quite low to induce a training effect, the fact that the participants in the EG could walk further during the re-assessment 2MWT, with a similar peak HR, nadir SpO_2, peak dyspnoea and end-test leg fatigue as measured during the baseline assessment, suggests that the training program was adequate to induce a physiological adaptations (see Table 5.6). Further, when compared to the CG, it can be seen in Figure 5.8 that more participants in the EG had an increase in the 2MWD ≥ the COR calculated for the 2MWD when two tests were performed on different days (i.e. 14m [see subheading 3.4.2]). This means that, participation in the training program appears to have the potential to improve functional exercise capacity beyond the threshold for changes that could have occurred due to measurement error or the natural variability inherent in the test. This finding corroborates data reported in one previous study of exercise training in people hospitalised with an AECOPD. Specifically, Borges et al. (71) demonstrated a significant between-group difference in the 6MWD following an average of only 5.6 exercise sessions in people hospitalised with an AECOPD. In addition, there are data to suggest that providing six weeks of home-based exercise after discharge from hospital to patients who commenced the exercise training program during an in-patient admission may be effective at sustaining the improvement in exercise capacity (241).

Unlike the findings from the current study and the study by Borges et al. (71), four studies that investigated the effect of exercise training initiated within two to three days of hospitalisation for an AECOPD did not report significant between-group differences in exercise capacity on the completion of the exercise (70, 72, 240, 242). The reasons that these studies did not demonstrate significant between-group

difference in this outcome are likely to relate to factors such as small sample sizes, differences in the training approach and low levels of program participation. For example, Tang et al. (70) evaluated the differences in exercise capacity between three groups, each of which comprised a small sample of 10 or 11 participants. They found that the differences in exercise capacity between the three groups were not significant (i.e. $p > 0.05$) but reported small to moderate effect sizes ($d = 0.4$ and $d = 0.6$). Therefore, it appears that this study lack adequate statistical power to detect changes in this outcome (70).

In the study by Troosters et al. (72), the lack of between-group difference in exercise capacity may be attributable to the fact that the exercise program they used was very specific for an improvement in muscle strength but not exercise capacity. That is, there was no walking component in the training program and the standard care given to all participants did not include early mobilisation (72). It is also important to note that the re-assessment of exercise capacity in the study by Troosters et al. (72) was not undertaken at the end of hospitalisation period but was conducted four weeks following hospital discharge without any post-discharge intervention. Therefore, any changes that might have occurred during the training program could have been reduced during the four-week period.

The lack of between-group difference in exercise capacity in the study by Eaton et al. (240) appears to reflect, at least in part, sub-optimal adherence with the exercise program. That is, in this study only 40% of the patients assigned to the rehabilitation group attended 75% or more of the out-patient sessions. The level of adherence to the in-patient exercise session was not reported. In contrast, in the present study, the participants completed more than 90% of their prescribed exercises. Of note, the participants in the present study were provided with one supervised and one unsupervised exercise training session daily on top of their standard usual care throughout their hospitalisation period. They were also given a diary card to monitor, on a daily basis, their adherence to the unsupervised training sessions.

5.6.1.2 QMF

The present study demonstrated that an early exercise program that included walking and resistance exercises improved QMF over and above any change seen in the CG. This finding is particularly important given that QMF has been identified as a

significant predictor for important outcomes such as the number of hospital admissions due to exacerbation (115), out-patients visits (115) and survival (116) in people with COPD. To date, only one RCT has investigated the effects of exercise training in people hospitalised for an AECOPD on both QMF and mortality (241). This study reported no significant between-group difference in the QMF following the training program, but, controversially, demonstrated a difference in mortality between the EG and the CG, such that those in the CG had better 12 month survival (241). Therefore, although QMF has been identified as a significant predictor for survival, it is unclear whether or not an exercise intervention initiated during or shortly following hospitalisation from an AECOPD, which is effective at increasing QMF, will influence survival.

The improvement in QMF after a short period of training is most likely explained by the involvement of neural adaptation to the continuous increasing stimulus given to the skeletal muscle (320). In addition, Troosters et al. (72), being the only previous study with a consistent finding, found that a short period of exercise training also appeared to have the potential to counterbalance the negative consequences of an AECOPD on muscle function (72). Specifically, they performed skeletal muscle biopsies on 20 individuals hospitalised with an AECOPD who had participated in only 6 ± 1 sessions of quadriceps strengthening exercise and found that (i) the level of myostatin, a negative regulator of muscle growth was significantly lower in the EG compared to the CG; (ii) the anabolic/catabolic balance was in favour of anabolism in the EG; and (iii) there was a trend for a higher myogenin/MyoD ratio in the EG compared to the CG (72). Myogenin is a transcription factor involved in the coordination, development and repair of skeletal muscle, while myoD is a protein that in a high dose suppresses cell renewal and induces apoptosis. Therefore, the improvement in QMF after only a short period of training in the present RCT may also be related to the changes that have occurred at the muscle level in addition to neural adaptation.

Although the finding in the present study was consistent with the study by Troosters et al. (72), the magnitude of change demonstrated in the EG in the present study was relatively greater than that seen in the EG of Troosters et al. (72) (i.e. 30% vs. 10% from baseline measures). This could be explained in part by the fact that Troosters et

al. (72) prescribed a lower dose of exercise sessions (i.e. once daily knee extension exercises) and the standard usual care provided to both the EG and the CG was limited to airway clearance techniques and breathing exercises. This is in contrast to the present study where the participants in the EG performed two sessions of a combination of three functional resistance exercises and walking training each day throughout their hospitalisation period, and the standard usual care also included encouragement to mobilise in the ward. The encouragement to mobilise that was given as part of the usual care in the present study could also explain the within-group improvement in QMF seen in the CG that was not observed in the study by Troosters et al. (72).

Unlike the findings from the current study and the study by Troosters et al. (72), four other studies (70, 71, 240, 241) were unable to show that the implementation of an exercise program changed QMF in people hospitalised with an AECOPD. The reasons for this are likely to relate to factors such as the small sample size (70) and the use of less sensitive outcome measures to evaluate muscle force (i.e. manual muscle testing) (70). Further, the training approach used in these studies may have been insufficient to produce significant benefits on QMF (71, 240, 241). Borges et al. (71) provided a lower dose of exercise (i.e. 2 sets of 8 repetitions daily) when compared to the present study (i.e. 2 training sessions/day with quadriceps being the primary muscle worked in all 3 resistance exercises). In the study by Greening et al. (241), participants completed an average of only 3 ± 3 sessions of exercises during their hospital stay.

5.6.1.3 STST and TUG test

This study demonstrated that, on completion of the training program, no between-group differences were observed in the STST and the TUG test. This finding is likely to be related to the fact that, at baseline, participants did not present with substantial impairment in either of these measures. Specifically, the mean STST of the participants at baseline were 12 ± 3 in the EG and 11 ± 4 in the CG. Although data pertaining to the STST in people hospitalised with an AECOPD are not available, the number of repetitions in STST in both the EG and CG in the present study were higher than that reported by Benton et al. (308) in people with stable COPD (i.e. 10 ± 1). Similarly, the mean time taken to complete the TUG test (i.e. 7.9 ± 2.4s in the EG

and 9.2 ± 3.0s in the CG) was better than the commonly used cut-off value to identify individuals at high risk of falls (i.e. TUG ≥ 13.5s) (183), and were similar with that reported by Chang et al. (321) in people with stable COPD (i.e. 8.8 ± 2.0s). To date, there is only one study that has investigated the TUG test among people hospitalised with an AECOPD (322). In this study, Crisan et al. (322) reported that the mean times required to perform the TUG test were 15.9s in people with an AECOPD, 12.3s in people with stable COPD and 8.6s in healthy controls (322). However, the results from this study must be interpreted with caution because the authors did not describe the TUG test protocol used in their study and therefore it is unknown whether similar test protocol was used between this study and the present study. Earlier work has demonstrated that the use of different TUG test instruction (e.g. 'to walk as fast as you can' vs. 'to walk at your comfortable pace') produced a difference of more than 2s time in the TUG test (184). Although the difference could have been due to the change in the test protocol, their healthy controls, in the absence of airflow obstruction, required a similar time to perform the TUG test as required by the participants in the present study. This may suggests that the participants in the present study did not present with substantial impairment in this measure.

The lack of effect of the exercise program on both of these measures may have also been influenced by the fact that the training program in the present study was not specific for improvement in these two outcomes. Specifically, during the resistance training, the participants were not given any set time to complete the prescribed number of exercises and were allowed to rest. Thus, the training may have had an effect on the participant's endurance to perform the STST but not the speed to perform the task within a specified time. Likewise, with the TUG test, earlier work has shown that in order to see improvement in balance, a balance specific training program (e.g. single leg stance or tandem stance) is required (188).

5.6.1.4 PA

This is the first RCT of an exercise program in people hospitalised for an AECOPD that investigated changes in PA using measures such as time spent walking at different physical intensities and average number of steps taken per day. This study demonstrated that, on completion of the training program, there were significant between-group differences in the amount of time the participants spent being

sedentary and walking at low intensity PA. Although there was no between-group difference in the average number of steps taken per day over the hospitalisation period, the p value for this difference ($p = 0.07$) approaches the cut-off p value to be regarded as statistically significant ($p < 0.05$). It is also important to note that the average number of steps taken per day in the EG was twice as many as the CG and both groups demonstrated with large variability in this measure. Therefore, the lack of between-group difference in this measure is likely to reflect a Type II error in the analysis.

An intervention that increases participation in PA in people with COPD is likely to be important given that low levels of PA has been identified in previous cross-sectional studies as a significant predictor for important outcomes such as the number of hospital admissions due to exacerbation (201, 323) and survival in this population (323). To date, only one RCT has investigated the effects of exercise training in people hospitalised for an AECOPD on the levels of PA (71). In this study, Borges et al. (71) found that participation in an early exercise intervention did not change the amount of time their participants spent sitting, lying, standing and walking. Participants in both groups (i.e. EG and CG) were equally inactive ($p > 0.05$). Further, this study did not report data in relation to survival. Therefore, it is unclear whether or not an exercise intervention initiated during or shortly following hospitalisation from an AECOPD, which is effective at increasing PA, will influence survival.

Factors such as differences in the training approach between the study by Borges et al. (71) and the present study may in part explain the lack of effect observed in the study by Borges et al. (71) which is in contrast to the finding of the present study. For example, a walking training was not included in the study by Borges et al. (71) whereas the EG in the present study performed two sessions of walking per day throughout their hospitalisation. This difference in findings highlights the importance of including a walking training component to improve level of PA in this group of patients.

5.6.2 Adherence to the exercise program and safety

Participants in the EG completed more than 90% of their prescribed exercises irrespective of the level of supervision they received during the exercise sessions.

This means that an exercise intervention initiated within two days of hospital admission was well tolerated. The high adherence to the training in the present study may be explained, in part, by the fact that both walking and resistance exercises elicited only low levels of symptoms (i.e. peak dyspnoea, leg fatigue and muscle soreness) and modest oxygen desaturation (see Figure 5.5).

Although earlier work has shown that, in people with COPD, aerobic exercise elicited higher cardiopulmonary stress and dyspnoea than resistance exercise (324), the present study demonstrated low levels of symptoms (i.e. dyspnoea, leg fatigue and DOMS) and only a small magnitude of oxygen desaturation not only in resistance exercise but also in walking (aerobic) exercise. However, comparison of the cardiorespiratory and symptom responses during the exercise training between the present study and the study by Probst et al. (324) must be made with caution because the training approach for both walking and resistance exercises between these studies were different. For example, the walking training program in the study by Probst et al. (324) was performed on a treadmill at 75% of the average walking speed during the 6MWT. In contrast, in the present study, participants were allowed to select their own walking speed and were also allowed to rest during the training session if required. The high level of adherence to exercise training in the present study also corroborates the finding from three other studies that reported the levels of adherence to exercise training were between 85% and 95% in people hospitalised with an AECOPD (70, 71, 241).

With regard to the safety of the exercise program, no adverse event was identified during both walking and resistance exercises. During the assessments, only one participant exhibited marked oxygen desaturation (i.e. $SpO_2 < 80\%$) that resolved completely within half an hour after a short burst of supplemental oxygen. The incidence of adverse events in this study (i.e. 1 of 16 participants [3%]) was much lower than the incidence of adverse events previously reported by Tang et al. (70). Specifically, in their study, four (19%) of the 21 participants in the EG experienced a total of 11 adverse events of which 10 were regarded as not serious. The higher incidence of adverse events reported in the study by Tang et al. (70) compared to the present study could have been influenced by the differences in the criteria used to define adverse events between these two studies. For example, with regard to the

criterion used to define an adverse event of reaching the maximum HR during exercise, the formula used in the study by Tang et al. (70) (i.e. 85% of 220-age) produced a value for maximum HR that is lower than that produced using the formula used in the present study (85% of 210 – [0.65 × age]). Similarly, the criterion used to define an adverse event of oxygen desaturation, Tang et al. (70) regarded a decrease in SpO_2 > 10% as an adverse event while the criterion used in the present study was SpO_2 < 80%. These differences suggest that lower cardiorespiratory responses were regarded as adverse events in the study by Tang et al. (70) compared to the criteria used in the present study.

5.6.3 Strengths and limitations

The present study is the first RCT to investigate the effect of an early exercise program in people hospitalised with an AECOPD in a Malaysian context. The main strengths of the present study include: (i) robust methodological factors such as analyses being conducted based on the intention-to-treat principle, blinding of the outcome assessor and minimal loss to follow-up; (ii) the inclusion of a broad range of outcome measures including PA and functional performance measures such as the STST and the TUG test and (iii) the measurement of QMF using the force gauge; an outcome measure that has been shown to be more reliable than the HHD and the MMT.

The present study also had some limitations. First, the method used for the prescription of the resistance exercise in this study (i.e. based on the baseline 30s STST) was found to be too intensive for a sample with a baseline STST as high as 12 ± 3. From Figure 5.6, it can be seen that the targeted prescription in the resistance exercise was not achieved by 50% of the participants despite high adherence to the training sessions. Second, due to the sample size being calculated to detect between-group differences in the QMF and 2MWD, it is possible that the non-significant between-group differences observed for some outcomes, such as daily step count, may have been the result of a Type II error. However, the sample (n = 32) reached the sample size prospectively calculated for this study and the number of participants included in this study is similar to those previously studied (70-72).

5.7 Conclusions

This study has demonstrated that an exercise program that comprised walking and resistance exercise significantly reduced the deleterious effects of an AECOPD on exercise capacity and QMF. Participation in the exercise program did not significantly improve the STST and TUG test over and above any changes observed in the CG. With regard to the PA measures, although participation in the exercise program did not significantly increase the total number of steps taken per day, it did decrease the total time the participants spent being sedentary and increase the total time they spent participating in low intensity PA. Therefore, it can be concluded that participating in the exercise program did have a positive effect on PA level. The high level of adherence to the exercise training and the occurrence of only one adverse event that resolved relatively quickly supports the findings from previous studies that exercise training initiated within two days of hospitalisation for patients with an AECOPD is safe and feasible. The present study also extends the findings from Chapter 3 that the 2MWT is safe and responsive in people hospitalised for an AECOPD, and can be used to prescribe an effective, safe and well tolerated exercise program.

CHAPTER 6
SUMMARY AND CONCLUSIONS

This program of research provides novel and important information pertaining to both the assessment and rehabilitation of people with chronic obstructive pulmonary disease (COPD) who are characterised by profound dyspnoea on exertion. Regarding assessment, data are provided pertaining to the measurement properties (i.e. effect of test repetition, validity and responsiveness), interpretation and feasibility of the two-minute walk test (2MWT). Regarding rehabilitation, data are provided from a randomised controlled trial (RCT) that investigated the feasibility and effectiveness of an exercise program initiated within two days of hospital admission in people hospitalised with an acute exacerbation of COPD (AECOPD) on outcomes such as functional exercise capacity, quadriceps muscle force (QMF) and levels of physical activity (PA).

6.1 Effect of test repetition, validity and responsiveness of the 2MWT

Data presented in Chapter 3 demonstrated that the two-minute walk distance (2MWD) is repeatable in people with moderate to severe COPD. Specifically, the 2MWD had a very small learning effect (i.e. mean difference; 95% CI, 4%; 1% to 7%) which appears to be smaller than the learning effect for the six-minute walk distance (6MWD) as reported in a previous study among people with moderate to severe COPD (i.e. 11%; 9% to 12%) (6). This finding suggests that a practice walk for the 2MWT is less important than for the 6MWT, and may not be necessary in people with moderate to severe COPD. The choice not to do a practice walk in this population may result in only a small over-estimation of the magnitude of a treatment effect. A previous study has demonstrated that people who report higher levels of dyspnoea during the 6MWT are more likely to demonstrate an increase in the 6MWD with test repetition (6). Future studies are needed to explore the characteristics of those who are most likely to increase their 2MWD with test repetition.

Regarding validity, a strong linear relationship ($r = 0.66$, $p = 0.003$) was found between the 2MWD and the 6MWD. This finding supports the concurrent validity of

the 2MWT as a measure of exercise capacity in people with moderate to severe COPD. Although reporting the concurrent validity of the 2MWD with the gold standard measure of exercise capacity (i.e. peak rate of oxygen uptake [VO_2 peak] measured during a laboratory-based exercise test) would have strengthened the conclusions about the validity of the 2MWT, collection of such data was not feasible among the participants in the study described in Chapter 3 because of the high proportion of the participants who were on ambulatory oxygen. As earlier work has demonstrated a strong association between the 6MWD and VO_2 peak ($r = 0.73$; $p < 0.001$) in people with moderate to severe COPD, the 6MWD was used as a surrogate for VO_2 peak in this study. The study described in Chapter 3 also found that people with moderate to severe COPD walked 31 ± 22m (27%) further during the 2MWT than one third of the distance walked during the 6MWT ($p < 0.001$). This information is particularly important for clinicians who evaluate the effect of an intervention (e.g. exercise program) using the 6MWT at baseline and are tempted to use the 2MWT on completion of the program in patients who develop an AECOPD or because the clinicians are under time pressure. Even though the 6MWT is three times as long as the 2MWT, comparing one third of the distance walked during the 6MWT performed at baseline with the 2MWD measured post-intervention will lead to an over-estimation of the effects of the intervention on this outcome.

With regard to the responsiveness of the 2MWD, data presented in Chapter 5 demonstrated that the 2MWD in both an exercise group (EG) (123 ± 34m vs. 162 ± 38m; $p < 0.001$) and control group (CG) (126 ± 44m vs. 146 ± 44m; $p < 0.001$) increased during the period of hospitalisation. This is consistent with the improvement seen in clinical status during the course of a hospital admission. More importantly, the 2MWD was shown to be responsive to exercise training in people hospitalised for an AECOPD. This is shown by the greater magnitude of increase in this outcome in favour of the EG (mean difference [95% confidence interval]: 13m [3 to 23m]). Further study is required to establish the minimal clinically important difference for the 2MWD.

6.2 Interpretation of the 2MWD

Data presented in Chapters 3 and 4 provides important and novel information to facilitate interpretation of the 2MWD. The study described in Chapter 3 calculated the coefficient of repeatability (COR) for the 2MWDs measured over two days in

people with moderate to severe COPD, and the study described in Chapter 4 developed regression equations to estimate the 2MWD in Malaysian adults without significant disease.

The COR for the 2MWD measured over two days in people with moderate to severe COPD was 14m. This suggests that, for an individual patient, a change of ≥ 14m in response to an intervention is needed in order for the clinician to be 95% confident that the difference in the 2MWDs is not due to measurement error or the natural variability inherent in the test. The COR for the 2MWD also appears to be smaller than the COR for the 6MWD as reported in previous studies among people with moderate to severe COPD (51m (234) and 63m (269)). This means that, in people with moderate to severe COPD, clinicians can be confident of a true change in the 2MWD with much smaller changes in the test result compared to the 6MWD.

The regression equations presented in Chapter 4 to estimate the 2MWD were

2MWD = 196 - (1.1 × age) + (1.0 × ΔHR [i.e. peak HR measured during the 2MWT - resting HR]) + (31.2 × gender) where females = 0 and males = 1

2MWD = 279 - (1.7 × age) + (35.9 × gender) where females = 0 and males = 1.

These equations will allow researchers and clinicians to estimate the 2MWD in the general Malaysian population and thereby express the 2MWD in a clinical population as a percentage of the estimated value (i.e. % predicted). Expressing the 2MWD as a % predicted value provides patients and clinicians with an indication of the impact their disease has had on exercise capacity. Although there have been two previously published regression equations to estimate the 2MWD (17, 18), data presented in Chapter 4 demonstrated little agreement in the 2MWD measured in a Malaysian sample and the 2MWDs estimated using either of the two published equations. Therefore, these two previous equations are unlikely to be suitable for use in the Malaysian population. Given that the equations presented in Chapter 4 are the first to estimate the 2MWD in adults living in the Asian region, they are likely to be the most appropriate equations to facilitate interpretation of the 2MWD not only in Malaysia but also in other Asian countries with similar cultural backgrounds and anthropometric characteristics to Malaysia, such as Indonesia, Singapore and Southern Thailand. Future studies are needed to validate these equations in a larger

sample of Malaysian adults and explore the differences in the 2MWDs (if present) between the three major ethnic groups in Malaysia (i.e. Malay, Chinese and Indian).

6.3 Tolerance of the 2MWT

The 2MWT appears to be better tolerated than the 6MWT among people with moderate to severe COPD. That is, data presented in Chapter 3 demonstrated that in participants with moderate to severe COPD, compared to the 6MWT, the 2MWT elicited a lower peak heart rate (112 ± 15bpm vs. 107 ± 13bpm; $p < 0.001$), less oxygen desaturation (82 ± 7% vs. 86 ± 6%; $p < 0.001$) and lower levels of dyspnoea (Borg score 5 ± 2 vs. 4 ± 2; $p < 0.01$). The proportion of participants who rested and the duration of rests were also lower during the 2MWT. Specifically, two (11%) participants rested once throughout the 2MWT while 13 (72%) participants required between one to three rest(s) during the 6MWT. The duration of rests for the 2MWT ranged between 7s and 13s while the duration of rest for the 6MWT ranged between 3s and 167s. When the 2MWT was used to measure exercise capacity in people hospitalised with an AECOPD, data in Chapter 5 demonstrated that 13 (34%) of the participants required one or two rest(s) when the test was performed within the first two days of hospital admission. The proportion of those requiring a rest reduced to four (11%) when the test was performed on the day of hospital discharge. Therefore, it appears that people hospitalised for an AECOPD are likely to tolerate the 2MWT. The low proportion of those requiring a rest during the 2MWT as well as the low frequency of rest required when the test was performed as early as within two days of hospitalisation for and AECOPD may also suggest that the test make more efficient use of clinician's time.

6.4 Rehabilitation in people hospitalised with an AECOPD

The study described in Chapter 5 was the first RCT to evaluate the benefits of an exercise program that comprised both walking and resistance exercise in people hospitalised with an AECOPD. The study design minimised the risk of bias by randomising the participants to the EG or CG, concealing the randomisation sequence, using a person who was blinded to group allocation to collect outcome measures, ensuring minimal loss to follow-up and analysing the data according to the intention-to-treat principle.

Data presented in Chapter 5 demonstrated that in people hospitalised for an AECOPD, an individualised, progressive exercise program that comprised walking and resistance exercise was effective at improving the 2MWD and QMF. Further, those who completed the exercise program spent less time being sedentary and more time walking at low intensity PA compared to the CG. Of note, in this study, training was initiated within two days of being hospitalised, participants completed only a mean of 4 ± 1 sessions of supervised exercise and 4 ± 1 sessions of unsupervised exercise sessions and all training was completed using minimal equipment. This program was therefore inexpensive and can be easily replicated in countries where the length of hospitalisation for an AECOPD is short and healthcare funding is limited (e.g. Malaysia).

Data presented in Chapter 5 were also the first to report no difference in the adherence to supervised and unsupervised exercise sessions among people hospitalised for an AECOPD. Participants in the EG completed 96 ± 9% of their scheduled supervised training and 92 ± 13% of their scheduled unsupervised training sessions ($p = 0.22$). The high adherence to the training sessions is likely to reflect the fact that the training program elicited low levels of symptoms (i.e. peak dyspnoea, leg fatigue and muscle soreness), no adverse events and was therefore well tolerated. The high adherence to the unsupervised sessions suggests that participants are likely to complete the training in the absence of direct supervision by a healthcare professional. This information is particularly relevant to clinicians working in a busy healthcare setting as it suggests that they do not need to provide two supervised sessions per day in order for participants to benefit from the exercise program described in Chapter 5. Future studies should explore the long-term effects of an exercise program initiated within two or three days of hospitalisation for an AECOPD on important outcomes such as exercise capacity, QMF, PA and readmission rate.

6.5 Conclusions

In people with COPD who are characterised by profound dyspnoea on exertion, such as those with severe COPD or those who are hospitalised for an AECOPD, the 2MWT appears to be an appropriate alternative to the 6MWT for measuring functional exercise capacity. An exercise program initiated within two days of hospitalisation for an AECOPD is safe and feasible. A combination of walking and

resistance exercise is effective at minimising the deleterious effect of an AECOPD on exercise capacity and QMF and appears to have a positive effect on PA. The three studies presented in this doctoral thesis have contributed important and novel information that both researchers and clinicians can use when developing a protocol to undertake a 2MWT in this population and to optimise the rehabilitation of people hospitalised for an AECOPD.

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APPENDICES

Appendix 1: Papers co-authored during the period of PhD study

i. Cavalheri V, **Tahirah F**, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken within 12 months following lung resection for patients with non-small cell lung cancer (Protocol). *Cochrane Database of Systematic Reviews.* 2012, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.

ii. Cavalheri V, **Tahirah F**, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken by people within 12 amonths following lung resection for non-small cell lung cancer. *Cochrane Database of Systematic Reviews.* 2013, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.pub2.

iii. Justine M, **Tahirah F**, Mohan V. Health-related quality of life, lung function and dyspnea rating in COPD patients. *Monaldi Archives for Chest Disease*. 2013;79(3-4):116-20.

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v. Cavalheri V, **Tahirah F**, Nonoyama M, Jenkins S, Hill K.. Exercise training for people following lung resection for non-small cell lung cancer – a Cochrane systematic review. *Cancer Treatment Reviews.* 2014; 40(4): 585-94.

Appendix 2: Contraindications to performing the exercise test in stable COPD

GUIDELINES FOR EXERCISE TESTING IN STABLE COPD

These guidelines apply when testing patients with stable lung disease in a hospital out-patient setting; modifications to the guidelines and protocol are required when testing patients in community settings, during an acute exacerbation and for patients with pulmonary arterial hypertension (PAH). Contraindications, criteria for terminating the test and safety issues have been developed based on published guidelines. (ACSM 2006; ATS 2002; ATS/ACCP 2003).

Contraindications for Exercise Testing
: When information is available

Absolute Contraindications	Relative Contraindications*
A recent significant change in the resting ECG suggesting significant ischemia, recent AMI (within 3-5 days) or other acute cardiac event	Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
Unstable angina	Moderate stenotic valvular disease
Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise	Left main coronary artery stenosis
Symptomatic severe aortic stenosis	Tachydysrhythmia or bradydysrhythmia
Uncontrolled symptomatic heart failure	High-degree atrioventricular block
Syncope	Ventricular aneurysm
Acute pulmonary embolus or pulmonary infarction	Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Acute myocarditis, pericarditis or endocarditis	Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands
Suspected or known dissecting aneurysm	Lower limb thrombosis (acute, untreated)
Acute infections	Electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia)
Severe arterial hypertension at rest (SBP>200mmHg, DBP>120mmHg)	Uncontrolled metabolic disease (e.g. diabetes)
Severe pulmonary hypertension (if data available)	Chronic infectious disease (e.g. hepatitis, AIDS)

* may be superseded if benefits outweigh risks

Appendix 2: Continued

Additional Contraindications
Unstable angina or AMI (Non STEMI) during the previous month. Stable exertional angina is not an absolute contraindication but the test should be performed after patient has taken anti angina medication and with rescue nitrate available
Resting $SpO_2 \leq 90\%$ (check accuracy of reading and consider placing sensor on another finger/try ear sensor if available, warm sensor site, palpate pulse to ensure it is consistent with rate measured on oximeter)
Pre-exercise heart rate > 125 (and irregular)
Disability or impairment leading to safety concerns (e.g. orthostatic hypotension, balance problems, unsteady gait, require one assistant to walk)

Criteria to terminate the test
Participant requests to terminate the test e.g. intolerable dyspnoea not relieved by rest; onset of palpitations; severe leg pain/cramps; feeling of profound weakness/fatigue; severe wheezing; pain from comorbid condition e.g. lower back pain
Any untoward medical occurrence, sign or symptom occurring during the test i. Onset of chest pain suggestive of ischemia ii. Abnormal heart rate response confirmed by palpitation (e.g. failure of HR to increase unless fixed rate pacemaker in situ; fall in HR); persistent tachycardia (HR > 210 – [0.65 × age]) iii. Signs and symptoms of poor perfusion (sudden pallor, dizziness or fainting) iv. Development of an abnormal gait/loss of coordination v. Signs suggestive of mental confusion

Criteria to impose rest during the test
Profound oxygen desaturation (SpO_2 < 80% and falling). In this instance, immediately instruct the patient to rest. When SpO_2 increases to >80% instruct the patient to recommence the test. Note that pulse oximeters are very accurate above 90% but much less accurate below 80%. Check signal strength/perfusion index/waveform on oximeter.

Safety considerations
Obtain history of patient's comorbid conditions and medications
Current CPR certification is a requirement of person conducting the test
Perform test where rapid emergency response is available
If patient is on oxygen therapy, test patient using prescribed flow rate and with usual method of O_2 transportation if performing a walking test (check if prescription states to increase flow rate by 1L/min for exercise)

Appendix 3: Flyers (English and Malay versions)

Curtin University

UNIVERSITI TEKNOLOGI MARA

✓Are you a non-smoker?

✓Are you between 40 and 75 years old?

✓Are you free of serious health conditions?

✓Are you able to walk for 2 minutes without any limitation?

If you answered **"yes"** to all these questions, are you interested in participating in a research study looking at the distance a healthy person can walk in 2 minutes?

Assessment will be made during a single visit and will include measurement of blood pressure and lung function . Your heart rate will be monitored during the walking test.

If you are interested in participating, or would like more information, please contact **Fatim Tahirah** by Phone: +6012-4862349 or Email: f.mirzamoh@postgrad.curtin.edu.au

Study approved by UiTM Campus Puncak Alam (600-FSK [PT. 5/2]) and Curtin University, Perth, Australia (HR127/2012).

Curtin University

UNIVERSITI TEKNOLOGI MARA

✓ Anda tidak merokok?

✓ Anda berusia diantara 40 hingga 75 tahun?

✓ *Anda sihat dari sebarang penyakit serius*?

✓Anda mampu untuk berjalan selama 2 minit tanpa sebarang halangan?

Jika jawapan anda adalah **"ya"** bagi kesemua soalan diatas, adakah anda berminat untuk terlibat di dalam kajian melihat sejauh mana mereka yang sihat boleh berjalan selama dua minit?

Ukuran akan diambil dalam satu sesi dan akan melibatkan ujian tekanan darah, dan ujian fungsi paru-paru. Semasa ujian berjalan, kadar denyutan jantung anda juga akan dipantau secara berterusan.

Jika anda berminat, atau ingin mengetahui dengan lebih lanjut, sila hubungi **Fatim Tahirah** melalui :-
Talian: +6012-4862349 atau Email: f.mirzamoh@postgrad.curtin.edu.au

Kelulusan kajian diperoleh dari UiTM Kampus Puncak Alam (600-FSK [PT. 5/2]) dan Curtin University, Perth, Australia (HR127/2012).

Appendix 4: Standardised health screening form

Participant No		wt/ht		BMI<40	
Age/gender/race		Medications/ supplements			

	Y	N
Inclusion criteria:		
Aged between 40 and 75 years		
Forced expiratory volume in one second (FEV_1) ≥ 80% of the predicted normal value and FEV_1 to forced vital capacity ratio ≥ 70%		
Exclusion criteria		
Smoking history greater than 10 pack-years		
History of significant condition that may adversely affect performance:		
Musculoskeletal (arthritis, recent joint replacement, amputee, do they walk with a limp, etc.)		
Neurological (stroke, Parkinson's disease, multiple sclerosis, ever seen a Neurologist…if so, why?)		
Cardiovascular (angina on exertion, previous myocardial infarction, history of arrhythmias, ever seen a Cardiologist…if so, why?)		
Respiratory (asthma, COPD, ever seen a Respirologist…if so, why?)		
Current medical status		
Resting blood pressure > 165/95mmHg		
Resting heart rate > 100 beats per minute		
Use of beta-blockers		
An upper respiratory tract infection within the previous 4 week period		
Use of gait aid		
Inability to understand either English or Malay		

Appendix 5a: Protocol for the 2MWT (English version)

PROTOCOL FOR 2MWT – English version

A standard protocol for the 2MWT was developed based on published guidelines.

Instructions
Introduce the Borg dyspnoea scale with its standard instructions and record pre-exercise dyspnoea intensity and heart rate. Be consistent in using either right or left arm when measuring BP. Describe the walking course to participant (e.g. explain to turn in front of cones)

Give the participant the following instructions:
"You are now going to do a 2 minute walking test. The object of this test is to walk as fast as you can for 2 minutes so that you cover as much ground as possible. You may slow down if necessary. If you stop I want you to continue to walk again as soon as possible. You will be regularly informed of the elapsed time and you will be encouraged to do your best. Your goal is to walk as far as possible in 2 minutes. Please do not talk during the test unless you have a problem or I ask you a question. You must stop walking and let me know if you have any chest pain or dizziness. Do you have any questions?"

Begin the test with **"Start Walking Now"** and use the following standard encouragements

30 Seconds	1 ½ minute remaining (participant name) Do your best
60 Seconds	Halfway (participant name) - 1 minute remaining You're doing well, Keep it up!
90 Seconds	30 seconds remaining (participant name) Do your best
120 Seconds	Stop there

If the participant stops, record dyspnoea and give the following encouragement
"Begin walking as soon as you feel able"
(Repeat this encouragement every 15 seconds if necessary)

Record:
Number of completed lengths and distance of any incomplete lengths walked; number and duration of rest periods (if present). At the end of the test, record HR, dyspnoea, and leg fatigue.

Appendix 5b: Protocol for the 2MWT (Malay version)

PROTOCOL FOR 2MWT – Malay version

Protokol Ujian Berjalan selama 2 minit ini telah diadaptasi dari protokol ujian berjalan selama 6 minit yang telah diterbitkan.

Arahan: Memperkenalkan skala Borg dengan menggunakan arahan seperti di dalam garis panduan. Rekod kadar kesesakan nafas dan denyutan jantung sebelum ujian dimulakan. Tekanan darah harus diukur secara konsisten dengan hanya menggunakan sama ada tangan kanan atau tangan kiri sahaja. Terangkan jarak koridor (seperti peserta diminta pusing sebelum kon).

Beri peserta arahan seperti berikut:
"Anda akan menjalankan ujian berjalan selama dua minit . Di dalam ujian ini, anda diminta untuk berjalan secepat yang anda mampu untuk menghabiskan jarak yang lebih jauh. Anda dibenarkan mengurangkan kelajuan jika perlu. Sekiranya and perlu berhenti, anda diminta untuk sambung semula berjalan secepat yang anda mampu. Anda akan sentiasa dimaklumkan tentang masa yang telah berlalu dan diberi galakan untuk melakukan yang terbaik. Anda tidak dibenarkan bercakap semasa sesi ujian kecuali jika anda mempunyai sebarang masalah atau sekiranya saya bertanyakan sebarang soalan. Anda dimestikan untuk berhenti berjalan dan memaklumkan kepada saya sekiranya anda mengalami sakit di bahagian dada atau berasa pening. Adakah anda mempunyai sebarang soalan?"

Mulakan ujian dengan arahan "**Anda boleh mula sekarang**" dan galakan:

30 Saat	Anda tinggal satu setengah minit (nama peserta). Cuba yang terbaik!
60 Saat	Separuh masa telah tamat (nama peserta) Anda tinggal 1 minit. Anda melakukannya dengan baik! Gandakan usaha!
90 Saat	Anda tinggal 30 saat (nama peserta) Cuba yang terbaik!
120 Saat	Berhenti

Jika peserta berhenti, rekod kadar kesesakan nafas (jika ada) dengan menggunakan skala Borg dan beri galakan seperti berikut:

"Mulakan berjalan apabila anda rasa mampu"
(Ulangi galakan ini pada setiap 15 saat)

Rekod: Bilangan ulangan 'lap' yang lengkap dan jarak ulangan yang tidak lengkap, bilangan dan tempoh setiap waktu rehat (jika ada). Semasa ujian berakhir, rekod kadar deyutan jantung, kesesakan nafas dan kepenatan pada otot kaki (jika ada).

Appendix 6: Distribution of the sample according to gender, age bracket and ethnicity

Gender	Female			
Age group / Ethnicity	**Malay**	**Chinese**	**Indian**	**TOTAL**
40-49 years	7 (54)	4 (31)	2 (15)	13
50-59 years	7 (54)	3 (23)	3 (23)	13
60-69 years	7 (58)	3 (25)	2 (17)	12
70-75 years	3 (50)	2 (33)	1 (17)	6
TOTAL				44

Data are presented as number (percentage) of each age bracket.

Gender	Male			
Age group / Ethnicity	**Malay**	**Chinese**	**Indian**	**TOTAL**
40-49 years	7 (58)	3 (25)	2 (17)	12
50-59 years	7 (54)	3 (23)	3 (23)	13
60-69 years	7 (58)	3 (25)	2 (17)	12
70-75 years	3 (50)	2 (33)	1 (17)	6
TOTAL				43

Data are presented as number (percentage) of each age group.

Appendix 7: Contraindications to performing the exercise test in AECOPD

GUIDELINES FOR EXERCISE TESTING IN PEOPLE HOSPITALISED FOR AN AECOPD

These guidelines apply when testing patients with an acute exacerbation of COPD in a hospital in-patient setting. Contraindications, criteria for terminating the test and safety issues have been developed based on published guidelines. (ACSM 2006; ATS 2002; ATS/ACCP 2003).

Contraindications for Exercise Testing
: When information is available

Absolute Contraindications	Relative Contraindications*
A recent significant change in the resting ECG suggesting significant ischemia, recent MI (within 2 days) or other acute cardiac event	Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
Unstable angina	Moderate stenotic valvular disease
Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise	Left main coronary artery stenosis
Symptomatic severe aortic stenosis	Tachydysrhythmia or bradydysrhythmia
Uncontrolled symptomatic heart failure	High-degree atrioventricular block
Syncope	Ventricular aneurysm
Acute pulmonary embolus or pulmonary infarction	Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Severe arterial hypertension at rest (SBP>200mmHg, DBP>120mmHg)	Electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia)
Severe pulmonary hypertension (if data available)	Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands
Suspected or known dissecting aneurysm	Uncontrolled metabolic disease (e.g. diabetes)
Severe pulmonary hypertension	Chronic infectious disease (e.g. hepatitis, AIDS)
Acute myocarditis, pericarditis or endocarditis	Lower limb thrombosis (acute, untreated)

* may be superseded if benefits outweigh risks

Appendix 7: Continued

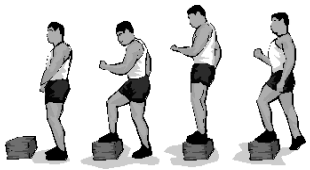
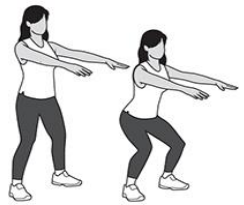
Additional Contraindications
Unstable angina or AMI (Non STEMI) during the previous month. Stable exertional angina is not an absolute contraindication but the test should be performed after patient has taken anti angina medication and with rescue nitrate available
Resting $SpO_2 \leq 88\%$ (check accuracy of reading and consider placing sensor on another finger/try ear sensor if available, warm sensor site, palpate pulse to ensure it is consistent with rate measured on oximeter)
Pre-exercise heart rate > 125 (and irregular)
Disability or impairment leading to safety concerns (e.g. orthostatic hypotension, balance problems, unsteady gait, require one assistant to walk)
Requiring NIV during waking hours

Criteria to terminate the test
Participant requests to terminate the test e.g. intolerable dyspnoea not relieved by rest; onset of palpitations; severe leg pain/cramps; feeling of profound weakness/fatigue; severe wheezing; pain from comorbid condition e.g. lower back pain
Any untoward medical occurrence, sign or symptom occurring during the test i. Onset of chest pain suggestive of ischemia ii. Abnormal heart rate response confirmed by palpitation (e.g. failure of HR to increase unless fixed rate pacemaker in situ; fall in HR); persistent tachycardia (HR > 210 − [0.65 × age]) iii. Signs and symptoms of poor perfusion (sudden pallor, dizziness or fainting) iv. Development of an abnormal gait/loss of coordination v. Signs suggestive of mental confusion

Criteria to impose rest during the test
Profound oxygen desaturation ($SpO_2 < 80\%$ and falling). In this instance, immediately instruct the patient to rest. When SpO_2 increases to >80% instruct the patient to recommence the test. Note that pulse oximeters are very accurate above 90% but much less accurate below 80%. Check signal strength/perfusion index/waveform on oximeter.

Safety considerations:
Obtain history of patient's comorbid conditions and medications
Current CPR certification is a requirement of person conducting the test
Perform test where rapid emergency response is available
If patient is on oxygen therapy, test patient using prescribed flow rate and with usual method of O_2 transportation if performing a walking test (check if prescription states to increase flow rate by 1L/min for exercise)

Appendix 8: Diary card to monitor the adherence to the unsupervised training sessions

ID					**Date/ Day**									
Walking		**Breathlessness**	0	0.5	1	2	3	4	5	6	7	8	9	10
		Target			Achieve									
Step ups		**Breathlessness**	0	0.5	1	2	3	4	5	6	7	8	9	10
		Target			Achieve									
Half squats		**Breathlessness**	0	0.5	1	2	3	4	5	6	7	8	9	10
		Target			Achieve									
Sit to stands		**Breathlessness**	0	0.5	1	2	3	4	5	6	7	8	9	10
		Target			Achieve									