

School of Physiotherapy

**Evaluation and Optimisation of Physical Activity in Individuals with Chronic
Obstructive Pulmonary Disease (COPD)**

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This thesis is presented for the Degree of

Doctor of Philosophy

of

Curtin University

March 2014

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.

Signature:

Date:

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy at Curtin University, Western Australia. Studies were undertaken between August 2009 and June 2012, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Physiotherapy Department at Sir Charles Gairdner Hospital and the Lung Institute of Western Australia.

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

ABSTRACT

Background and research questions

The studies in this thesis evaluated the physical activity (PA) in individuals with chronic obstructive pulmonary disease (COPD), identified strategies to optimise PA, determined the effects of a supervised walking training program on performance during the endurance shuttle walk test (ESWT) and determined the minimal detectable difference for the ESWT.

The specific aims of the studies in this thesis, in individuals with COPD, were to:

1. Determine the impact of exercise training on PA through a systematic review and meta-analysis.
2. Evaluate the measurement properties of two novel motion sensors: the StepWatch™ Activity Monitor (SAM) and the ActivPAL™.
3. Evaluate the effects of using a wheeled walker (WW), an assisted walking device, for use in the community on daily PA, health-related quality of life (HRQoL) and fear of falling.
4. Examine the magnitude of change in clinical outcomes, namely ESWT performance and PA after a short-term, supervised, individually tailored, ground walking training program.
5. Determine the minimal detectable difference (MDD) for ESWT performance.

Methods

Study 1: Systematic review and meta-analysis to evaluate the effect of exercise training on physical activity (addressing the first aim)

Electronic searching of computerised databases, hand searching reference lists of all identified studies and clinical trials registries were undertaken to evaluate the impact of exercise training on PA in individuals with COPD. Quality assessment for the randomised controlled trials (RCTs) and randomised trials (RTs) was rated using the 10-point PEDro scale while single-group interventional studies were rated using a modified Downs and Black tool. Consistency between reviewers for both quality

assessment methods was calculated using Kappa statistics. Due to the heterogeneity in PA outcome measures, the random-effects approach was used in the meta-analysis. A funnel plot was assessed visually to detect publication bias. Effect sizes were calculated by dividing the differences in PA (before and after the intervention) by the pooled standard deviation (SD).

Study 2: Measurement properties of the StepWatch™ Activity Monitor and ActivPAL™ – A validation study (addressing the second aim)

Some motion sensors have been shown to underestimate steps in individuals who adopt a slow walking speed. Measuring PA also appears to be particularly problematic in those who use a WW to assist with ambulation. This is likely to relate to the slower walking speeds characteristic of people who require gait aids. The simplest of motion sensors, namely pedometers, often lack the sensitivity to detect slow or shuffling gait patterns and thus tend to underestimate the number of steps taken by some patients with COPD. Further, for motion sensors that attach to the arm such as the SenseWear armband, the use of a WW stabilises the arm during ambulation, and therefore data received by the accelerometers within such devices are dampened. This serves to reduce the precision of any measurements.

As slow walking is likely to diminish movement in the lower limbs to a lesser extent than movement at the centre of mass, motion sensors that attach to the leg, rather than the waist, may yield accurate measures in individuals with COPD who are known to adopt slower walking speeds during daily life. The measurement properties of two motion sensors, the SAM and the ActivPAL™ that attach to the leg, were examined as they have yielded encouraging data in other clinical populations who walked slowly, including those who use a gait aid.

Both the SAM and the ActivPAL™ are small, easily concealed by clothing and simple to use; features that make them attractive for monitoring PA in both the research and clinical setting. Nevertheless, the capacity of these motion sensors to collect accurate information in people with COPD, who may use a WW to assist with ambulation, is unknown.

Twenty participants (8 males, 40%) completed this cross-sectional validation study to evaluate the measurement properties of two motion sensors: the SAM and the ActivPAL™. The study was undertaken in the Perth metropolitan area, Western Australia, during which data collection for each participant was completed during a single 2-hour session. The SAM and ActivPAL™ were attached to each participant and they completed five tasks, performed in a standardised order. The first four tasks were completed in the following order; supine lying for 5 minutes, sitting over the edge of a plinth for 5 minutes, 12 repetitions of transitioning between sitting and standing at their own pace and upright standing for 5 minutes. The fifth task was a set of four walking tasks of 5 minutes in duration each, performed within a 20 m level, enclosed corridor, separated by 30 minutes of seated rest. The first two walking tasks were undertaken at a speed considered to be 'slow' by the participants with the final two walking tasks undertaken at a speed considered to be 'normal' by the participants. The first walk at both speeds was completed without a WW and the second walk at both speeds was completed using a WW. The speed during each walking task was kept constant by using audio-signals that corresponded to a specific walking speed. During each walking task, for each participant, the investigator counted the number of steps taken over three separate 30-second intervals (i.e. at the beginning of the second, third and fourth minutes). The average of these three samples was used to determine the average step rate, for each participant, for each walking task.

Data collected during each stationary task were examined to determine whether either activity monitor had recorded movement. Data collected during the transitions from sit to stand were examined to determine if steps were detected during the tasks and data from the ActivPAL™ were examined to determine the number of changes in posture recorded from sedentary to upright. A repeated measures analysis of variance (ANOVA) was used to examine the effect of WW, walking speed and the interaction between the two, on the difference in step rate measured by the both activity monitors and to compare the data with that obtained by direct observation.

Study 3: Effect of using a wheeled walker on physical activity – A cross over study (addressing the third aim)

A prospective randomised cross-over study was conducted. A total of 19 participants with COPD were recruited from pulmonary rehabilitation programs (PRPs) within the Perth metropolitan area, Western Australia. All participants completed an 8-week hospital-based PRP. During the final 2 weeks of the PRP, two assessment sessions were undertaken in order to: (i) familiarise the participants with wearing the motion sensors that would be used to collect PA data and, (ii) collect descriptive baseline data. On completion of the PRP, participants were then randomised to one of two groups. Those allocated to Group 1 were provided with a WW for 5 weeks immediately following completion of the PRP but not the next 5 weeks. Participants allocated to Group 2 were not given a WW for the first 5 weeks but were thereafter provided with a WW for the next 5 weeks. In the final week of each 5-week period, two motion sensors were applied to participants in both groups to measure PA. Participants were instructed to wear both motion sensors 24 hours a day for 5 consecutive days. At the end of this 5-day period, all participants were visited at home to collect the motion sensors and complete questionnaires pertaining to their HRQoL and fear of falling. During this home visit, Group 1 participants had their WW removed and were encouraged to continue with their home exercise program and attend the maintenance PRP, whereas Group 2 participants were provided with a WW to use for the following 5 weeks and provided with standardised instructions regarding its use (as per Group 1). In the final week of the 5-week period, the same motion sensors were applied to participants in both groups and participants were instructed to wear both motion sensors 24 hours a day for 5 consecutive days. At the end of this period, a final home visit was made to collect the motion sensors and repeat the questionnaires.

The SAM was used to determine step rate as it has been shown to be accurate in those who walk slowly, including individuals who use a gait aid. The ActivPAL™ was used to complement the SAM in order to quantify the time spent being less active (sitting and lying down) compared to the time spent being active (standing and walking). The primary outcome measure was PA, measured concurrently using two separate motion sensors: the SAM and the ActivPAL™. The secondary outcome

measures were HRQoL, fear of falling, the distance travelled by the WW over the data collection period and barriers to using the WW.

**Study 4: The impact of a supervised ground walking training program
(addressing the fourth aim)**

A total of 143 participants were recruited from patients who had been referred to the PRPs in Sydney, New South Wales (86 participants) and Perth, Western Australia (57 participants) and randomised into one of three groups: a supervised ground walking training group (WG), a supervised ground walking training with post-training feedback group (WFG) and a usual care group. Both the WG and WFG underwent an identical ground walking training intervention over an 8-week period. The initial training intensity prescribed was equivalent to 80% of the average walking speed achieved during the 6-minute walk test (6MWT) that yielded the maximum distance at the baseline assessment. The total exercise time (excluding rests) was 30 minutes at the commencement of the walking training program. This was progressed by increasing the distance walked during training by increasing the duration of exercise by 5 minutes after every sixth session to a maximum of 45 minutes by session 19. During walking training, a rating of three (moderate breathlessness) to four (somewhat severe) on the modified Borg scale for dyspnea was used to titrate exercise intensity. After the 8-week period, the participants in both the WG and WFG were followed up over a 12-month period. The participants in the WG were provided with written instructions to walk for 45 minutes on at least 3 days a week and a weekly diary to record the duration of each walk. The participants in the WFG received biofeedback in the form of a pedometer and regular phone calls to set goals and provide support, in addition to the same written instructions and weekly diary to record the steps taken during each walk. The data of the participants in both the WG and WFG, relating to baseline and post effects of the 8-week walking training intervention, were used for Study 4 of this thesis. Participants randomised to the usual care group did not perform any exercise training and were not given any instructions regarding exercise.

In all participants, the outcome measures were assessed before and immediately after the 8-week intervention period. These outcomes included exercise capacity measured

using three field-based walking tests, HRQoL, anxiety and depression, self-efficacy and daily PA. Analysis of covariance was conducted for the between-group comparisons with baseline values as the covariate. Intention-to-treat analyses were conducted regardless of the participants' attendances to the exercise sessions with no imputation of missing values. Within this thesis, only data relating to the change in ESWT and PA measured immediately after the 8-week walking training intervention are reported in detail, thus data from both WG and WFG were combined as the participants in both groups underwent the same walking training during the 8-week period.

Study 5: The minimal detectable difference of endurance shuttle walk test performance (addressing the fifth aim)

The data from the supervised ground walking training program were used to determine the MDD for the change in performance during the ESWT, expressed in both time (sec) and distance (m). The anchor-based approach to determining the MDD comprised four steps. First, responses to the global rating of change (GRC) scale were collapsed from seven categories to three categories. The GRC scale is a balanced 15-point numerical scale, where individuals ranked their improvement or deterioration using the written descriptors ranging from a very great deal worse (-7) to a very great deal better (+7). Given the limited number of participants in some of the categories, the GRC scores were collapsed to three categories, where no change or a GRC score of 1 were categorised as no change, GRC scores of 2 to 3 were categorised as a small change and GRC scores of 4 to 7 were categorised as a substantial change. Second, the relationship between the collapsed GRC responses and the magnitude of change in ESWT performance following training was determined. Third, a receiver operating characteristics (ROC) curve was constructed to determine the optimal operating point which resulted in the best blend of sensitivity and specificity to discriminate between participants who rated their walking ability following training as 'changed' versus 'unchanged'. Finally, the software package 'R' was used to establish the 95% confidence interval (CI) for this optimal operating point, using bootstrapping methods. Three separate distribution-based approaches were used to estimate the MDD: half the SD of the baseline

measure; half the SD of change in measures collected before and after training and; the minimal detectable change (MDC), derived from the SEM.

Results

Study1:

Seven relevant studies were identified from the literature search. Reviewers agreed on 100% of all PEDro items (Kappa statistic = 1). The mean±SD PEDro score for the RTs was 5±0 points. Reviewers agreed on 96% of all Downs and Black items with a Kappa statistic of 0.92. The mean±SD Downs and Black score was 19±3 points. Asymmetry was observed in the funnel plot for PA in the RTs and single-group interventional studies, suggesting that publication bias could not be excluded. Taken together, PA data entered into the meta-analysis from the RTs and the single-group studies were homogeneous ($I^2 = 0\%$, $p = 0.60$). The effect size for PA though significant was small (0.12; $p = 0.01$).

This is the first systematic review and meta-analysis to evaluate the effect of exercise training on measures of PA in individuals with COPD. The important findings of the review are that; (i) there are no published RCTs that examine the effects of at least 4 weeks of supervised exercise training on PA and, (ii) data from the RTs and single-group interventional studies indicate that, in individuals with COPD, supervised exercise training confers a significant, but small effect on PA.

Study 2:

Twenty participants (8 males) aged 73.0±8.5 years with a 35±13% predicted FEV₁ (volume exhaled during the first second of a forced expiration) wore both the SAM and the ActivPAL™ during the performance of five tasks. Neither the SAM nor the ActivPAL™ detected any steps during the stationary tasks or during sit to stand transitions. Regarding data collected using the SAM, the ANOVA demonstrated no interaction (WW x walking speed; $F_{1, 19} = 0.24$; $p = 0.63$), effect of WW ($F_{1, 19} = 0.12$; $p = 0.73$) or walking speed ($F_{1, 19} = 0.03$; $p = 0.86$) on the difference between step rate derived using this motion sensor and via direct observation. This indicated that the difference between step rate derived using the SAM and direct

observation was similar across all walking tasks. Regarding data collected using the ActivPAL™, there was no interaction (WW x walking speed; $F_{1, 19} = 0.58$; $p = 0.46$) or effect of WW ($F_{1, 19} = 0.01$; $p = 0.91$) on the difference between step rate derived using this device and via direct observation. This indicated that any difference between the step rate derived using the ActivPAL™ and direct observation was not affected by the use of a WW. However, there was a significant effect of walking speed ($F_{1, 19} = 5.75$; $p = 0.03$) on the difference between step rate derived using the ActivPAL™ and direct observation. This indicates that the difference between the step rate derived using the ActivPAL™ and direct observation differed between walking speeds. Thus both motion sensors were able to detect the difference in step rate associated with changing walking speeds and using a WW.

Study 3:

Nineteen participants (11 males) aged 73 ± 8 years with a 38 ± 19 FEV₁ % predicted were randomised to one of two groups, whereby those allocated to Group 1 were provided with a WW for 5 weeks but not the next 5 weeks while those allocated to Group 2 were not given a WW for the first 5 weeks but were thereafter provided with a WW for the next 5 weeks. For the SAM and ActivPAL™ data, no order effect was found ($F_{1, 16} = 3.11$; $p = 0.10$ and $F_{1, 14} = 2.00$; $p = 0.18$, respectively), thus data from both groups were combined for the purpose of comparing outcomes between walking with a WW or without a WW.

Using data collected by the SAM, compared with the period when the WW was not available, the mean number of steps taken daily significantly increased by $732 \pm 1,027$ steps ($p < 0.02$) when the WW was available. The mean time spent walking at a moderate intensity significantly increased by 9 ± 13 min/day ($p < 0.02$) when the WW was available. Using the data collected by the ActivPAL™, compared with the period when the WW was not available, there was a trend for the mean time spent walking each day to increase by 7 ± 16 min/day when the WW was available ($p = 0.09$). The difference in mean time spent standing each day when the WW was available was 9 ± 25 min/day ($p = 0.18$). The mean time spent sitting and lying down when the WW was not available was similar to that measured when the WW was available (-15 ± 35 min/day; $p = 0.11$). In the primary analysis, the magnitude of

change in PA was greater when data from the participants who had an exacerbation were removed from the analysis.

Compared with the period when the WW was not available, the magnitude of change in HRQoL for all domains of the Chronic Respiratory Disease Questionnaire (CRDQ) when the WW was available did not reach statistical significance. Nine of the 19 participants expressed a fear of falling (i.e. scored > 0 on the Survey of Activities and Fear of Falling in the Elderly scale) and the use of a WW reduced this fear in seven of these nine participants. The greatest barrier towards the use of the WW was lifting a WW in and out of the car.

Study 4:

A total of 143 participants (84 males) aged 69 ± 8 years with a 43 ± 15 FEV₁ % predicted were randomised into one of three groups: a walking training group (WG), a walking training with post-training feedback group (WFG) and a usual care group. A total of 95 participants were randomised to the walking training groups (WG and WFG) and 48 participants were randomised to the usual care group. The duration and distance achieved in the ESWT increased for participants in the walking training groups after the 8-week period by 245 ± 313 sec and 289 ± 376 m respectively ($p < 0.001$), representing an improvement of 92 ± 148 %. In contrast, the duration and distance achieved in the ESWT for the usual care group did not change significantly over time (38 ± 229 sec and 54 ± 325 m respectively [$p = 0.26$]; representing a difference of 34 ± 102 %).

A total of 61 participants in the walking training groups and 38 participants in the usual care group had at least 3 days of valid PA data before and after the 8-week intervention period, during which the SenseWear armband had been worn for at least 85% of each day. The walking training groups increased their total energy expenditure (TEE) by 16 ± 132 kilocalories (kcal) ($p = 0.35$) and steps per day by $404 \pm 1,608$ ($p = 0.05$), while the usual care group increased their TEE by 28 ± 160 kcal ($p = 0.29$) and steps per day by $268 \pm 1,616$ ($p = 0.31$). However there was no significant difference in TEE and steps taken per day between the walking training groups and the usual care group ($p > 0.7$).

Study 5:

The data from 78 participants (44 males), aged 70 ± 9 years with a 43 ± 15 FEV₁ % predicted, who were randomised to walking training (both WG and WFG) and who completed the ESWT before and after the 8-week walking training were used to determine the MDD for ESWT performance. The MDD for ESWT performance expressed in time and distance as determined by the anchor-based approach using the ROC curve were 113 sec (95% CI, 23 to 139 sec) and 192 m (95% CI, 60 to 200 m) respectively. The MDD for ESWT performance expressed in time and distance as determined by the distribution-based approaches ranged between 104 to 158 sec and 162 to 189 m, respectively. The estimated consensus for MDD for ESWT performance on completion of an 8-week supervised, individually tailored, ground walking training program was approximately 113 sec (95% CI, 23 to 139 sec) or 192 m (95% CI, 60 to 200 m).

Discussion and conclusions

Individuals with COPD are generally less active, most likely because they try to minimise dyspnea and fatigue in daily life. Inactivity leads to deconditioning and muscle weakness, both of which contribute importantly to the overall level of disability. Reduced PA is also likely to contribute to the increased risk of cardiovascular disease demonstrated in individuals with COPD and may be a predictor of survival. Despite the importance of increasing PA, the optimal measurement method is unclear. As individuals with COPD walk less and slower than healthy peers, suitable motion sensors that are responsive should be used to measure PA in these individuals. In the research setting, a comprehensive assessment of the measurement properties of the SAM and the ActivPAL™ will determine whether or not these devices are appropriate to evaluate PA in the subgroup of individuals with COPD who require a WW to assist with ambulation. This in turn will allow the impact of a WW, provided to those with the greatest functional limitation, on PA to be accurately evaluated.

As PA has been found to have a protective effect on the risk of hospitalisation for acute exacerbations and mortality, it is important to look at strategies that might improve PA levels in individuals with COPD. Therefore, it is possible that an

increase in the level of PA in response to the use of the WW may impact these important clinical events. The lower limb muscles in individuals with COPD are also weak and metabolically inefficient, thus endurance exercise of the leg muscles, such as walking is an essential component of exercise training during pulmonary rehabilitation. Walking training is particularly suitable as a method of exercise training for individuals with COPD as it is an activity that is part of their daily lives, inexpensive as no specialised equipment is required, serves as a form of transport and protects against mobility loss in older adults. Therefore, it is possible that walking training may impact exercise capacity in terms of endurance and may increase the level of PA.

The ESWT is an externally paced, constant workload field walking test that has been shown to be more responsiveness than other field-based assessments of exercise capacity. Determining the MDD for the ESWT using both anchor- and distribution-based approaches will allow changes in endurance shuttle walking distance and duration to be evaluated in terms that are meaningful to individuals with COPD.

ACKNOWLEDGMENTS AND FUNDING

First and most importantly, GOD, who provided me the grace and strength through these years, watching over my loved ones back home in Singapore and keeping me healthy and safe as I flew multiple times between Perth and Singapore.

Associate Professor Sue Jenkins and Associate Professor Kylie Hill, my two PhD supervisors, for their complete dedication, support, and full commitment to this project. I value their understanding for my fly in- fly out between Perth and Singapore to spend time with my family while being committed to this PhD.

Professor Peter Eastwood, Dr David Hillman, Professor Jennifer Alison, Dr Zoe McKeough, Dr Kathy Stiller and Dr Christine Jenkins for their invaluable expertise, and generous assistance and feedback with these PhD studies.

Nola Cecins for her support and help during testing and training of my participants as well as her valuable feedback on my work.

Michelle Melang and Nikki Newton, my wonderful research assistants, without whom this PhD would not be possible as they assisted in collecting some of these data.

Sally Watts, my ‘other half’ for part of my PhD, for her dedication and listening ear.

My husband Patrick, who showered me with love, encouragement and emotional support during these 4 years.

Jedidiah, my son, who grew up understanding Mummy is not always at his side and allowing me to work full time on this PhD thesis.

My parents for their love and for providing me with a joy for education as well as their precious time and effort taking care of my son while I was in Perth.

Dr Roger Collinson, statistician at the School of Physiotherapy and Exercise Science for his support in data analyses and for reading through my results.

Dr Mika Nonoyama, for her input and advice with regards to my meta-analysis.

The staff of the Pulmonary Physiology Department (Sir Charles Gairdner Hospital) for conducting the general respiratory function tests of my subjects.

The staff of the Physiotherapy Department (Sir Charles Gairdner Hospital) for sharing their office with me.

Mr Jeffery Tapper, Mr Ian Cooper and the Physiotherapy Department (Sir Charles Gairdner Hospital) for their generosity in providing space and the use of facilities for the testing and exercise training of my participants.

The statisticians of Sir Charles Gairdner Hospital for assisting me in boot strapping my data.

Faith Png, Sandra Dumas and Vanessa Jackaman, physiotherapists working with patients at Bentley Hospital, who willingly passed on suitable patients to me for my studies and who provided such valuable support and expertise.

Caitlin McCamley from COPD linkage who provided the relevant data for some of my participants.

My fellow PhD students, namely Vin, Mohammed and Fatim for their encouragement.

All of the people who participated in this study, for their time commitment and enthusiasm for this research.

Financial support for this study was provided by:

Curtin Postgraduate Scholarship (CIPRS #323247)

National Health and Medical Research Council (Grant 570814)

Sir Charles Gairdner Hospital Research Foundation (Grant #2007-346800)

PUBLICATIONS AND PRESENTATIONS

Publications arising from this thesis

Ng LWC, Jenkins S & Hill K. Accuracy and responsiveness of the Stepwatch Activity Monitor and ActivPAL in patients with COPD when walking with and without a rollator. *Disability and Rehabilitation* 2012; 34:1317-1322. (Cited 3 times).

Ng LWC, Mackney J, Jenkins S & Hill K. Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis. *Chronic Respiratory Disease* 2012; 9:17-26. (Cited 25 times).

Wootton SL, Ng LWC, McKeough ZJ, Jenkins S, Hill K & Alison JA. Estimating endurance shuttle walk test speed using the six-minute walk test in people with chronic obstructive pulmonary disease. *Chronic Respiratory Disease* (published online 21st March 2014).

Manuscripts in preparation

Ng LWC, Wootton SL, Hill K, McKeough ZJ, Jenkins S, Eastwood P, Hillman D, Cecins N, Spencer L, Jenkins C & Alison JA. Effects of ground-based walking training on exercise capacity and quality of life in people with COPD: a randomised controlled trial.

Ng LWC, Jenkins S, Cecins N, Eastwood P & Hill K. Wheeled walker use increases physical activity in COPD: A randomised cross-over trial.

Wootton SL, Ng LWC, McKeough ZJ, Jenkins S, Hill K, Cecins N & Alison JA. The minimal detectable difference for endurance shuttle walk test performance in people with COPD on completion of an exercise training program.

Presentations arising from this thesis

Ng C, Jenkins S, Cecins N, Eastwood P & Hill K. Measurement of physical activity in people with COPD who use a wheeled walker. Poster presentation at Sir Charles Gairdner Hospital (SCGH) research week, September 2010, Perth, Western Australia.

Ng C, Jenkins S, Cecins N, Eastwood P & Hill K. Evaluation and optimisation of physical activity in individuals with COPD: The use of wheeled walkers. Oral presentation at Lung Institute of Western Australia, 12th August 2010, Perth, Western Australia.

Ng C, Mackney J, Jenkins S, & Hill K. Does exercise with or without counselling change physical activity in people with COPD? A systematic review. Oral presentation at Lung Institute of Western Australia, March 2011, Perth, Western Australia.

Ng C, Mackney J, Jenkins S, & Hill K. Does exercise with or without counselling change physical activity in people with COPD? A systematic review. Oral presentation at the Thoracic Society of Australia & New Zealand (TSANZ) 3rd April 2011, Perth, Western Australia. *Respirology* 2011; 16 (Suppl. 1): TO-012 (p 11).

Ng C, Jenkins S, Cecins N, Eastwood P & Hill K. Measurement properties of two accelerometers in people with COPD: Effect of walk speed and 4-wheeled walker use. Poster presentation at TSANZ, 4th April 2011, Perth, Western Australia. *Respirology* 2011; 16 (Suppl. 1): TP-161 (p 77).

Watts S, Ng L, McKeough Z, Jenkins S, Hill H, Eastwood P, Hillman D, Jenkins C & Alison J. Relationship between six-minute walk distance (6MWD) and average daily physical activity levels in people with COPD. Poster presentation at TSANZ, 6th April 2011, Perth, Western Australia. *Respirology* 2011; 16 (Suppl. 1): TO-099 (p 33).

Ng C, Mackney J, Jenkins S & Hill K. Does exercise training or patient encouragement change physical activity in people with COPD? A systematic review.

Oral presentation at The Australian Society for Medical Research (ASMR) 3rd June 2011, Curtin University, Perth, Western Australia.

Ng C, Jenkins S, Cecins N, Eastwood P & Hill K. Measurement properties of two accelerometers in people with COPD: Effect of walk speed and 4-wheeled walker use. Poster presentation on 28th November 2011 at SCGH Physiotherapy Department, Perth, Western Australia.

Ng C, Jenkins S, Cecins N, Eastwood P & Hill K. A wheeled walker on physical activity in people with COPD: Preliminary data. Poster presentation at TSANZ, 1st April 2012, Canberra, Australian Capital Territory. *Respirology* 2012; 17 (Suppl. 1): TP-074 (p 60).

Watts S, Ng C, McKeough Z, Jenkins S, Hill K, Eastwood P, Hillman D, Jenkins C & Alison J. Walk speeds for the 6-minute walk test and endurance shuttle walk test are similar in people with COPD. Poster presentation at TSANZ, 1st April 2012, Canberra, Australian Capital Territory. *Respirology* 2012; 17 (Suppl. 1): TP-080 (p 61).

Ng C, Watts S, McKeough Z, Alison J, Jenkins S, & Hill K. Minimal detectable difference for the endurance shuttle walk test following ground walking training in people with COPD. Poster presentation at TSANZ, 25th March 2013, Darwin, Northern Territory. *Respirology* 2013; 18 (Suppl. S2): P074 (p 56).

Watts S, Ng C, McKeough Z, Jenkins S, Hill K, Eastwood P, Hillman D, Jenkins C, Cecins N, Spencer L & Alison J. Effects of ground walking training in COPD: A randomised controlled trial. Oral presentation at TSANZ, 26th March 2013, Darwin, Northern Territory. *Respirology* 2013; 18 (Suppl. S2): O064 (p 26).

LIST OF ABBREVIATIONS

a: accelerometer
ActivPAL: ActivPAL™
AEE: active energy expenditure
ANOVA: analysis of variance
AUC: area under the curve
AUD: Australian dollar
BMI: body mass index
bpm: beats per minute
BODE: body mass index, airflow obstruction, dyspnea and exercise capacity index
cm: centimetres
COPD: chronic obstructive pulmonary disease
CRDQ: Chronic Respiratory Disease Questionnaire
CI: confidence interval
DALYs: disability-adjusted life years
DLW: doubled labelled water
ESWT: endurance shuttle walking test
F: female
FEV₁: forced expiratory volume in one second
FEV₁/FVC: the ratio of forced expiratory volume at one second to forced vital capacity written as a percentage
FVC: forced vital capacity
g: grams
GEP: general exercise program
GPS: global positioning system
GRC: global rate of change
GOLD: Global Initiative for Chronic Obstructive Lung Disease
GSES-12: General Self-efficacy Scale
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
hr: hour
HR: heart rate
Hz: hertz
ICC: intraclass correlation
ISWD: incremental shuttle walk distance
ISWT: incremental shuttle walking test
ITEP: individually targeted exercise program
Kcal: kilocalories
kg: kilograms
kg/m²: kilograms per metre squared
km: kilometers
km/hr: kilometers per hour
L: litres
LOA: limit of agreement
m: metres
M: male
m/s: metres per second
MARCA: Multimedia Activity Recall for Children and Adults

MCID: minimal clinically important difference
METs: metabolic equivalents
MID: minimal important difference
MDC: minimal detectable change
MDD: minimal detectable difference
min: minutes
MMRC: Modified Medical Research Council
MVV: maximum voluntary ventilation
n: number
NETT: National Emphysema Treatment Trial
O₂: oxygen
OR: odds ratio
p: pedometer or probability
ppi: points per item
PA: physical activity
PRP: pulmonary rehabilitation program
r: spearman or pearson's correlation coefficient
RCT: randomised controlled trial
ROC: receiver operating characteristic
RPE: rating of perceived exertion
RT: randomised trial
SAFE: Survey of Activities and Fear of Falling in the Elderly
SAM: StepWatchTM Activity Monitor
SCGH: Sir Charles Gairdner Hospital
SD: standard deviation
sec: seconds
SEM: standard error of measurement
SF-36: 36-Item Short Form Health Survey
SGRQ: Saint George's Respiratory Questionnaire
SpO₂: percutaneous oxygen saturation
SD: standard deviation
SRM: standardised response mean
Std: standard
TEE: total energy expenditure
TORCH: TOwards a Revolution in COPD Health
TSANZ: Thoracic Society of Australia & New Zealand
UCSD: University of California San Diego
US: United States
UK: United Kingdom
VMU: vector magnitude units
VO_{2peak}: peak rate of oxygen consumption
WAFt: walking and feedback training
WFG: walking training with post training feedback group
WG: walking training group
WW: wheeled walker
6MWD: six minute walk distance
6MWT: six minute walk test
%: percent
% pred: percent predicted

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CHAPTER 1

INTRODUCTION

Many individuals with chronic obstructive pulmonary disease (COPD) are inactive in daily life, most likely as a strategy to minimise dyspnea (1). The deleterious effects of inactivity are becoming increasingly apparent and include impaired health-related quality of life (HRQoL), increased healthcare utilisation and possibly reduced survival (2-4). Evaluating and optimising function, including increasing physical activity (PA), is an important goal in the management of people with COPD. Possible strategies include the use of an assistive walking aid such as a wheeled walker (WW) and exercise training as part of pulmonary rehabilitation. However, little is known regarding the optimal methods to measure PA in this population. Further, exercise training has also been shown to reduce dyspnea and fatigue (5-7), increase exercise capacity and improve HRQoL (5-7). The improvements observed after exercise training must extend beyond showing changes that are statistically significant to demonstrating changes that are perceived as beneficial by the individual (8). Thus, this PhD comprises of studies that will explore the evaluation approaches and effectiveness of therapeutic interventions that aim at optimising daily PA in individuals with COPD, as well as determine the minimal detectable difference (MDD) of outcome measures, namely the endurance shuttle walk test (ESWT) performance and PA.

This program of research consisted of four studies that were conducted in individuals with COPD. They were a systematic review and meta-analysis of the impact of exercise training on PA, a cross-sectional observational study that evaluated the measurement properties of two motion sensors, a prospective randomised cross-over study that examined the effects of the use of a WW on PA, HRQoL and fear of falling, as well as a prospective, single-blind, randomised controlled trial on the impact of supervised walking exercise training on ESWT performance and PA.

1.1 Research questions

- What is the impact of exercise training on PA in individuals with COPD?

- What are the measurement properties of two novel motion sensors: the StepWatch™ Activity Monitor (SAM) and the ActivPAL™ in individuals with COPD?
- What are the effects of using a WW, an assisted walking device, for use in the community on daily PA, HRQoL and fear of falling in individuals with COPD?
- What is the magnitude of change in clinical outcomes such as functional exercise capacity and PA after a short-term, supervised, individually tailored, ground walking training program in individuals with COPD?
- What is the MDD for the ESWT in individuals with COPD?

This chapter presents an overview of the literature pertaining to the development of each primary research question. The hypotheses for each research question are described and the significance of the research program is discussed.

1.2 Primary question

Does exercise training increase PA in individuals with COPD?

1.2.1 Hypothesis

Exercise training will increase PA in individuals with COPD.

1.2.1.1 Background

The cornerstone of pulmonary rehabilitation is supervised exercise training (5) and exercise training is the intervention within a pulmonary rehabilitation program (PRP) that has been shown to be most likely to change PA. A systematic review and meta-analysis was undertaken to determine the impact of exercise training on PA in individuals with COPD.

1.3 Primary question

Do the SAM and the ActivPAL™ detect movement when individuals with COPD perform stationary tasks and during a sit to stand task, and are they accurate and responsive in detecting steps when individuals with COPD walk at slow and normal pace with and without a WW?

1.3.1 Hypothesis

The first hypothesis is that both monitors will not detect steps when individuals with COPD perform stationary tasks, namely lying supine, sitting and standing as well as during the transition from sitting to standing.

The second hypothesis is that both the SAM and ActivPAL™ will be accurate and responsive at detecting steps in individuals with COPD during:

- i. slow and normal walking pace;
- ii. slow and normal walking pace when using a WW.

1.3.1.1 Background

In individuals with COPD, the level of daily PA has been demonstrated to influence healthcare utilisation, morbidity and mortality (9, 10). Despite the importance of optimising daily PA in this population, selecting an appropriate device to obtain valid measures remains a challenge. This is especially true for those individuals who walk slowly or use a WW to assist with ambulation (11-13). Some motion sensors underestimate steps in individuals who adopt a slow walking speed as there is insufficient magnitude of movement at the centre of mass to be detected by these motion sensors (13-15). Measuring PA also appears to be particularly problematic in those who use a gait aid to assist with ambulation (13). Following a review of the literature (11, 16-19), the measurement properties of two motion sensors that attach to the leg were explored as they have yielded encouraging data in other clinical populations. These motion sensors were the StepWatch™ Activity Monitor (SAM; OrthocareInnovations, Seattle, Washington, United States [US]) and the ActivPAL™ (PAL Technologies Ltd, Glasgow, Scotland, United Kingdom [UK]). Nevertheless, the capacity of these motion sensors to collect accurate information in individuals with COPD, who may use a WW to assist with ambulation, is unknown. Further, the capacity of these motion sensors to detect a small increase in PA is unknown. This is particularly important if these motion sensors are used to evaluate the effect of therapies aimed at increasing PA in individuals with COPD.

1.4 Primary question

Does providing a WW to individuals with COPD for home and community use increase PA, improve HRQoL and reduce the fear of falling?

1.4.1 Hypothesis

Individuals with COPD will benefit from the use of a WW in the home and community. Specifically, compared to a 5-week period without a WW, the use of a WW for 5 weeks will result in significant improvements in:

- i. PA;
- ii. HRQoL and;
- iii. Fear of falling.

1.4.1.1 Background

Individuals with COPD who are characterised by marked functional limitation due to intolerable dyspnea may benefit from ambulating with a WW (20). The use of a WW has been shown to decrease dyspnea and rest duration during a 6-minute walk test (6MWT) (21) and increase 6-minute walk distance (6MWD) (22).

The improvements in 6MWD and dyspnea were greater in individuals with COPD with greater functional limitation. Solway et al (21) found that 6MWD significantly increased when individuals with COPD who walked < 300 m unaided in their 6MWT were provided with a WW (with a WW, 6MWD = 243±14 m versus without a WW, 6MWD = 220±12 m; $p = 0.02$).

The reasons for the improvements seen when walking with a WW most probably relate to the use of a forward lean position, the capacity to brace the arms on the WW and decreases in the metabolic cost of walking (23, 24).

This reduction in dyspnea and improvement in functional capacity when using a WW may enable individuals with COPD to increase their PA. Despite the acute improvements in dyspnea and functional capacity which have been documented in the laboratory setting, no study has evaluated the effects of a WW on daily PA in the community. Further, it is possible that using a WW will decrease the fear of falling

and increase confidence when walking. This is particularly important given the evidence demonstrating a reduction in the balance and coordination of individuals with COPD (25-27) which is likely to result, at least in part, from a less active lifestyle.

1.5 Primary question

Does an 8-week supervised, individually tailored, ground walking training program change ESWT performance and PA in individuals with COPD?

1.5.1 Hypothesis

In individuals with COPD, functional exercise capacity, namely ESWT performance, as well as PA will improve after participating in an 8-week supervised, individually tailored, ground walking training program.

1.5.1.1 Background

Pulmonary rehabilitation has been shown to be effective at increasing exercise capacity, improving HRQoL and reducing hospital admissions in individuals with COPD (5). In pulmonary rehabilitation, exercise training is of paramount importance (5). The lower limb muscles in individuals with COPD are weak (28), thus endurance exercise of the leg muscles, such as walking (ground-based or treadmill) and stationary cycling is an essential component of exercise training during pulmonary rehabilitation (5). Walking training is particularly suitable as a method of exercise training for individuals with COPD as it is an activity that is part of their daily lives (29), is inexpensive as no specialised equipment is required, serves as a form of transport and protects against mobility loss in older adults (30).

Despite the strong evidence that supervised exercise training reduces dyspnea and fatigue (7), increases exercise capacity as well as improves HRQoL (5-7), the impact on PA seems modest ((31-38)). Exercise training is muscle and activity specific. Walking training has been shown to improve outcomes in field walking tests to a greater extent than cycling training (39) and upper limb training (40). Thus, it is possible that walking as a sole modality of exercise training may confer greater gains

in daily PA than other exercise modalities such as cycling as walking is an integral part of daily life for individuals with COPD (9).

In summary, there is little evidence that supervised, individually tailored ground walking training alone, in which the exercise intensity is progressed to ensure optimal training responses, is effective at improving exercise capacity and PA in individuals with COPD. This gap in evidence is important to address as, if found to be effective, a walking program has the advantage over cycling training in that it is low cost and requires few resources. This in turn would support the widespread establishment of walking training programs, particularly in rural and remote areas, as well as in programs run in metropolitan areas. This would potentially provide a large number of individuals with COPD access to such programs, which could be conducted independent of expensive exercise equipment.

One of the studies presented in this thesis was part of a multi-centre trial conducted in Sydney, New South Wales and Perth, Western Australia, that sought to determine the effect of supervised ground walking training on the exercise capacity and HRQoL of individuals with COPD. The impact of a short-term, supervised, individually tailored, ground walking training as a sole exercise modality on ESWT performance and PA in individuals with COPD has been presented in this thesis.

1.6 Primary question

What is the MDD for ESWT performance using both anchor-based and distribution-based approaches in individuals with COPD?

1.6.1 Hypothesis

The hypothesis for this study is that there will be a significant relationship between objective measurement of the change in ESWT performance and the subjective global rate of change (GRC) ratings as perceived by the individuals with COPD after an 8-week supervised, individually tailored, ground walking training program. It is hypothesised that the estimate of the MDD derived using anchor-based approaches will be similar to the estimate of the MDD derived using distribution-based approaches (calculated using statistical methods).

1.6.1.1 Background

The MDD has been defined as the smallest difference in the outcome of interest that is noticeable to an individual after treatment (41). This term is often used interchangeably with terms such as the minimal important difference (MID) and minimal clinically important difference (MCID). The main difference between these terms is that the MDD is the smallest difference noticeable (or detectable) by an individual, whereas, both the MID and MCID aim to ensure that the magnitude of this difference is important to the individual (8).

The MDD has been determined using two approaches, namely anchor- and distribution-based approaches (8). Anchor-based approaches relates the magnitude of change in an outcome measure following an intervention to an objective external criterion (8). For example, several studies have related the magnitude of change in field-based measures of exercise capacity, following pulmonary rehabilitation, with self-report scores on the GRC scale (42-44). Specifically, a GRC scale is simple to use and administer, and asks individuals to rank their improvement or deterioration using a balanced 7-point numerical scale with written descriptors ranging from a very great deal worse (-7) to a very great deal better (+7) (45). Distribution-based approaches establish the MDD using some measure of variability in the outcome of interest. Distribution-based approaches are not anchored to a GRC scale and therefore do not take into consideration an individual's perception of the change. There have been several distribution-based approaches that have been used to determine the MDD for outcomes commonly used to evaluate the effects of pulmonary rehabilitation. These comprise calculating an effect size, the standardised response mean (SRM) or standard error of measurement (SEM) (8). Effect size has been defined as the standardised measure of change obtained by dividing differences in the outcome measure of interest (i.e. from baseline to post-intervention) by the standard deviation (SD) of the baseline value (8). An effect size of 0.5 is considered to be moderate (8) and the MDD is calculated by multiplying the SD of the baseline measure by 0.5. The SRM has been defined as the changes in a group of values or scores obtained by dividing differences in the outcome measure of interest (i.e. from baseline to post-intervention) by the SD of the change in the outcome measure (46). Half a SD of the change in the outcome of interest was used to estimate the MDD.

The SEM is the measure of within individual variability (8), as it estimates the standard error in a set of repeated scores. It is defined as variability between an individual's observed score and the true score, and can be calculated using an intra-class correlation coefficient (ICC) or via repeated measures analysis of variance (ANOVA) (47).

The only study to date to attempt to estimate the MDD for ESWT performance reported the SRM using a distribution-based approach (48). The authors did not attempt any anchor-based approaches due to the weak relationship between the ESWT performance and the GRC scores after rehabilitation ($r < 0.4$) which was attributed to either recall bias or the high level of commitment and personal investment required to complete the 7-week pulmonary rehabilitation program; both of which were likely to affect the individual's perception of his or her exercise performance (48).

In this thesis, besides distribution-based approaches, the anchor-based approach of determining the MDD for ESWT was determined as the value that confers the optimal blend of sensitivity and specificity using a receiver operating characteristic (ROC) curve to discriminate between individuals who rate themselves as changed versus unchanged at the end of an intervention (8). In addition to not being dependent on a moderate to strong relationship between GRC ratings and improvement in ESWT, using the ROC method has the advantage of accommodating all available data and not being influenced to small number of values within a category of the GRC scale (49).

1.7 Significance and novelty of the research

Individuals with COPD are less active during their daily life (1, 50). This inactivity imposed by the fear-provoking symptom of dyspnea limits individuals with COPD from participating in life to the fullest (51). Inactivity leads to deconditioning and muscle weakness, both of which contribute importantly to the overall level of disability (52). Reduced PA is also likely to contribute to the increased risk of cardiovascular disease demonstrated in COPD (53, 54) and may be a predictor of survival (9). Therefore, it is possible that an increase in the level of PA in response to therapies such as the use of a WW and high-intensity walking training may impact

these important clinical events.

Despite the importance of increasing PA, the optimal measurement method is unclear. In the research setting, a comprehensive assessment of the measurement properties of the ActivPALTM and the SAM will determine whether or not these motion sensors are appropriate to evaluate PA in the subgroup of individuals with COPD who require a WW to assist with ambulation. This in turn will allow the impact of a WW, provided to those with the greatest functional limitation, on PA to be accurately evaluated.

Although exercise training is paramount in pulmonary rehabilitation, the effectiveness of a solely walking exercise on ESWT performance and PA is lacking and this gap in knowledge is important to address as this would support the establishment of such cost effective exercise program. The MDD for changes in ESWT performance following PRP has also not been convincingly established using anchor-based approaches. Determining the MDD for ESWT performance will allow changes in these outcomes to be evaluated in terms that are meaningful to patients with COPD.

CHAPTER 2

LITERATURE REVIEW**2.1 Overview**

This literature review is divided into five parts. Part 1 (Section 2.2) includes information regarding the definition, prevalence, burden and impact of chronic obstructive pulmonary disease (COPD). Part 2 (Sections 2.3 to 2.4) describes the literature which has reported on the physical activity (PA) of individuals with COPD and the various approaches for measuring PA. Part 3 (Sections 2.5) reviews literature which has described strategies to increase PA in individuals with COPD, focussing on two possible strategies [the use of a wheeled walker (WW) and undertaking a pulmonary rehabilitation program (PRP)]. Part 4 (Section 2.6) comprises a systematic review and meta-analysis of data pertaining to the impact of exercise training on PA in individuals with COPD. This section has been published in a peer-reviewed scientific journal (55). Part 5 (Section 2.7) pertains to the methodologies reported for determining the minimal detectable difference (MDD) for outcome measures commonly used to evaluate the effectiveness of interventions in individuals with COPD.

PART 1

This part will first provide a definition for COPD and discuss the prevalence of the disease. In addition, the impact and costs associated with COPD are described.

2.2 Definition of COPD

Chronic obstructive pulmonary disease is characterised by progressive airflow obstruction due to a loss of elastic recoil and airway narrowing that is not fully reversible with bronchodilators (56). Fixed airflow obstruction is diagnosed via post-bronchodilator spirometry and is defined as the ratio of the volume exhaled during the first second of a forced expiration (FEV_1) to the forced vital capacity (FVC) of less than 0.70 (56). In those with evidence of fixed airflow obstruction, the severity of the disease is determined by expressing the FEV_1 as a percentage of the predicted value in healthy individuals (Table 2-1) (56). The main risk factor for developing

COPD is cigarette smoking (56), however only 45-50% of smokers progress to develop COPD (57). Other risk factors for COPD include occupational exposure to dusts or chemicals, childhood respiratory infections and alpha-1-antitrypsin deficiency (56).

2.2.1 Prevalence of COPD

Chronic obstructive pulmonary disease is one of the most common lung disorders in the world (58). A study by Buist et al (2007) (58) measured lung function in 600 adults from 12 sites around the world, including Australia (Sydney), and found the prevalence of COPD that was at least of moderate severity to be 10%. In Australia solely, the prevalence of COPD was estimated to be 7.5% for individuals aged 40 years and above and 29.2% in those aged 75 years and above (59). In 2008, COPD was estimated to affect more than 2.1 million Australians (nearly 1 in 5 aged over 40 years), of whom 1.2 million described symptoms that affected their daily lives (60). Notably, COPD is the fifth leading cause of death and third most burdensome disease in Australia (61). The World Health Organisation Global Burden of Disease study estimated COPD to be the fifth leading cause of death worldwide in 2002 (62). By 2030, it is envisaged that COPD will become the third leading cause of death worldwide (62). According to the Australian Bureau of Statistics, in 2011, COPD was directly responsible for the death of 5,878 Australians aged 55 years and above (i.e. 4% of all deaths) and there was 59,265 hospitalisations for COPD in 2011-2012 (63).

Table 2-1: Classification of the severity of airflow limitation by Global Initiative for Chronic Obstructive Lung Disease (based on post-bronchodilator FEV₁) in individuals with FEV₁/FVC < 0.70.

GOLD Grade	Description	Spirometry
I	Mild COPD	FEV ₁ ≥ 80% predicted
II	Moderate COPD	50% ≤ FEV ₁ < 80% predicted
III	Severe COPD	30% ≤ FEV ₁ < 50% predicted
IV	Very severe COPD	FEV ₁ < 30% predicted or < 50% with chronic respiratory failure

COPD, chronic obstructive pulmonary disease; FEV₁, volume exhaled during the first second of a forced expiration; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; %, percent.

2.2.2 Cost of COPD

The direct costs associated with COPD in the United States (US) have been estimated to be AUD \$15.7 billion per annum (64). This cost is driven largely by hospital admissions (64) and the medical management of the disease, which includes outpatient visits and medications (65). Indirect costs associated with COPD include loss of work time and productivity as well as the toll on the family and society resulting from the disease (65). In Australia, the direct cost of COPD was estimated to be AUD \$8.8 billion in 2008 with an additional cost of AUD \$89.4 billion due to loss of quality of life (60). Disability-adjusted life years (DALYs) are defined as the number of healthy years lost due to ill-health, disability or premature death (66). In 2010, the global ranking of the burden of COPD measured in DALYs was 9th (67) and was projected to increase to the 7th position by 2030 (68).

2.2.3 Impact and burden of COPD

Dyspnea and fatigue are symptoms experienced by individuals with COPD (69). Muscle weakness is also a major problem in individuals with COPD, affecting exercise tolerance (70). Mood disturbances are also prevalent (71) and there is increasing recognition of the importance of co-morbid conditions among individuals with COPD (72). These symptoms and conditions are described in the following paragraphs.

Dyspnea is the main complaint among individuals with COPD (56). In people with COPD, expiratory flow limitation leads to air trapping and an increase in lung volume, known as pulmonary hyperinflation. As the ventilatory demand increases during exercise, air trapping worsens; a process known as dynamic hyperinflation (73). This process is characterised by a progressive increase in end-expiratory lung volume which results in the tidal volumes being generated along the less compliant portion of the pressure-volume curve of the respiratory system, as well as a shortening and flattening of the diaphragm (74). When inspiratory reserve volume decreases to 0.5 litres (L), dyspnea becomes intolerable (74). This is because the large elastic loads on the respiratory muscles coupled with their reduced mechanical advantage serve to create disequilibrium between efferent outflow to the respiratory

muscles and the corresponding afferent input from the respiratory system (74). This is perceived as unrewarded inspiration, or dyspnea.

Another prominent symptom of COPD is fatigue (75). The increased work of breathing and dyspnea lead to deconditioning of muscles and fatigue (76). The systemic inflammation that occurs in people with COPD may also contribute to fatigue (77). Of note, fatigue was found to be a strong predictor of the risk of hospitalisation independent of the severity of airflow obstruction (78). The length of hospital stay was found to increase by a factor of almost four for every unit increase in fatigue experienced measured using an Identity-Consequences Fatigue Scale, a self-reported validated questionnaire to assess feelings of fatigue (78). Both dyspnea and leg fatigue could limit the ability to perform exercise in individuals with COPD (79) and impair health-related quality of life (HRQoL) (80).

Weakness of the lower extremity muscles has been associated with the decline in exercise capacity in individuals with COPD (81, 82). There is evidence to confirm the loss of skeletal muscle mass and strength, in particular of the quadriceps muscles, in individuals with COPD (82, 83). This muscle atrophy is caused by a number of factors, including low levels of PA, chronic inflammation, malnutrition, the side effects of medications such as statins, blood-gas abnormalities as well as compromised oxygen delivery due to right heart dysfunction (83). The quadriceps muscles are one of the main muscles used for ambulation and there is a significant reduction in quadriceps endurance capacity in individuals with COPD (84, 85). Computed tomography scans of the thigh muscles in individuals with COPD have demonstrated a loss of skeletal muscle mass compared to healthy individuals (86). Individuals with COPD are also more susceptible to leg fatigue (87). The impact that muscle weakness and leg fatigue have on exercise intolerance was demonstrated by Hamilton et al (88) where those patients with weaker muscles reported more leg fatigue and demonstrated reduced peak exercise capacity. Saey et al (89) showed that in individuals with COPD, the presence of leg fatigue during cycling exercise prevented optimal bronchodilatation from increasing exercise tolerance. Thus, both muscle weakness and leg fatigue limit cycle-based exercise tolerance in individuals with COPD (88).

It is also reported that mood disturbances such as depression and anxiety disorders are common among those with COPD, with the prevalence ranging from 10 to 96% depending on the criteria used to define them (90). Mood disturbances are often associated with increased disability and morbidity (71), and have a major impact on HRQoL (91, 92). One study reported that the incidence of depression and anxiety disorders was doubled in those who were physically less active (93). Physical inactivity due to depression, anxiety, dyspnea and fatigue leads to muscle weakness and deconditioning, further contributing to inactivity and disability (52).

There are also systemic consequences and co-morbidities associated with COPD with the most common being cardiovascular disease, hypertension, lung cancer, anaemia, osteoporosis, and metabolic diseases such as diabetes and obesity (72, 94, 95). The aetiological factors for these co-morbidities in individuals with COPD are likely to be multifactorial and inter-related, including systemic inflammation (96) associated with exposure to cigarette smoke, tissue hypoxia, oxidative stress and inactivity (97). These co-morbidities have a negative impact on hospitalisation and healthcare costs in COPD (98).

In summary, COPD results in symptoms that include dyspnea and fatigue as well as a decrease in exercise intolerance, and is associated with mood disturbances and co-morbidities. The impact and burden of these symptoms and associated disorders can be observed in the daily lives of individuals with COPD.

PART 2

This part reviews the literature pertaining to the levels of daily activity seen in individuals with COPD, the impact of low levels of PA, as well as the various methods used to measure PA.

2.3 Low levels of physical activity in individuals with COPD

Physical activity is defined as any bodily movement produced by skeletal muscle that results in energy expenditure beyond the resting state (99). There is robust evidence showing that individuals with COPD participate in less PA when compared with age and gender-matched healthy individuals (1, 100-103). Specifically, individuals with COPD appear to walk slower and for less time per day (1, 100, 102, 104). Pitta et al

(1) used a tri-axial accelerometer to measure PA, and found that individuals with moderate to severe COPD walked for a mean±standard deviation (SD) of 44±26 minutes and stood for 191±99 minutes per day. This was significantly ($p < 0.05$) less than age-matched healthy individuals who walked for 81±26 minutes and stood for 295±109 minutes per day (105). Further, individuals with COPD spent more time sitting and lying down than the healthy individuals (374±139 versus 306±108 minutes per day sitting; $p = 0.04$ and 87±97 versus 29±33 minutes per day lying down; $p = 0.004$) (1). Data pertaining to levels of daily PA in individuals with COPD were reviewed by Vorrink et al (100), who concluded that the duration and counts of daily PA in individuals with COPD were affected more markedly than the intensity of PA. This review concluded that, on average, individuals with COPD were approximately 40% less active than their healthy counterparts (100). Individuals with COPD also walked approximately 25% slower when compared to age-matched healthy individuals (1, 100). In a study by Hernandez et al (102), individuals with COPD walked at a slower intensity compared to healthy individuals (1.9±0.4 versus 2.3±0.6 m/s²; $p = 0.004$). These data were consistent with earlier work by Pitta et al (1) who demonstrated that individuals with COPD walked with lower movement intensity when compared with age and gender matched healthy individuals (1.8±0.3 versus 2.4±0.5 m/s²; $p < 0.0001$).

Although decrements in PA have been reported among individuals with mild COPD, it appears that those with more advanced disease have more profound impairments. For example, Watz et al (106) found that PA levels were lower in those individuals with more advanced COPD, measured using a multi-component index that considers the systemic manifestations of COPD (i.e. the BODE index which represents body mass index (BMI), airflow obstruction, dyspnea and exercise capacity index). Other studies have shown that the walking speed of individuals with COPD decreases with increasing disease severity (106-108).

There are also some data pertaining to the way in which PA is accumulated among individuals with COPD showing that individuals with COPD walk in short intermittent bursts rather than long continuous walking (33, 108). For example, Jehn et al (108) in a study involving 107 individuals with COPD, demonstrated that the time spent walking each day was accumulated in short intermittent bouts of less than

5 minutes. Similarly, Pitta et al (33) found that before and after pulmonary rehabilitation, walking time during daily life accumulated largely in very short bouts (up to 1 minute).

In summary, individuals with COPD are less active and move slower than their healthy counterparts. These decrements in PA worsen with advancing disease.

2.3.1 Clinical outcomes associated with low levels of physical activity in individuals with COPD

The adoption of a sedentary lifestyle by individuals with COPD is presumably a strategy to minimise dyspnea and fatigue during daily life (1). This reduced daily PA has been associated with impaired skeletal muscle endurance (84), muscle strength (1) as well as the severity of the respiratory impairment (105, 106). The consequences of this inactive lifestyle are likely to include cardiovascular (4, 109) and peripheral muscle de-conditioning (84, 110) which in turn can impact on exercise capacity and HRQoL (111).

Besides being less active than their healthy peers, individuals with COPD have increased functional disability and reduced exercise capacity (81, 82). Several studies have demonstrated a relationship between decreased PA and functional disability in COPD (93, 112). A population-based cohort study of 206 individuals with COPD showed that lower baseline PA was a strong indicator of increased disability (93). In this study, disability was measured using the Value Life Activities scale, which assessed the difficulty performing 28 activities such as cooking, visiting with family and getting around the neighbourhood (93). The results showed that physical inactivity was a strong predictor of a prospective increase in disability (odds ratio [OR] 2.5, confidence interval [CI] 1.1 to 5.3) (93). That indicates that the odds of an increase in disability were 2.4 times higher among individuals who were inactive at baseline (93). Daily PA, expressed as walking time, has been shown to be correlated with 6-minute walk distance (6MWD) and quadriceps force ($r = 0.76$ and 0.45 , respectively; both $p < 0.05$) (1). Similar associations with 6MWD have been demonstrated between steps taken each day and the number of minutes spent participating in moderate PA ($r = 0.63$ and 0.47 , respectively; both $p < 0.001$) (106).

Low levels of PA have been associated with the reduced HRQoL in people with COPD (113). Jehn et al (114) demonstrated that time spent walking at more than 5 km/h, measured using a motion sensor, was the only independent predictor of the physical function, role physical and general health domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) ($r = 0.4$, $r = 0.28$ and $r = 0.27$, respectively; all $p < 0.05$). The time spent walking at more than 5 km/h was also a significant independent predictor of the activity domain of the Saint George's Respiratory Questionnaire (SGRQ) ($r = -0.4$; $p < 0.001$) (114). These results indicate that individuals with COPD with the lowest daily walking intensities had the poorest HRQoL.

Reduced levels of PA in individuals with COPD also appear to be associated with increased healthcare utilisation (115) and mortality (116). A large ($n = 2,386$) cohort study found that individuals with COPD who reported performing at least 2 hours a week of walking or cycling (as determined by a self-report questionnaire) had a significantly 30 to 40% lower risk of hospital admissions due to exacerbations as well as a greater survival rate over a 20-year period (9). These data concur with those of Benzo et al (115) who, in 610 individuals with COPD, found that a minimum of 2 hours of self-reported PA per week had a protective effect against all cause hospitalisation. Specifically, their data showed that the odds of being hospitalised were significantly lower in individuals with COPD who reported undertaking ≥ 2 hours of PA per week (OR 0.60, 95% CI, 0.41 to 0.88, $p = 0.01$) (115). In another study, where 340 individuals with COPD were followed up for 1 year, the risk of re-admission was reduced in those individuals with PA levels which burnt more than 232 kilocalories per day (kcal/day) compared to individuals with PA levels of < 79 kcal/day or between 79 to 232 kcal/day (117).

There is also a link between regular PA and reduced risk of all-cause mortality in COPD (9). In a prospective cohort study of 170 individuals with stable COPD, Waschki et al (116) found that the best predictor of all-cause mortality was PA, when compared to other possible factors including lung function, 6MWD, cardiovascular status, nutritional and muscular status, systemic inflammatory markers, MMRC dyspnea grade, SGRQ and mortality scores. These authors found that every 0.5 SD increase in the number of daily steps (equivalent to 1845 steps), measured using a

multi-sensor accelerometer, was associated with a significantly lower risk of mortality (hazard ratio 0.49, 95% CI, 0.34 to 0.69) (116). Another study that looked at the prognostic value of PA, measured using a tri-axial accelerometer in 173 individuals with moderate to severe COPD, found that for every increase in PA of 10 vector magnitude units (VMU), mortality and hospitalisation risks decreased by 14% and 11% respectively after adjusting for confounders such as gender, age, BMI, current smoking, Charlson co-morbidity index and treatment with inhaled corticosteroids or long term oxygen therapy use (118).

In summary, low PA among individuals with COPD has a negative impact on exercise capacity, HRQoL, healthcare utilisation and mortality.

2.4 Measuring physical activity

Physical activity can be measured by subjective or objective methods (119), each with their own specific advantages and disadvantages. These are discussed in the following paragraphs.

2.4.1 Subjective methods to measuring physical activity

Subjective methods of measuring PA refer to asking an individual to self-report their level of activity through the use of questionnaires, diaries or logs, surveys or interviews (120). These subjective approaches are inexpensive and quick to administer (121). However, the information they yield appears to be inaccurate (3) as individuals with COPD tend to overestimate the time spent walking and underestimate the time spent standing (105), reflecting recall and social desirability bias (122). Garfield et al (123) tested the validity of four PA questionnaires (i.e. Stanford 7-day Physical Activity Recall Questionnaire, Baecke Questionnaire, Physical Activity Scale for the Elderly, and Zutphen Physical Activity Questionnaire) in individuals with COPD. Only the Stanford 7-day Physical Activity Recall Questionnaire was found to correlate with measures obtained using a validated multi-sensor accelerometer ($r = 0.54$; $p < 0.001$). Even so, PA measured using this questionnaire lacked precision as demonstrated by the inability of the questionnaire to accurately quantify the amount of PA for individuals (123). Further, the measurements obtained using PA questionnaires did not correlate ($r < 0.3$) with

objective measures of light or moderate intensity PA (3, 124). One other alternative is the Multimedia Activity Recall for Children and Adults (MARCA), a computer based time instrument that records and construct detailed daily PA through a structured interview format (125). The MARCA has been found to be reliable and valid in individuals with COPD (126). However the measures obtained using the MARCA is not as precise as motion sensors that record exact movements (126). Notwithstanding these limitations, questionnaires are often the only method available to clinicians to measure PA due to their low cost and simplicity (106).

2.4.2 Objective methods to measuring physical activity

Objective methods for measuring PA most commonly use motion sensors to detect body movement, with devices ranging from simple pedometers to more advanced tri-axial accelerometers (3). These devices are used to objectively quantify PA over a period of time, thus they are more accurate in providing individualised and detailed information of body movement and walking than questionnaires (3). Further, individuals with COPD are characterised as less active, thus the use of motion sensors will result in greater precision in detecting slow or low intensity activities (3). In the following text, pedometers and accelerometers are described, with particular emphasis on that the devices that were used in the studies undertaken as part of this thesis.

2.4.2.1 Pedometer

Pedometers, which constitute the simplest motion sensors, are inexpensive and easy to use. They record the number of steps taken (127). Most models comprise a horizontal spring lever that detects vertical displacement of the waist during walking. However other movements in the vertical plane, such as vibrations when seated in a car (3, 50), may also trigger the device and inaccurately record it as a step. Most pedometers are relatively accurate for recording step counts when compared to direct observation among individuals who walk at speeds equivalent to 80 m/min (127). However, pedometers often lack the sensitivity to detect slow or shuffling gait patterns (127, 128) and thus tend to underestimate step count in many individuals with COPD (11, 16). For example, the study by Furlanetto et al (14) involving individuals with COPD, found that the number of steps recorded by a pedometer was

significantly lower than that observed on video at slow walking speeds of 23.3±5.0 m/min (26±26 versus 79±17 steps; $p < 0.05$). This was similarly observed when pedometer readings were compared to video recordings at a faster walking speeds of 48.3±8.3 m/min (73±35 versus 105±20 steps; $p < 0.05$) (14).

2.4.2.2 StepWatch™ Activity Monitor

The StepWatch™ Activity Monitor (SAM) (OrthocareInnovations, Seattle, Washington, US) not only is able to record step counts at walking speeds beyond 80 m/min (129), it also overcomes some of the problems associated with the pedometer underestimating steps during slow walking. This monitor has a dual axis microprocessor-controlled step counter and records steps taken in a variety of gait styles and cadence (18). The SAM is a small (2 x 7.5 x 5 cm) and lightweight (38 g) step counter that attaches to the right ankle and has a sampling frequency of 128 Hertz (Hz) (130). The SAM costs approximately AUD \$525 each, and the computer interface docking station costs AUD \$2,500. The SAM has been shown to accurately measure step counts in populations who walk very slowly at < 48m/min (with up to 99% accuracy) (11, 16) including individuals who use mobility aids to ambulate (17). Further, measurements of the number of steps obtained using the SAM was accurate at 99.7±0.7 % when compared to manual counting at various walking speeds ranging from 27 to > 80 m/min (129). Step counts derived from the SAM in 22 healthy participants have also yielded excellent intra-device reliability (intraclass correlation coefficient [ICC] = 0.96) (131). Despite the accuracy of the SAM demonstrated by these studies (11, 16-18, 129), gait speed was not controlled during testing in two of the studies (11, 17). Further, the accuracy of these devices has not been explored in individuals with COPD, who are known to walk slowly during daily activities.

2.4.2.3 Accelerometers

Accelerometers are technologically more advanced motion sensors that measure acceleration along an axis to record rate and intensity of body movement in up to three planes, namely anterior-posterior, medio-lateral and vertical (130). These sensors are either uni-axial or multi-axial and they generate an electrical output proportional to the acceleration detected (132). The advantage of using

accelerometers is their ability to accurately determine the quantity and intensity of movement (133). Some accelerometers have the capacity to discriminate brisk walking from other domestic activities (134).

Uni-axial accelerometers detect motion along the vertical plane only (35). The ActivPAL™ (PAL Technologies Ltd, Glasgow, Scotland, United Kingdom [UK]) is one such uni-axial device that is small (0.7 x 5.3 x 3.5 cm) and lightweight (20 g) (135). The ActivPAL™ costs AUD \$550 for each unit with associated costs including software licence which costs AUD \$3,100. The ActivPAL™ attaches to the anterior aspect of the right thigh (130). The ActivPAL™ combines data pertaining to gravitational acceleration and acceleration from segmental movement of the thigh (136) and has been shown to yield accurate measurements of the time spent being less active (supine/sitting) versus active (standing/walking) in community-dwelling older adults (19). Step counts derived from the ActivPAL™ in 22 healthy individuals have yielded excellent intra-device reliability (ICC = 0.95) (131). The ActivPAL™ was also found to be 99% accurate when compared to video recordings for measuring the cadence of 20 healthy individuals walking at speeds ranging from 54 to 119 m/min (136). The accuracy of the ActivPAL™ compared to video observations in 10 healthy individuals carrying out a range of activities ranged from 88% to 100% (137), with accuracy the lowest for short duration walks separated by short intervals of standing lasting only 1 to 2 sec (137). Of note, these studies were all conducted in a laboratory setting with healthy individuals and thus may not reflect activity in real time in the community, especially for those individuals who walk slowly or with altered gait patterns. Uni-axial accelerometers are also known to be inaccurate at detecting PA with static trunk movements, such as cycling (35).

2.4.2.4 SenseWear armband

Technology in the area of multi-sensor motion devices is advancing rapidly and a new generation of sensors have become available. The SenseWear armband (BodyMedia Inc., Pittsburgh, Philadelphia, US) is one such device and is worn on the bulk of the triceps brachii muscle. It measures 2.4 x 8.8 x 5.6 cm, weighs 82g (135), and is considered to be a portable metabolic monitor that integrates multi-axial accelerometry with non-invasive physiologic sensors that detect galvanic skin

resistance, heat flux, body temperature and near body ambient temperature (138). The galvanic skin response is the conductivity of the wearer's skin which varies dependent on physical and emotional stimuli. The heat flux sensor measures the amount of heat dissipated by the body by measuring the heat loss along a thermally conductive pathway between the skin and a vent on the side of the SenseWear armband. The body temperature and near body ambient temperature are measured by sensitive thermistors. The SenseWear armband combines the signals from all the sensors and utilises pattern detection algorithms to estimate energy expenditure across the spectrum of activities of daily living (139, 140). The SenseWear device costs approximately AUD \$1,355 per device and an additional AUD \$1,765 for the USB dongle key and software licence. Compliance with wearing this device has been found to be excellent. For example, the median wearing time of the SenseWear armband in 134 individuals with COPD in the Netherlands and UK was at least 98%, with at least 94% of individuals wearing the armband for a minimum of 5 days (duration each day \geq 22 hours) (141).

The SenseWear armband has been shown to provide an accurate estimate of energy expenditure when compared to indirect calorimetry (142) and energy expenditure measured using the doubly labelled water (DLW) technique (143) in healthy adults. In the study by Jakicic et al (142), the ICC of total energy expenditure between indirect calorimetry and SenseWear armband data for aerobic exercises was > 0.8 . In the study by Johannsen et al (143), regression analysis showed significant associations for total energy expenditure measured using the SenseWear armband and DLW ($R^2 = 0.68$; $p < 0.001$). In studies involving individuals with COPD, Hill et al (13) found that the SenseWear armband was sensitive and accurate in measuring energy expenditure while completing five tasks comprising supine lying, sitting, standing and walking at two different speeds. In this study, the SenseWear armband was able to detect small changes in energy expenditure that accompanied a modest increase in walking speed of 14 m/min (13). The overall difference between energy expenditure measured using the SenseWear armband and indirect calorimetry was small (-0.2 metabolic equivalents [METs]) with a limit of agreement of 1.3 METs (13).

Although the SenseWear armband has been shown to be accurate at measuring energy expenditure, it appears to significantly underestimate step count compared to manual counting and video observation. Langer et al (12) found that, compared to manual counting, the SenseWear armband underestimated step counts during 53 minutes of walking by 465 steps (95% CI, -717 to 213 steps). Similarly, Furlanetto et al (14) found that the SenseWear armband significantly underestimated step count when compared to video observation at walking speeds ranging from 23.3 ± 5.0 to 80.0 ± 13.3 m/min. When compared to direct observations, Hill et al (13) found step rate recorded by the SenseWear armband was lower at slow walking speeds of 51.4 ± 11.1 m/min (77 ± 26 versus 87 ± 9 steps/min; $p = 0.04$), but at faster walking speeds of 65.4 ± 12.4 m/min, the steps recorded were similar to that observed (93 ± 22 versus 99 ± 10 steps/min; $p = 0.22$). Besides underestimating steps at slow walking speeds, the SenseWear armband has also been shown to underestimate the number of steps taken when a WW was used during walking (13). The lack of movement of the upper arm and body position when arms are fixed on the WW may dampen the input from the accelerometry in the SenseWear armband, thus reducing the step rate compared to direct observation (24 ± 29 versus 87 ± 9 steps/min; $p < 0.01$) (13).

2.4.3 'Gold standards' of measuring physical activity

There are several 'gold standards' for measuring PA and these include direct observation, video recording, global positioning system (GPS) and energy expenditure measured using DLW.

Direct observation of PA involves observers watching or video-recording PA in order to quantify activities undertaken by individuals (144). However, such direct observation is intrusive on the individual's privacy and time consuming, thus impractical in the home environment (3, 145).

Global positioning system technology uses radio signals broadcast from satellites orbiting the earth to identify structures such as transportation and green space to address questions about PA (146). Although GPS technology is portable, non-intrusive and is able to measure movement continuously outdoors, the number of GPS satellites available limits the ability to detect PA in an individual (145). The

other disadvantage for GPS receivers are that they are limited in detecting radio signals especially indoors (139). Thus the GPS technology is recommended to be used in conjunction with accelerometers to augment measurements of PA in the adult population (145).

The DLW method of measuring energy expenditure is an isotope-based technique to estimate carbon dioxide production during the interval between the first and last body fluid samples, and thus energy expenditure (147). This method is often described as the ‘gold standard’ for the measurement of total energy expenditure, but its usefulness is limited by its laboratory setting, technical demands, participant burden and excessive cost (approximately AUD \$1,500 per person) (139, 145, 147).

2.4.4 Optimising the measurement of physical activity

Overall, the measurement of PA is known to be highly variable (148). Several factors appear to influence the measurement of PA including the number of days over which PA is monitored (149), whether measurements are taken over weekdays versus weekend days (150) as well as the impact of seasonal variation (151).

In order to minimise individual burden and reliably measure daily average PA outcomes that reflect an individual’s habitual activity, it is necessary to determine the minimum number of days individuals are required to wear a motion sensor to measure PA (147, 149). Habitual activity is highly variable among healthy adults (148, 150) and therefore 3 to 7 days of accelerometer monitoring has been recommended to obtain a reliable estimate of usual PA (148-150). However, individuals with moderate to severe COPD have been shown to have a smaller day-to-day variation in PA compared with their healthy counterparts and therefore a minimum of 3 days of PA data collection has been suggested to be sufficient to adequately capture average daily activity for individual with moderate to severe COPD (106). In the study by Pitta et al (1), a between-day ICC of ≥ 0.70 was considered acceptable to determine the number of days required to obtain a reliable measure of PA in individuals with COPD. These authors found a very low measurement error of the motion sensor that they were using (Dynaport activity monitor), and found that only 2 weekdays of PA monitoring were necessary to accurately assess the time spent in various postures (lying down, sitting, standing and

walking) and movement intensity during walking for the 33 individuals which included 18 with mild to very severe COPD [GOLD grades I to IV] and 15 age-matched healthy peers (1). However, Watz et al (106) found that for an ICC of ≥ 0.70 , at least 3 days of PA monitoring were necessary for individuals with mild to severe COPD (GOLD grades I to III), while those individuals with very severe COPD (GOLD grade IV) only required 2 days of PA monitoring. Another study found that at least 3 days of data were required for motion sensor to provide a stable comparison with an activity recall questionnaire (ICC = 0.69) to measure of PA in individuals with moderate to severe COPD (106, 152). Thus, a minimum of 3 days of PA data collection would be appropriate to adequately capture average daily activity for individuals with COPD.

Although majority of the above studies suggest that a minimum of 3 days of PA monitoring is required in order to provide an accurate assessment of PA, it is important to determine whether consecutive days or a combination of any 3 days are required in order to gain a reliable measurement of PA in individuals with COPD. Some studies involving healthy adults have demonstrated that reduced PA occurs on Sundays compared to other days of the week (150, 153). However, earlier work showed that there was little day to day variability in PA in sedentary individuals with COPD (50). A more recent study involving 23 individuals with COPD with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades ranging from II to IV, found that accelerometer activity counts were similar between three within-week measurement periods or between weekdays and weekend days ($r > 0.97$; $p < 0.001$) (103). Based on these results, it would seem that any 3 days of PA measurement, regardless of weekdays or weekend days, were sufficient to assess PA in individuals with COPD.

Seasonal variation may also affect PA, with lower levels of PA being observed during winter compared to summer ($p = 0.02$) (151). In the UK, individuals with COPD who started a PRP in winter attained a greater change in daily PA compared to those who commenced a PRP in summer ($p = 0.04$) (151). In this study by Moy et al (154), individuals with COPD who had their baseline visit in winter and follow-up in spring, experienced a significant increase in step count, while those who had their

baseline visit in autumn and follow up in winter had a decline in step count, after controlling for baseline step count ($p = 0.013$).

In summary, individuals with COPD appear to be relatively less active and tend to walk slower than their healthy peers. This inactivity has a negative impact on clinical outcomes, such as exercise capacity and HRQoL. There are different approaches to measuring PA and a minimum of 3 days may be sufficient to assess PA in individuals with COPD.

PART 3

Given that individuals with COPD are generally less active (1, 104), which can impact on health care utilisation (115), it is important to enhance PA in these individuals. The following sections describe strategies that may increase PA among those with COPD.

2.5 Strategies that may increase physical activity in individuals with COPD

Physical inactivity in individuals with COPD appears to be related to important healthcare outcomes such as the frequency of exacerbations, hospitalisations and mortality (118, 155). Strategies that have the potential to increase PA levels include the use of ambulatory oxygen, pharmacotherapy such as bronchodilators, lung transplantation, the use of a WW and pulmonary rehabilitation.

Ambulatory oxygen

The provision of ambulatory oxygen to individuals with COPD has been shown to confer significant acute increases in exercise tolerance (156-159). For example, compared with exercise testing performed with the individuals breathing room air, the time to symptom-limited cycling at work rates equivalent to 75% of peak work rate increased by 5.2 minutes when breathing supplemental oxygen ($p < 0.05$) (156). Similarly, the use of 2 L/min of ambulatory oxygen increased 6MWD equivalent to 3 to 20% of baseline measures, depending on the severity of airflow (157). Such improvements appear to be dose-dependent, with maximal gains achieved using a fraction of inspired oxygen equivalent to 0.5 (160). The mechanisms underpinning the gains in exercise tolerance with ambulatory oxygen relate mainly to reductions in

ventilatory demand, dynamic pulmonary hyperinflation and dyspnea at submaximal exercise intensities (73). Further, during cycle-based activity, the administration of ambulatory oxygen has been shown to optimise oxygen delivery to quadriceps and increase the anaerobic threshold (161). Despite these gains, which were demonstrated in the laboratory setting, the effects of providing ambulatory oxygen for use in the home setting on PA are limited. There were only two randomised controlled trials (RCTs) that investigated the effect of ambulatory oxygen provided in the home over an 8-week period (162) and over a 12-week period (163). Neither demonstrated any change in PA. This may be related, at least in part, to the fact that the individuals with COPD were expected to transport their oxygen cylinders using back-packs and the weight may have offset any advantage derived from the use of ambulatory oxygen during PA (162). Other possible reasons include the poor portability of the cylinder, difficulty with changing the regulator, fear of dependence on oxygen and embarrassment when using ambulatory oxygen (163). Of interest, this study reported an increase in oxygen cylinder usage over the 8-week study period, suggesting that individuals may have been gradually perceiving a benefit or became dependent on the oxygen, but this was not evident at the time the follow-up assessments of PA were completed (162). Additionally, ambulatory oxygen did not significantly increase domestic activity or activity spent outside the home, at least in the short term (162).

Bronchodilators

There is a lack of evidence regarding the effect of bronchodilators on PA. In theory, bronchodilators have the potential to improve PA by their effect of increasing airway calibre and alleviating airflow limitation (164), thereby reducing the work of breathing and dyspnea. Only one study was identified that evaluated PA when a bronchodilator (tiotropium) was given in conjunction with pulmonary rehabilitation (165). In this study where all participants completed a 12-week PRP, the group that received tiotropium improved self-reported PA by 262 ± 96 minutes from baseline ($p = 0.013$), while the placebo group improved PA by 60 ± 93 minutes ($p = 0.529$) (165).

Lung transplantation

One intervention that appears to be effective at increasing PA is lung transplantation, particularly when combined with exercise training. A cross-sectional study demonstrated that lung transplant recipients (66±48 months post-transplant) were significantly more active compared to individuals awaiting lung transplantation (6,642±2,886 versus 1,407±1,166 steps/day; $p < 0.001$) (166). In another study where PA was assessed 3 months post-lung transplantation, the participants receiving usual care where they were only advised to increase participation in daily PA increased daily step count by 750 steps whereas the participants who received supervised exercise training three times weekly increased their daily step count by 2,100 steps; a difference of 1,376 steps/day (95% CI 481 to 2,269 steps/day; $p = 0.004$) (167). Both groups continued to increase their PA at 1 year post-transplant although the group that had post-transplant rehabilitation for 3 months increased their PA significantly more than the control group (3,017 steps/day; 95% CI 1,185 to 4,849 steps/day; $p = 0.002$) (167). This implies that in individuals with COPD who underwent transplantation, rehabilitation post-lung transplantation may augment daily PA.

Other strategies

Other strategies that may optimise daily PA in individuals with COPD include the use of a WW and participation in supervised exercise training. The effects that these two strategies have on PA form the basis of two studies within this thesis. Therefore the following sections provide a detailed description of the potential mechanisms by which these interventions may confer gains in PA in individuals with COPD.

2.5.1 Effects of wheeled walkers on respiratory muscle mechanics

A WW, also called a rollator frame, is a gait aid that has four wheels, hand brakes, a basket for carrying items and a seat for rest (22, 168). Individuals with COPD often report less dyspnea when pushing a shopping trolley due to the forward lean position and fixed shoulder girdle (169). As early as 1957, a case report of a patient with emphysema described that the use of a portable walking aid with the forward lean posture allowed the individual to increase tidal volume and exercise tolerance (170). Adopting a forward lean position optimises the pressure-generating capacity of the inspiratory muscles, most likely because it improves the length-tension relationship

of the diaphragm (171, 172). O'Neill et al (172) demonstrated that the forward lean position was the most effective of six different positions (i.e. standing, supine, upright seated, seated leaning forward at a 45° angle as well as right and left lateral decubitus) at relieving dyspnea in 40 individuals with COPD. This forward lean position is likely to decrease the level of neuromechanical dissociation, defined as the mismatch between the afferent input from the mechanoreceptors of the respiratory system and the efferent output or motor output to breathe, which is perceived by the individual as a reduction in dyspnea (173). Besides this, the arm bracing posture when using a WW in the standing position has been shown to increase maximum voluntary ventilation (MVV) (168, 174), which may also contribute to a reduction in dyspnea (22, 174). The increased ventilatory capacity associated with arm bracing is most likely due to the increased capacity to use the accessory muscles of respiration, namely the serratus anterior, scalenes and sternocleidomastoid (175). Thus, the arm bracing posture adopted when using a WW may allow individuals with COPD to rely on the accessory muscles to assist in respiration (176). This reduction of dyspnea would likely explain the improvement in functional capacity observed when a WW was used in individuals with COPD (21, 22, 177, 178).

2.5.1.1 Effect of wheeled walkers on 6-minute walk distance

Three studies have shown that the use of a WW in individuals with COPD increased the 6MWD as compared to walking unaided (22, 177, 178). In two of these studies, both of crossover design, participants increased their 6MWD when walking with a WW compared to walking without a WW ([259±28 versus 226±28 m; $p < 0.005$ (177)] and [462 m (interquartile range 424 to 477 m) versus 416 m (interquartile range 396 to 435 m); $p = 0.04$ (22)]). This improvement in 6MWD was also demonstrated in a RCT where 6MWD was higher in participants randomly allocated to walk with a WW than those allocated to walk without a WW (baseline: 292±67 versus 263±67 m, $p = 0.013$; post 8 weeks of being provided with a WW: 283±65 versus 259±68 m, $p = 0.013$) (178). This positive impact of the WW on 6MWD was however not seen in one randomised crossover study involving 40 individuals with COPD (312±17 m without WW versus 317±16 m with WW; $p = 0.3$) (21). However, a sub-analysis in this study demonstrated that greatest gains were conferred when a

WW was used by participants who had the lowest unaided 6MWD. In this sub-analysis, 19 participants who walked < 300 m unaided improved their 6MWD from 220±12 m without a WW to 243±14 m with a WW ($p = 0.02$) (21).

2.5.1.2 Effect of wheeled walkers on the fear of falling

Wheeled walkers are often recommended to improve ambulation and reduce the risk of falls among the elderly (179). Individuals with COPD have a susceptibility to falls, with approximately 32% of 101 participants with COPD in an observational cohort study reporting at least one fall over a 6-month period, with most of these falls occurring during an outdoor walking activity (25). This finding is particularly important given data demonstrating a reduction in the balance and coordination of individuals with COPD (27, 180), an impairment that is likely to result, at least in part, from their less active lifestyle (26).

It is possible that as well as decreasing the risk of falling, using a WW may decrease the fear of falling and thus increase confidence with walking. Among 80 individuals with COPD, 45% of those who had experienced a prior fall reported a fear of falling, while only 23% who had not experienced a prior fall expressed this fear (181). Among those participants who expressed a fear of falling, 50% reported activity avoidance because of this fear whereas there was no activity avoidance reported by those without a fear of falling (181). Solway et al (21) in a study involving 40 individuals with COPD, found that 60% reported feeling safer when using a WW during the 6-minute walk test (6MWT).

Therefore, it seems possible that individuals with COPD who have marked functional limitation due to intolerable dyspnea or fear of falling, may be able to walk more during daily life if provided with a WW (20).

2.5.2 Pulmonary rehabilitation for individuals with COPD

Pulmonary rehabilitation is defined as an evidence-based, multidisciplinary and comprehensive intervention for individuals with COPD (5, 6), where exercise training is the cornerstone of pulmonary rehabilitation (5). Exercise training has been shown to reduce dyspnea and fatigue (5-7), increase exercise capacity and improve HRQoL (5-7).

2.5.2.1 Effect of pulmonary rehabilitation on exercise capacity

Randomised controlled trials of pulmonary rehabilitation have demonstrated that 6 to 12 weeks of lower limb training increased field-based walking tests distance up to 80 m, treadmill endurance by 10 minutes and cycle ergometer time at submaximal work rates by 5 minutes in individuals with COPD (182). A meta-analysis of 16 trials that used 6MWD as an outcome in individuals with COPD favoured exercise training over control (no exercise training) with a weighted mean improvement of 48 m (7). Exercise training such as walking or cycling can lead to clinical improvement in exercise capacity (39, 183).

In individuals with COPD, physiological adaptation of the quadriceps to exercise training has been shown via muscle biopsies (184, 185). Following a PRP, there is a significant increase in the mean cross sectional area of quadriceps muscles as well as an increase in oxidative muscle fiber type in individuals with COPD (186). In addition, exercise training also improves oxidative enzyme capacity in muscles (185, 187), increases capillary and mitochondrial density (188), and reduces lactic acidosis for a given work rate (189). The improvement in exercise capacity and the morphological adaptations of the quadriceps muscles to exercise training has been shown to be consistent across GOLD grades II to IV (186). Further, Gosselin et al (188) showed that physically active individuals with COPD also had the capacity to further improve their exercise capacity after PRP. The improvement in oxidative capacity of the quadricep muscles from exercise training has the potential to lead to less alveolar ventilation which may reduce dynamic hyperinflation and thus decrease exertional dyspnea and fatigue (6). However the aforementioned studies were conducted using only cycle based training (185-189) which is dependent on the availability of the cycle equipment and space, unlike walking which is a cheap and easily available training modality (39).

Walking exercise training as compared to cycling training has been shown to result in greater improvements in exercise capacity for individuals with COPD. In the study by Leung et al (39) which compared supervised ground walking training to cycling training over 8 weeks, the participants randomised to ground walking demonstrated an improvement in endurance shuttle walk test (ESWT) performance to a greater extent than those participants randomised to supervised cycling training (279 sec;

95% CI 70 to 483 sec). There are a number of studies that have studied the effect of walking training on exercise capacity, but in many of these studies walking training was part of a comprehensive exercise training program (7, 190, 191). There are two randomised controlled studies that had a solely supervised walking training program (40, 192). Both of these studies reported an improvement in 6MWD (40, 192). As walking is an integral part of daily life for individuals with COPD (9), it is possible that walking as a sole modality of supervised exercise training may confer greater gains in daily PA than other exercise modalities such as cycling.

2.5.2.2 Effect of pulmonary rehabilitation on dyspnea and fatigue

Dyspnea and fatigue are the two most common symptoms experienced by individuals with COPD (193). In a Cochrane review of 11 RCTs, pulmonary rehabilitation was shown to be effective at relieving dyspnea and fatigue as determined from the forest plots of the dyspnea and fatigue scores of the Chronic Respiratory Disease Questionnaire (CRDQ) (mean difference of 1.0 points per item and 0.92 points per item, respectively) (7). The improved exercise capacity may explain the reduction in these symptoms (5). Desensitisation may also be one possible mechanism to explain the benefit of pulmonary rehabilitation on dyspnea and fatigue, with the hypothesis that fear is alleviated by repetitive performance of the same exercise in a safe and supervised environment (194).

2.5.2.3 Effect of pulmonary rehabilitation on health-related quality of life and feelings of anxiety and depression

The health status of individuals with COPD has been shown to improve with pulmonary rehabilitation (5), with a meta-analysis showing that at least 4 weeks of exercise training is sufficient to result in an improvement in HRQoL (195). Measurement of HRQoL using disease-specific questionnaires, namely the CRDQ and SGRQ has been found to provide a valid measure that is responsive to the effects of pulmonary rehabilitation (7, 196).

In individuals with COPD, feelings of anxiety and depression are common (197). There have been numerous studies that have found that exercise training can significantly reduce anxiety and depression. A meta-analysis found that a

comprehensive PRP that included exercise sessions up to three times a week along with education and psychosocial support, reduced anxiety and depression more than standard medical care in individuals with COPD (198). Another meta-analysis by Coventry et al (199) found that exercise interventions, with or without psychological components within PRP, were the only sub-group intervention that reduced both depression and anxiety.

In summary, strategies such as the use of ambulatory oxygen, the use of bronchodilators, lung transplantation, the use of a WW and pulmonary rehabilitation may have the potential to increase PA among those with COPD.

PART 4

The cornerstone of pulmonary rehabilitation is supervised exercise training (5) and exercise training may be able to change PA. Therefore, a systematic review and meta-analysis was undertaken on the impact of exercise training on PA in individuals with COPD as part of this PhD research. This systematic review and meta-analysis has been published (55) and is reproduced in the following sections.

2.6 Systematic review and meta-analysis

The aim of this review was to systematically search the literature and undertake a meta-analysis of data from studies that have evaluated the effect of exercise training on PA in individuals with COPD.

2.6.1 Data source

Study identification began with electronic searching of computerised databases, namely MEDLINE, PubMed, EMBASE, CINAHL, Physiotherapy Evidence Database (PEDro) and Cochrane Central Register of Controlled Trials from inception to week 27 in 2010 (Table 2-2). The subject headings used in the search were ‘COPD/chronic obstructive pulmonary disease’, ‘therapy’ and ‘exercise’ with key terms comprising of ‘accelerometer’, ‘pedometer’, ‘physical activity’, and ‘energy’. Secondary searches included hand searching reference lists of all identified studies and PubMed ‘related articles’ function. Clinical trials registries were also reviewed to identify any RCTs that may have been ‘in press’.

2.6.2 Study selection

Studies were eligible for inclusion if they: (i) were written in English, (ii) recruited individuals with COPD, (iii) investigated the effect of supervised exercise training of at least 4 weeks in duration on PA, (iv) measured PA using motion sensors and, (v) reported PA in absolute values such as steps or activity counts. Studies that utilised any design other than case reports were eligible for inclusion. Where necessary, authors were contacted to obtain PA data in absolute values. If the authors did not respond, the study was excluded from the meta-analysis.

Table 2-2: Search strategy (Limits: Humans; English language).

Searches	Database	No. of records
1 = Chronic obstructive pulmonary disease (COPD) 2 = Therapy (Occupational therapy / Relaxation therapy / Behavior therapy / Exercise therapy / Respiratory therapy / Physical therapy/ Combined modality therapy) 3 = Motor activity 4 = Accelerometer / Pedometer 1 + 2 + 3 + 4	MEDLINE 1950 to 7 th July 2010	5
1 = Chronic obstructive pulmonary disease (COPD) 2 = Exercise (Treadmill exercise / Leg exercise / Open kinetic chain exercise / Breathing exercise / Aerobic exercise / Static exercise / Aquatic exercise / Exercise intensity / Dynamic exercise / Isokinetic exercise / Anaerobic exercise / Isotonic exercise / Closed kinetic chain exercise / Arm exercise / Exercise tolerance / Exercise / Stretching exercise / Muscle exercise / Isometric exercise) 3 = Activity (Motor activity / Physical activity / Daily life activity) 4 = Therapy (Respiratory therapy student / Maintenance therapy / Therapy effect / Therapy / Therapy delay / Recreational therapy / Physical therapy education / Physical therapy student / Movement therapy / Device therapy / Occupational therapy practice / Occupational therapy education / Occupational therapy student / Therapy resistance) 1 + 2 + 3 + 4	EMBASE 1988 to 6 th July 2010	385
COPD AND Physical activity	PEDro Accessed on 7th July 2010	20

Table 2-2: Continued

<p>1 = Chronic obstructive pulmonary disease (COPD) 2 = Therapy (Respiratory therapy student / Maintenance therapy / Therapy effect / Behavior therapy / Therapy / Therapy delay / Recreational therapy / Physical therapy education / Physical therapy student / Movement therapy) 3 = Physical activity 4 = Exercise (Treadmill exercise / Leg exercise / Open kinetic chain exercise / Breathing exercise / Aerobic exercise / Static exercise / Aquatic exercise / Exercise intensity / Dynamic exercise / Isokinetic exercise / Anaerobic exercise / Isotonic exercise / Closed kinetic chain exercise / Arm exercise / Exercise tolerance / Exercise / Stretching exercise / Muscle exercise / Isometric exercise) 5 = Accelerometer / Pedometer</p> <p>1 + 2 + 3 + 4 + 5</p>	<p>EMBASE 1988 to 6th July 2010</p>	<p>9</p>
<p>1 = Pulmonary 2 = Disease 3 = Therapy 4 = Physical OR Motor 5 = Activity 6 = Accelerometer OR Pedometer</p> <p>1 + 2 + 3 + 4 + 5 + 6</p>	<p>PUBMED Accessed on 7th July 2010</p>	<p>891</p>
<p>1 = COPD 2 = Exercise 3 = Activity</p> <p>1 + 2 + 3</p>	<p>PUBMED Accessed on 8th July 2010</p>	<p>330</p>
<p>COPD and physical activity in Keywords</p>	<p>Cochrane Central Registry of Controlled Trials Accessed on 7th July 2010</p>	<p>171</p>
<p>1 = Pulmonary 2 = Therap* 3 = Physic* OR Motor* 4 = Activ* 5 = Accelerometer OR Pedometer</p> <p>1 + 2 + 3 + 4 + 5</p>	<p>CINAHL 2003 to 2008 Accessed on 7th July 2010</p>	<p>3</p>

2.6.3 Quality of articles

Data were independently extracted using a standardised assessment form. Quality assessment for the RCTs and randomised trials (RTs) was rated using the 10-point PEDro scale (200). This scale uses criteria related to blinding, randomisation, and loss to follow-up with a higher score indicative of superior internal validity (200). Quality assessment for the single-group interventional studies was rated using a modified Downs and Black tool (201). This tool consists of 27 questions, that relate to study description, external validity, internal validity and statistical power (201). To minimise ambiguities, the question pertaining to statistical power was assigned one point if prospective sample size calculations were provided (and 0 points if these details were absent), which resulted in a maximum score of 28 for the Downs and Black tool. This modification has been used previously (202).

2.6.4 Data extraction and analysis

Consistency between two reviewers for both quality assessment methods was calculated using Kappa statistics. Due to the heterogeneity in PA outcome measures, the random-effects approach was used in the meta-analysis. Effect sizes were calculated by dividing the differences in PA (before and after the intervention) by the pooled SD. Regarding interpretation, ≤ 0.2 was considered small, 0.5 was considered moderate and ≥ 0.8 was considered large effect sizes (203). The I^2 test was used to quantify statistical heterogeneity of the studies (204). A value of $\leq 25\%$ reflects low heterogeneity, 50% moderate and 75% high heterogeneity. A p value of < 0.1 was used to indicate that the heterogeneity was not due to chance alone and it would be inappropriate to combine the results in a summary. A funnel plot was assessed visually to detect publication bias where a symmetric inverted funnel shape indicates that bias is unlikely. Comprehensive Meta Analysis version 2.2.050 (BiostatTM, New Jersey, US) was used for meta-analysis.

2.6.5 Results

The search strategy yielded 1,840 records of which 128 (7%) were duplicates and thus excluded (Figure 2-1). Of the remaining 1,712 records, 1,686 (98%) were excluded based on title or abstract and 19 (1%) were excluded after reviewing the full text. There were no RCTs that met our study criteria. A total of seven studies met

the criteria for inclusion; two (29%) were RTs in which two groups of participants received different interventions, both of which were designed to optimise PA, and five (71%) were single-group interventional studies in which all participants received the same intervention (Figure 2-1). Authors of two of the studies were contacted for PA data in absolute values.

2.6.5.1 Quality of articles

Tables 2-3 and 2-4 present the quality assessment score for each of the RTs and single-group studies. Reviewers agreed on 100% of all PEDro items (Kappa statistic = 1). The mean \pm SD PEDro score for the RTs was 5 \pm 0 points. Reviewers agreed on 96% of all Downs and Black items with a Kappa statistic of 0.92. The mean \pm SD Downs and Black score was 19 \pm 3 points.

2.6.5.2 Participants characteristics

Tables 2-3 and 2-4 summarise the participant characteristics of the RTs and single-group interventional studies. The sample sizes ranged from 8 (31) to 116 (36). Considering all studies together, the participants were predominantly male (n = 419/582, 72%). Based on the FEV₁ expressed as a percentage of the predicted normal value, participants in most studies had severe airflow obstruction (205).

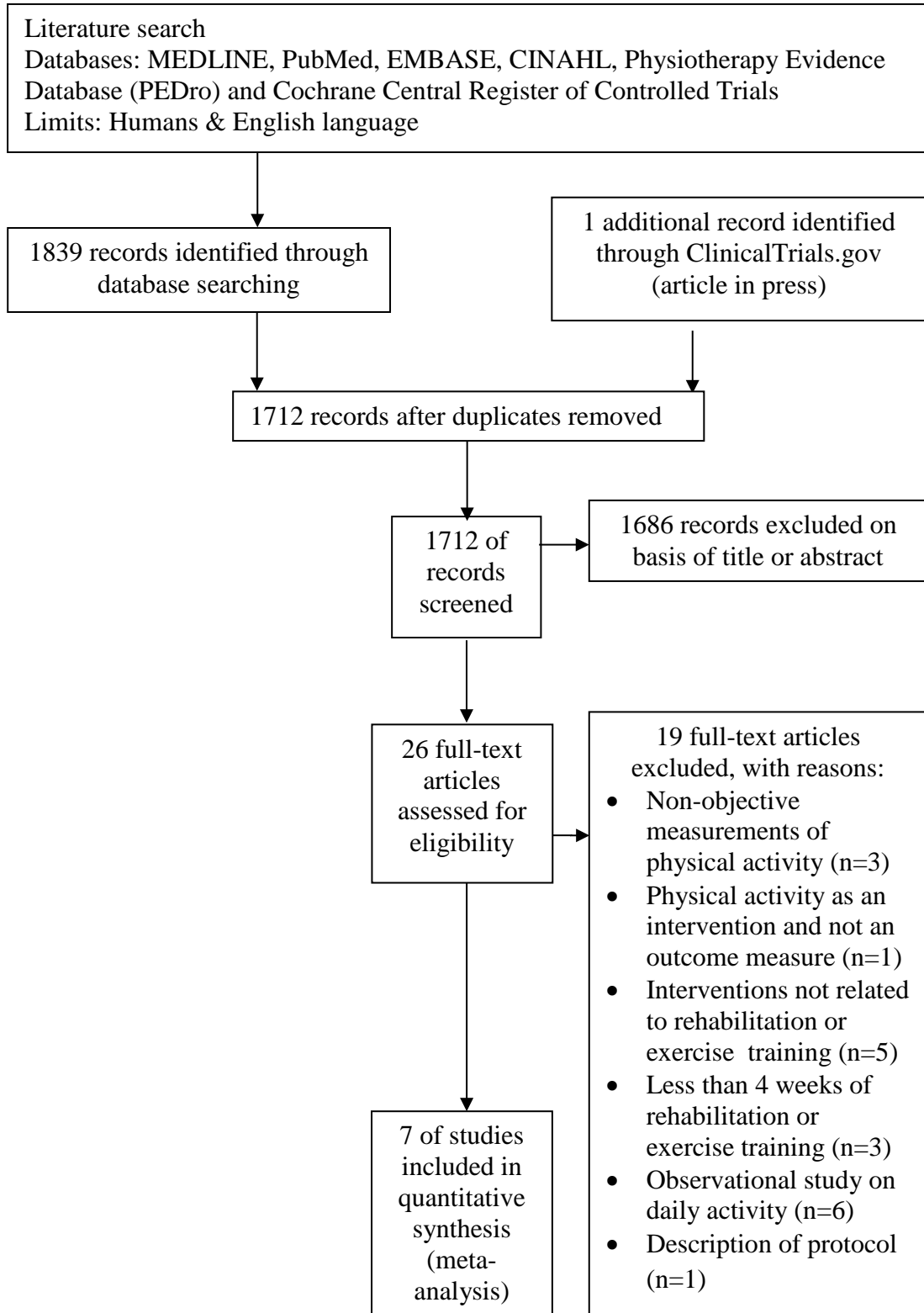


Figure 2-1: Flow of information through the different phases of the systematic review.

n, number of articles.

Table 2-3: Characteristics of study participants of randomised trials.

Study	PEDro score	Sample size (n)	Gender (M/F)	Age (years)	BMI (kg·m ²)	FEV ₁ (L) (%pred)	Protocol
Sewell 2005 (34)	5	90	51/39	67.3±8.4	N/A	0.97±0.45	Individually targeted exercise program (ITEP) performed twice a week. One day comprised aerobic exercise and the other day comprised exercises based on daily functional activities identified during the Canadian Occupational Performance Measure + 2 hours of education per week
		90	60/30	69.3±8.7	N/A	0.93±0.39	General exercise program (GEP) performed twice a week. One day comprised aerobic exercise and the other day comprised standard exercises including step-ups, sit to stand and stationary cycling, wall push-ups, small and large arm circling and shoulder shrugs trunk flexion, trunk rotation and pelvic tilt + 2 hours of education per week
de Blok 2006 (31)	5	10	5/5	65.7±10.4	29.3±8.4	1.44±0.80 (52±22%)	Pulmonary rehabilitation exercise program + dietary + psychosocial-education modules + lifestyle PA counselling based on pedometer data
		11	4/7	62.5±12.3	28.2±6.6	1.24±0.62 (43±13%)	Pulmonary rehabilitation exercise program + dietary + psychosocial-education modules

Data are mean±standard deviation. BMI, body mass index; F, female; FEV₁, forced expiratory volume in one second; kg, kilograms; L, litres; M, male; m, metres; n, number of participants; %pred, percent predicted.

Table 2-4: Characteristics of study participants of single-group interventional studies.

Study	Downs & Black score	Sample size (n)	Gender (M/F)	Age (years)	BMI (kg·m ²)	FEV ₁ (L) (%pred)	Protocol
Steele 2003 (206)	14	38	37/1	63.7±7.8	87±4.6 kg	1.2±0.5 (39±17%)	Twice weekly exercise classes. On completion of the first 2 to 3 weeks of the program a home exercise program was given and encouraged at least 3 days a week
Pitta 2008 (33)	21	29	23/6	67±8	25±6	- (46±16%)	Multi-disciplinary rehabilitation including education, support and/or counselling, circuit exercise training (cycling, walking, strength training for quadriceps, pectoralis and triceps, arm cranking and stair climbing) Months 1 to 3, exercise was performed 3 times a week; months 4 to 6, exercise was performed 2 times a week
Walker 2008 (38)	17	23	12/11	66±9	24.4±4.4	0.93±0.32 (36±12%)	2 supervised + 1 unsupervised exercise sessions per week comprising whole body endurance exercises + peripheral muscle strengthening
Dallas 2009 (32)	21	45	21/24	69±8	27±5	(45±18%)	Exercise classes 2 to 3 times per week. Multi-modality aerobic and strength training of lower and upper extremities + education + psychosocial support
Steele 2010 (36)	20	20* 116 [†]	130/6	67.0±9.0 66.8±10.4	28.6±6.3 30.8±7.5	- (36±15%) - (40±16%)	Twice a week rehabilitation-progressive resistance exercises with hand weights, elastic resistance tubing, and/or weight machines. Cardiovascular/ endurance training included use of treadmills, stationary cycles, NuStep, and upper extremity ergometers.

Data are mean±standard deviation. *COPD participants who had an exacerbation during the study; [†]COPD participants who had no exacerbation during the study; 10 participants did not complete the study. COPD, chronic obstructive pulmonary disease; BMI, body mass index; F, female; FEV₁, forced expiratory volume in one second; kg, kilograms; M, male; m, metres; n, number of participants; %pred, percent predicted.

2.6.5.3 Interventions and methods for measuring physical activity

The duration of supervised exercise training ranged between 6 weeks and 6 months (31-34, 36, 38, 206). The monitors used to measure PA comprised the NL-2000 pedometer (32), the Yamax Digi-Walker SW-200 pedometer (31), the DynaPort Activity Monitor (33), the Z80-32K Activity Monitor (34), the Actiwatch (38), the TriTrac-R3D[®] accelerometer (206) and the RT-3 accelerometer (36).

2.6.5.4 Effects on physical activity

Tables 2-5 and 2-6 summarise the findings of the RTs and single-group studies. In the RTs, both groups received exercise training. One study compared an individualised targeted exercise program (ITEP) based on daily activities with a general exercise program (GEP) (34), and the other investigated the effect of using a pedometer to provide feedback regarding walking targets, over and above a program of supervised exercise training (31). As both treatment groups in these two studies examined the effect of exercise training on PA, we entered the data from each arm into the meta-analyses. The intervention for all five single group studies comprised supervised exercise training at least twice a week. Asymmetry was observed in the funnel plot for PA in the RTs and single-group interventional studies (Figure 2-2), suggesting that we could not exclude publication bias. Taken together, PA data entered into the meta-analysis from the RTs and the single-group studies were homogeneous ($I^2 = 0\%$, $p = 0.60$). The effect size for PA though significant was small (0.12; $p = 0.01$) (Figure 2-3).

Table 2-5: Summary of findings for randomised trials.

Study	Duration of intervention	Days of activity monitoring		PA pre	PA post	Within group findings
Sewell 2005 (34)	7 weeks	2	ITEP	4537±8465 activity counts	5819±5665 activity counts	Improvement of 40.6%, p=0.02
			GEP	3587±4357 activity counts	3835±6453 activity counts	Improvement of 29.2%, p=0.03
de Blok 2006 ^y (31)	9 weeks	4	Added counselling + pedometer	2059±941 steps/day	3594±1657 steps/day	Improvement of 1535 steps/day (75%)
				2312±916 steps/day	2985±1730 steps/day	Improvement of 673 steps/day (29%)
						p=0.24 between groups

Data are mean±standard deviation. GEP, general exercise program; ITEP, individualised targeted exercise program; p, probability; PA, physical activity.

^yData from 8 participants were assessed over 4 days without rehabilitation including 1 weekend day. The 4 days data was used in the meta-analysis as it had a greater effect size than that of the 6 days without rehabilitation (including 2 weekend days) data and 7 days data was excluded as it included rehabilitation. Activity counts rounded to the nearest whole number.

Table 2-6: Summary of findings for single-group interventional studies.

Study	Duration of intervention	Days of activity monitoring		PA pre	PA post	Within group findings
Steele 2003 (206)	8 weeks	5		82±34 VMU	90±38 VMU	p=0.06
Pitta 2008 (33)	3 months 6 months	5		55±26 min/day	59±27 min/day 65±29 min/day	After 3 months; 7% improvement in walking time, p=0.21 After 6 months; 20% improvement in walking time, p=0.008
Walker 2008 (38)	8 weeks	3		82±53 (x10 ³ counts/hr)	117±84 (x10 ³ counts/hr)	Improvement of 36±49 (x10 ³ counts/hr), p=0.002
Dallas 2009 (32)	6-12 weeks	7		207±139 counts/hr	240±153 counts/hr	Improvement of 33±149 counts/hr, p=0.14
Steele 2010 (36)	8 weeks	6	Exacerbation (n=20) Non exacerbation (n=92)	165±143 VMU 163±89 VMU	143±59 VMU 167±81 VMU	No within group data. p=0.56 between those that had an exacerbation and those that did not

Data are mean±standard deviation. hr, hour; min, minutes; p, probability; PA, physical activity; VMU, vector magnitude units. VMU and activity scores rounded to the nearest whole number.

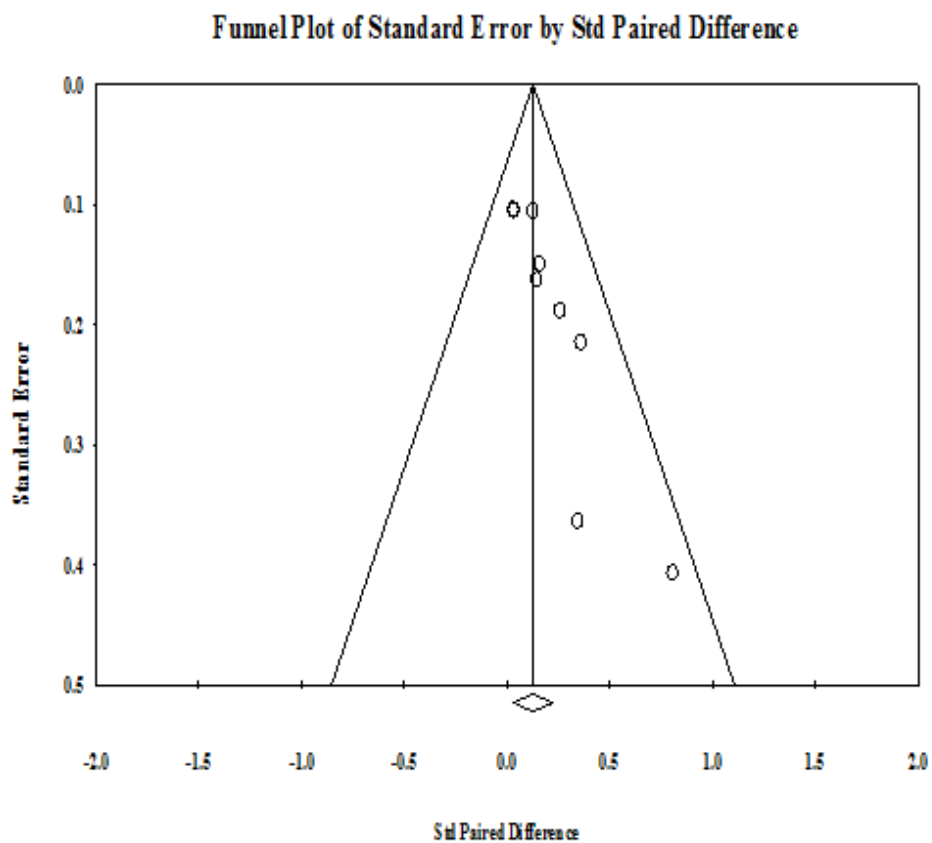
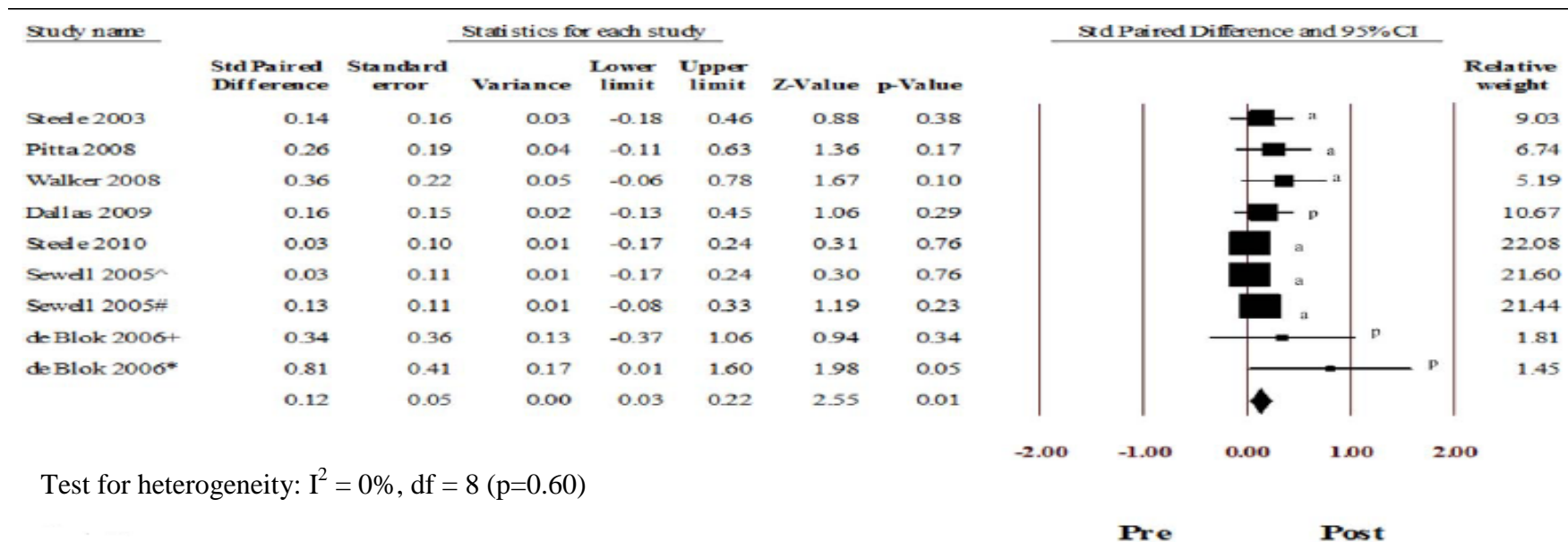


Figure 2-2: Funnel plot of physical activity as an outcome measures in the randomised trials and single-group interventional studies.

The tendency for data points to fall predominantly on the right of the 0 suggests a publication bias may be present. Std, standardised.



Test for heterogeneity: $I^2 = 0\%$, $df = 8$ ($p=0.60$)

Legend:

- Square represents effect of individual study. The size reflects the relative weight of a particular study on the overall analysis.
- Black line represents the confidence interval of each study.
- ◆ Diamond represents the overall effect. The outer edges of the diamond represent the confidence interval.

The two interventions in both randomised trials have been entered separately into this plot where ^ represents the group that completed a general exercise program, # represents the group that completed an individualised targeted exercise program, + represents the group that completed pulmonary rehabilitation and * represents the group that completed pulmonary rehabilitation with counselling and feedback based on pedometer data. a, accelerometer; df, degree of freedom; p, pedometer; p-value, probability value;

Figure 2-3: Forest plot for physical activity measured in the two randomised trials and five single-group interventional studies.

2.6.6 Discussion of findings related to a systematic review and meta-analysis

This is the first systematic review and meta-analysis to evaluate the effect of exercise training on measures of PA in individuals with COPD. The important findings of our review are that; (i) there are no published RCTs that examine the effects of at least 4 weeks of supervised exercise training on PA and, (ii) data from the RTs and single-group interventional studies indicate that, in individuals with COPD, supervised exercise training confers a significant, but small effect on PA.

Regarding the RTs included in this review, the two intervention groups in both RTs demonstrated a similar magnitude of change in PA following the intervention period. This is perhaps not surprising as both groups in these studies received an intervention that aimed to increase PA and it was the effectiveness of an additional strategy (such as feedback using pedometer data or individualisation of exercises) that was being examined. Thus, any difference between the two groups was likely to be small. When the results of the five single-group studies included in this review were considered individually, two (40%) reported a significant increase in PA on completion of the intervention period (33, 38). Relative to baseline measures, one reported an improvement of 20% ($p = 0.008$) (33) while the other reported a difference of 36 ± 49 ($\times 10^3$) counts/hour or approximately 40% ($p = 0.002$) (38). Although the remaining three of the single-group studies reported an improvement in PA, this was not significant (32, 36, 206). When these results of the RTs and single-group studies were combined the effect size for PA was small, but significant (0.14; $p = 0.04$). Exclusion of the data from the RTs from the meta-analysis produced a trivial change in the magnitude of the overall effect size (i.e. from 0.14 to 0.12). To appreciate this change in real terms, using the study by Pitta et al (33) as a reference, an overall pooled effect size of 0.12 or 0.14 is equivalent to an increase of approximately 4.6 or 5.4 minutes of walking per day following the intervention. In addition to this small effect, the wide 95% CIs for data pertaining to five of the seven studies in Figure 2-3 indicates that there was considerable variability in PA between individuals. Our data revealing a modest effect size together with substantial variability suggests that future RCTs that aim to demonstrate an effect of supervised exercise training on PA will require very large sample sizes.

It is possible that the capacity of individual studies to demonstrate a significant increase in PA may be influenced not only by the nature of the intervention, but by other factors such as; (i) the method used to measure PA, (ii) the frequency of supervised exercise training and, (iii) the clinical stability of participants over the duration of the study period. Regarding the outcome measures, earlier work has demonstrated that in individuals with COPD, questionnaires do not yield an accurate measure of PA (1) and pedometers lack the sensitivity to detect steps at the slow walking cadence characteristic of this clinical population (11, 16). In contrast, accelerometers yield accurate measures of PA in individuals with COPD and have emerged as a more reliable choice (3). Given the superior accuracy of accelerometers at measuring PA, we considered the possibility that those studies that utilised an accelerometer to measure PA may have been more likely to demonstrate improvements in PA. Examination of Figure 2-3 revealed that of the five studies which measured PA using an accelerometer, three (60%) demonstrated a significant effect (33, 34, 38). Differences in the nature of interventions and potentially the effectiveness of the interventions used in each of the studies preclude us from drawing conclusions regarding the superiority of an accelerometer as an outcome measure. However, future studies may have a greater likelihood of demonstrating change if reliable, valid and responsive accelerometers are used in preference to pedometers or self-report methods.

Regarding the possibility that the frequency of supervised exercise training impacted on PA, both studies that utilised exercise training three times a week, for at least 8 weeks demonstrated a significant improvement in PA (33, 38). In contrast, of the five studies that offered exercise training only twice a week, only one demonstrated a significant improvement in PA (34). This suggests that more frequent exercise training may be necessary to result in a significant increase in PA. The data from Pitta's study (33) suggests that the duration over which exercise training is offered is also important. Specifically, the participants in his study demonstrated a small non-significant increase in PA after 3 months of supervised exercise training, with an additional three months of training required to confer a significant increase in PA. These results are in line with a recent review which concluded that PRPs that exceed 12 weeks in duration were more likely to promote long-term maintenance of training effects (207). Earlier work suggests that at least 3 months is required for most

individuals with COPD to change a habit (208) and therefore, studies that investigate interventions offered over an extended period that comprises frequent supervised exercise training are perhaps the most likely to show significant improvements in outcomes.

Regarding the impact that the clinical stability of study participants may have had on PA levels, only Steele et al (36) separated those who experienced an acute exacerbation during the follow-up period from those who did not, with participants who experienced an acute exacerbation in the study by Steele et al (36) were the only subgroup to demonstrate an effect suggestive of deterioration in PA. This is consistent with earlier work that reported a dramatic decline in PA among individuals with COPD following an exacerbation (209). Notably, this deterioration in PA has been shown to persist for several weeks (209).

As this systematic review did not find any published RCTs that examine the effects of supervised exercise training on PA, this is a gap in evidence to address the effectiveness of a supervised exercise training on PA in individuals with COPD.

PART 5

When interpreting outcomes in research, a statistically significant difference is desirable as it implies that the change is unlikely to be caused by chance. Although statistical significance may be achieved, the magnitude of change in the outcome measure of interest might be too small to be noticed by the individual (210). This section will define and address this improvement or change that is noticeable or perceived by the individual (46, 211). This term, MDD, is used throughout this thesis to define the smallest change in an outcome measure detected by individuals with COPD.

2.7 Definition of the minimal detectable difference

The MDD is defined as the smallest difference in the outcome of interest that individuals perceive or detect as either beneficial or harmful, and this can lead the individual or clinician to consider a change in the management (41, 212). The MDD can be determined by both anchor- and distribution-based approaches (212). Other terms used to define this meaningful change include the minimal clinically important

difference (MCID) and minimal important difference (MID). The term MCID was first introduced by Jaeschke et al in 1989 (213). The word ‘clinical’ has since been omitted from the term ‘MCID’ as greater weight has been placed on the preferences of patients than clinicians in determining the MID (41). The MDD is often used interchangeably with MID and MCID. The main difference between these terms is that the MDD is the smallest difference noticeable (or detectable) by an individual, whereas, both the MID and MCID aim to ensure that the magnitude of this difference is important to the individual (8). Importance is related to a judgement by the individual that the magnitude of benefit is considered to be worth the effort, inconvenience or cost associated with completing the treatment (8). Alternatively, importance may be related to a reduction in the risk of some clinical event (e.g. mortality or hospitalisation). The MDD does not link the magnitude of change with whether or not the individual perceives the change to be important; it is simply the magnitude of change that is noticeable or detectable by the individual (8).

The word ‘detectable’ was later used to replace the word ‘important’. This is because many of the studies estimating this minimal difference described a detectable level of change or effect (214), either using statistical calculations or having individuals indicate their perception of the change, rather than requiring the individual to indicate if the change was important (46). Some authors have used the term minimal detectable change (MDC) to define the amount of change at an individual level that must be observed before it is considered above the boundaries of measurement error (215, 216).

2.7.1 Relevance of the minimal detectable difference

In a study, a statistically significant difference is desirable as it implies that the change observed is unlikely to be due to chance and that the sample size tested is appropriate to demonstrate this (8). However, even small changes following an intervention may meet the threshold for statistical significance if there was minimal variability in response to the intervention and/or data were available for a large number of participants (8). The concept of the MDD evolved to represent a change that is noticeable to an individual and it can be determined using two approaches, namely the anchor- and distribution-based approaches (8). These are explained in detail below. Anchor-based approaches compare a change in the outcome of interest

to some other measure of change which is considered an anchor or an external criterion (8). Distribution-based approaches are based solely on statistical criteria and depends on the effect estimate and its relationship to a measure of variability (217). The concurrent use of both approaches is recommended to evaluate the effects of the intervention on the final estimate of the MDD (215).

2.7.1.1 Anchor-based approaches for determining the minimal detectable difference

Anchor-based approaches for determining the MDD compares the magnitude of change in the outcome of interest with an external criterion or anchor such as the global rate of change (GRC) scale or an assessment tool with an established MDD (8). One method is the use of Pearson correlations to determine the magnitude of change in the outcome of interest to the anchor (212). This relationship needs to be reasonably strong (i.e. $r > 0.5$) to proceed with the plotting of a linear regression model between the anchor and the change in the outcome of interest to estimate the MDD (217, 218). The external criterion or anchor can be based on clinician judgement, individual perception, an anchor with an established MDD or a specific health criterion. Another method is to use a receiver operating characteristic (ROC) curve to discriminate between individuals who rated themselves as changed versus unchanged at the end of an intervention (8). These methods that can be used in the anchor-based approaches to estimate the MDD are described in the following paragraphs.

First, the external criterion or anchor can be based on clinician judgement and this has been used for estimating the MDD of outcomes including the CRDQ (213) and SGRQ (219) in individuals with COPD. In these studies, a group of clinicians were consulted to achieve consensus of what constitutes a MDD for these HRQoL questionnaires based on their clinical experience with the questionnaires and management of people with COPD (214).

Second, the MDD can be defined as the change in the outcome of interest based on the individual's perception of their change using an external criterion, using, for example, a GRC scale (213). The GRC scales are simple, easy to administer, have a high face validity and can be made relevant to any health condition (45). The GRC

scales are used by individuals to rate themselves as 'better', 'unchanged' or 'worse' over time or in response to an intervention (45). The MDD represents the mean change in the outcome measure of interest achieved by those individuals who rate themselves as having changed by ± 2 or ± 3 points, defined as 'a little or somewhat better or worse', on a 15-point GRC scale (220). This method was used by Jaeschke et al (213) to confirm the clinicians' judgements concerning the MDD of the CRDQ. Similarly, this GRC scale has been used to determine the MDD for the Asthma Quality of Life Questionnaire (220). The GRC scale was shortened and used to estimate the MDD for the outcomes of walking based tests, namely the incremental shuttle walk test (44), ESWT (48) and 6MWT (43). A different methodology was used in studies by Redelmeier et al (42, 221) which relied on between-individual ratings on the GRC scale where individuals were asked to rate themselves against others. The MDD for 6MWD and FEV₁ were determined using the mean difference in values between those individuals who rated themselves as 'a little better' rather than 'about the same' (42, 221). In some studies, arbitrary cut-offs by combining several levels of the GRC scale were used to define MDD (45). An example is the study by Holland et al (43) who collapsed a 7-point GRC scale into three categories, where the scores of 0 to 1 of the GRC scale were combined as no change, scores of 2 to 3 combined as small change and scores of 4 to 7 combined as substantial change. Although combining levels on a scale is common when determining MDD, the decision of which levels to combine is arbitrary (8). Further, the use of a GRC scale may be prone to recall bias (222).

Third, the MDD can be estimated using linear regression analysis between the change in the outcome and the change in an anchor that has an established MDD (217). For example, the CRDQ, which has an established MDD of 0.5 points per item (218, 223) and the SGRQ domain and total scores which have an established MDD of 4 points (217), can be used as an anchor to estimate the MDD for exercise tests (217, 223) and the Hospital Anxiety and Depression scale (218) in individuals with COPD.

Fourth, a specific health criterion can be used as an anchor to estimate the MDD and this may include hospital admissions, death, the need for a major change of treatment or a change in the clinical state of the individual (214). This method has only been

used for HRQoL as HRQoL is assumed to be worse in individuals who have a major health event compared to those who do not (214). This method was used to determine the MDD of the SGRQ based on hospital re-admissions (224) and the MMRC dyspnea grade (225).

Fifth, the MDD can be defined as the value that confers the optimal blend of sensitivity and specificity using a ROC curve to discriminate between individuals who rate themselves as changed versus unchanged at the end of an intervention (8). That is, sensitivity is defined as the proportion of individuals who reported an improvement using the GRC scale and demonstrated an improved in the outcome of interest (i.e. true positive), while specificity is defined as the proportion of individuals who did not report an improvement using the GRC scale and the outcome of interest did not improve (i.e. true negative) (8). This technique was used by Holland et al (43) to determine the MDD for the 6MWD after pulmonary rehabilitation in individuals with COPD. It has the advantage of accommodating all available data, independent of the number of responses in each category of the GRC scale (49).

2.7.1.2 Distribution-based approaches for determining the minimal detectable difference

Distribution-based approaches for the MDD use statistical methods. These methods include the effect size or half a SD of the baseline measure, the standardised response mean (SRM) and the standard error of measurement (SEM) (8). These statistical methods are described in the following paragraphs.

The effect size is the measure of change obtained by dividing differences in values from baseline to post intervention by the SD of the baseline values (8). Regarding interpretation, an effect size of 0.2 is considered small, 0.5 is moderate and 0.8 is large (203). The estimate of the MDD for change in outcomes of HRQoL in individuals with COPD has been shown, in a systematic review, to fall close to half of a SD (46). As an effect size of 0.5 is considered to be moderate (8), the MDD is calculated by multiplying the SD of the baseline measure by 0.5.

The SRM has been defined as the changes in a group of values or scores obtained by dividing differences in the outcome measure of interest (i.e. from baseline to post-intervention) by the SD of the change in the outcome measure (46, 226). The SRM is also known as another form of effect size (226) and some authors have used the definition of SRM synonymously with the term effect size (217, 223). The criteria for moderate change of half a SD of change in the outcome of interest was also used for the SRM to estimate the MDD (46, 226).

The SEM is defined as the variability between an individual's observed score and the true score and is computed as the baseline SD multiplied by the square root of one minus the ICC (47). It can also be calculated via repeated measures analysis of variance (ANOVA) (47). The important property of the SEM is that it is invariant (227) as it based on internal consistency or test-retest method of the outcome measure (212). The statistical formula for using the SEM is sometimes termed MDC: $1.96 \times \text{SEM} \times \sqrt{2}$, which relates to the smallest change that can be considered outside random variation (i.e. measurement error) (8). The SEM has been able to identify clinically meaningful intra-individual change in the CRDQ in individuals with COPD (227).

The limitation with using a distribution-based approach for determining the MDD is that it is based solely on statistical calculations (212). Further, the distribution-based approach is cohort specific, thus dependent on the variability of scores in the cohort (8). Distribution-based approaches are considered inferior to anchor-based approaches (212) as they do not consider the individual's perception or opinion of his or her outcome.

2.7.1.3 Approaches used previously to determine clinical importance for outcomes in individuals with COPD

In individuals with COPD, the MDD for field walking tests and HRQoL have been estimated using both anchor- and distribution-based approaches. These are listed in Tables 2-7 and 2-8)

The 6MWD is widely used as an outcome measure in clinical trials involving individuals with COPD (228). Thus change in 6MWD following an intervention is

most often used to determine the clinical importance of a study's findings. Redelmeier et al (42) were the first to determine the MDD for the 6MWD using between-individual comparisons after a PRP. A difference of 54 m (95% CI 37 to 71 m) in 6MWD was required in order for an individual to stop rating themselves as 'about the same' and start rating themselves as either a 'little bit better' or a 'little bit worse' compared to others (42). In the National Emphysema Treatment Trial (NETT), the anchor-based estimate of the MDD for the 6MWD was 26 ± 2 m (217). This study involved 1,218 individuals and used the SGRQ and the University of California San Diego Shortness of Breath Questionnaire as external criteria for the anchor-based MDD estimation (217). This MDD for 6MWD from the NETT trial was similar to the 25 m determined by Holland et al (43) using the ROC curves and the GRC scale. Both the NETT trial (217) and the study by Holland et al (43) found that distribution based estimates for determining the MDD for the 6MWD yielded similar values to their anchor-based estimates. However, the MDD of 54 m determined by Redelmeier et al (42) was double that of the NETT trial (217) and Holland et al (43). Puhan et al (223) conducted a pooled analyses of nine studies with a total of 460 individuals with COPD and estimated the MDD for 6MWD as 35 m using distribution-based approaches (effect size and SEM). This range of values for the MDD of the 6MWD may be explained by the different methods used in the estimation as well as the nature of the interventions or treatments provided to the individuals with COPD in these studies.

There is only one study that attempt to estimate the MDD for performance on the ESWT. In the study by Pepin et al (48), the MDD for the ESWT outcomes (i.e. time or distance walked) were very different when comparing the response to a PRP and following administration of inhaled bronchodilators. The distribution-based method of SRM for outcomes in ESWT in response to PRP suggested an MDD of 186 sec or 203 m, while the planned anchor-based approach could not be used as the correlation (r) between the GRC scale and ESWT performance was < 0.4 ($p < 0.001$) (48). The poor correlation between the GRC scale and ESWT performance was speculated to be due to poor recall over the 7-week PRP period and because rehabilitation required a level of commitment and personal investment in the treatment, thus individuals were expecting more from rehabilitation than from an inhaled bronchodilator (48). The anchor-based estimate for the MDD for the outcomes in ESWT in response to a

bronchodilator was 65 sec (95% CI 45 to 85 sec) or 85 m (95% CI 60 to 115 m), supporting the use of ESWT in clinical trials evaluating the effectiveness of such medications (48). There was also only one study that estimated the MDD for incremental shuttle walk test (ISWT) using the GRC scale. In this study, the MDD was estimated to be 47.5 m which was the mean improvement in ISWT distance by the individuals with COPD who perceived their exercise tolerance as 'slightly better' after a 7-week PRP.

Table 2-7: Summary of studies that determined the minimal detectable difference (MDD) in field walking tests in individuals with COPD.

Outcome	Study	Sample size (n)	Intervention	Field walking tests			
				Anchor-based approach	MDD	Distribution-based approach	MDD
6MWD	Redelmeier 1997 (42)	112	PRP	Between individuals comparison using GRC scale	54 m	-	-
	Puhan 2008 (223)	460 (data from 9 studies)	PRP	-	-	SEM	35 m (95% CI 30 to 42 m)
						SRM	29 m
						Conclusion	35 m (threshold 29 to 42 m)
	Holland 2010 (43)	75	7-week PRP	GRC scale and ROC analysis	24.5 m (95% CI 20-61 m)	SEM	25.5 m
	Puhan 2011 (217)	1,218	6 months follow-up after completing PRP	SGRQ impact domain as anchor	18.9 m (95% CI 18.1 to 20.1 m)	Effect size	26.5 m
				SGRQ activities domain as anchor	24.2 m (95% CI 23.4 to 25.4 m)	Effect size	25.7 m
SGRQ total score as anchor				24.6 m (95% CI 23.4 to 25.7 m)	SEM	26.8 m	
Polkey 2013 (229)	2,112	Over 1 yr as a function of mortality and hospitalisation	UCSD Shortness of Breath Questionnaire total score as anchor Death and hospitalisation	26.4 m (95% CI 25.4 to 27.4 m)	30 m	-	-
ISWD	Singh 2008 (44)	372	7-week PRP	GRC rating of slightly better	47.5 m (95% CI 38.6 to 56.5m)	-	-
ESWT performance	Pepin 2011 (48)	132	7-week PRP	-	-	SRM	186 sec or 203 m
		69	Bronchodilatation	GRC scale and linear regression	65 sec (95% CI 45 to 85 sec) 85 m (95% CI 60 to 115 m)	SRM	70 sec or 115 m

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESWT, endurance shuttle walk test; GRC, global rating of change; ISWD, incremental shuttle walk distance; m, metres; n, number of participants; PRP, pulmonary rehabilitation program; ROC, receiver operator curve; sec, seconds; SEM, standard error of measurement; SGRQ, Saint George's Respiratory Questionnaire; SRM, standardised response mean; UCSD, University of California San Diego; 6MWD, 6-minute walk distance.

Table 2-8: Summary of studies that determined the minimal detectable difference (MDD) in HRQoL in individuals with COPD.

Outcome	Study	Sample size (n)	Intervention	HRQoL			
				Anchor-based approach	MDD	Distribution-based approach	MDD
CRDQ	Jaeschke 1989 (213)	-	-	Survey of individuals with experience using the CRDQ (consensus panel)	Dyspnea 0.6 ppi Fatigue 0.5 ppi Emotional 0.57 ppi	-	-
	Jaeschke 1989 (213)	31	24 weeks after inpatient PRP	GRC scale of ± 1 to ± 3 (almost the same to somewhat better or worse)	Dyspnea 0.43 ppi (range 0.28 to 0.62) Fatigue 0.64 ppi (range 0.55 to 0.7) Emotion 0.49 ppi (range 0.35 to 0.8)	-	-
	Redelmeier 1996 (230)	112	PRP	Between individuals comparison using GRC scale	Dyspnea 0.09 ppi Fatigue 0.5 ppi Emotion 0.87 ppi Mastery 0.23 ppi	-	-
	Wyrwich 1999 (227)	393	Nil	-	-	SEM	Dypnea 0.51 ppi Fatigue 0.52 ppi Emotional 0.44 ppi Mastery 0.64 ppi
	Schünemann 2005 (41)	51	PRP	-	-	Effect size	Dyspnea 0.61 ppi Fatigue 0.67 ppi Emotional 0.60 ppi Mastery 0.60 ppi

Table 2-8: Continued

Outcome	Study	Sample size (n)	Intervention	HRQoL			
				Anchor-based approach	MDD	Distribution-based approach	MDD
SGRQ	Jones 1991 (219)	152	Nil	Consensus panel made up of clinicians who used the SGRQ (minimal difference between two hypothesised populations based on frequency of cough, frequency of wheeze, level of dyspnea, level of depression and 6MWD using multivariate model)	SGRQ total score 3.9 units	-	-
	Jones 1997 (231)	283	16 weeks of treatment with Salmeterol versus placebo	Patients rated the use of Salmeterol as effective treatment using a scale worded as 'no effect', 'satisfactory', 'effective' and 'very effective'	SGRQ total score 4.3 units (95% CI 1.8 to 6.9)	-	-
	Bestall 1999 (225)	64	Nil	Based on MMRC dyspnea grade as criterion (Grade 5 [housebound] versus Grade 4 [non-housebound])	SGRQ total scores 3.9 units (95% CI 1.8 to 9.4)	-	-
	Schünemann 2003 (232)	84	PRP	Using CRDQ dyspnea domain (0.5 ppi) as anchor	SGRQ total score 3.05 units (95% CI 0.39 to 5.71)	-	-

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRDQ, Chronic Respiratory Disease Questionnaire; GRC, global rating of change; HRQoL, health-related quality of life; MMRC, Modified Medical Research Council; n, number of participants; ppi, points per item; PRP, pulmonary rehabilitation program; SEM, standard error of measurement; SGRQ, Saint George's Respiratory Questionnaire; 6MWD, 6-minute walk distance.

The MDD has been estimated for some outcomes of HRQoL following a PRP in individuals with COPD, namely for the CRDQ and SGRQ. Using the GRC scale of ‘almost the same’ to ‘somewhat better or worse’, Jaeschke et al (213) estimated the MDD for CRDQ to be 0.5 points per item for each domain. Redelmeier et al (230) using between individual global ratings, had an estimated MDD for the domains of CRDQ ranging from 0.09 (dyspnea domain) to 0.87 (emotional function domain), with a pooled MDD across domains of 0.42 (95% CI of 0.32 to 0.53). The estimated MDD for all domains of the CRDQ for a moderate effect size ranged between 0.52 to 0.64 points per item (232). A systematic review by Schünemann et al (41) summarised the above studies and suggested that the MDD estimate for the CRDQ was 0.5 points per item for each domain. As for the SGRQ total score, the MDD estimate determined in individuals with COPD was approximately 4 units regardless of treatment, namely the use of Salmeterol or after discharged from hospital following an acute exacerbation (214).

2.7.1.4 Uses and misuses of the minimal detectable difference

The MDD is useful as it can be used to make clinical decisions based on the magnitude of change seen in an outcome and for sample size calculations (212, 233). However, the MDD calculated on a group average is often extrapolated to individuals (211), where individuals who improve beyond the MDD are considered ‘responders’ (234). This is a misuse of the MDD as measures, especially of exercise capacity, have inherent variability and if this variability is greater than the MDD, using the MDD to classify ‘responders’ is inappropriate (234). Further, approximately 30% of individuals with COPD do not appear to show any clinical improvement in terms of exercise capacity or HRQoL after a PRP (235, 236). Thus, an individual’s improvement when benchmarked against established MDD values may not be reflective of the change perceived on an individual level (233).

In individuals with COPD, different estimates for MDD for outcomes have been reported and are dependent on the methods used. One example is the 6MWD where the estimated MDD ranged from 25 m using ROC analysis (43), 35 m using the SEM (223) and 54 m using between-person comparisons (42). These different MDD estimates would identify different number of responders to a treatment, thus highlighting the limitation of applying group data to the interpretation of the outcome

in an individual (234). Another example is the MDD for the CRDQ emotional function domain which ranged from 0.49 points per item for within-person comparison estimated by Jaeschke et al (213) to 0.87 points per item for between-person comparison estimated by Redelmeier et al (230). Likewise this is seen for the MDD for the CRDQ dyspnea domain which ranged from 0.09 points per item (230) to 0.6 points per item when perceived by a panel of clinicians (213, 237). Yet, the consensus for the MDD for this outcome has been agreed at 0.5 points (211).

Conversely, the distribution-based approaches use statistical methods to calculate a value that could be considered beyond the intrinsic variability of the test (233).

2.8 Conclusion

Chronic obstructive pulmonary disease is one of the most common lung diseases in the world and is the third leading cause of disease burden in Australia (238). Individuals with this disease are generally less active than their healthy peers, most likely because they try to minimise dyspnea and fatigue in daily life (1). As PA has been found to have a protective effect on the risk of hospitalisation (239), it is important to look at strategies that might improve PA levels in individuals with COPD. Possible strategies include the use of an assistive aid such as a WW and exercise training as part of pulmonary rehabilitation. As individuals with COPD walk less and slower than healthy peers (1, 100), suitable motion sensors that are accurate and responsive must be used to measure PA in these individuals. Exercise training has been shown to reduce dyspnea and fatigue (5-7), increase exercise capacity and improve HRQoL (5-7). The improvements observed after exercise training must go beyond statistical significance and also be perceived by the individual (8). Various outcomes measures used in the assessment of individuals with COPD have had their MDD determined and these MDD values will assist in the management of individuals with COPD in the clinical setting.

CHAPTER 3

MEASUREMENT PROPERTIES OF THE STEPWATCH™ ACTIVITY MONITOR AND ACTIVPAL™ IN INDIVIDUALS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

3.1 Overview

In people with chronic obstructive pulmonary disease (COPD), the level of daily physical activity (PA) has been demonstrated to influence healthcare utilisation, morbidity and mortality (9, 10). Despite the importance of optimising daily PA in this population, selecting an appropriate device to obtain valid measures remains a challenge. This is especially true for those individuals who walk slowly or use a wheeled walker (WW) to assist with ambulation (11-13). Some motion sensors underestimate steps in individuals who adopt a slow walking speed as there is insufficient magnitude of movement at the centre of mass to be detected by these motion sensors (13-15). The simplest of motion sensors, namely pedometers, often lack the sensitivity to detect slow or shuffling gait patterns (127, 128) and thus tend to underestimate the number of steps taken by some patients with COPD (11, 16). Measuring PA appears to be particularly problematic in those who use a WW to assist with ambulation (13). This is likely to relate to the slower walking speeds characteristic of people who require gait aids. Further, for motion sensors that attach to the arm such as the SenseWear armband, the use of a WW stabilises the arm during ambulation, and therefore data received by the accelerometers within such devices is dampened. This serves to reduce the precision of any measurements (13).

As slow walking is likely to diminish movement in the lower limbs to a lesser extent than movement at the centre of mass (130), we proposed that motion sensors which attach to the leg, rather than the waist, may yield accurate measures in individuals with COPD who are known to adopt slower walking speeds during daily life (1). Following a review of the literature (11, 16-19), we decided to explore the

measurement properties of two motion sensors that attach to the leg as they have yielded encouraging data in other clinical populations.

Data reported by Resnick and colleagues (17) suggested that the StepWatch™ Activity Monitor (SAM; OrthocareInnovations, Seattle, Washington, United States [US]) may yield accurate measures of PA in individuals who walk slowly, including those who use a gait aid. This device attaches to the ankle. Similarly, the ActivPAL™ (PAL Technologies Ltd, Glasgow, Scotland, United Kingdom [UK]) has been shown to yield accurate measures of PA in a healthy elderly population who walked at slow speeds (19). This device attaches to the anterior aspect of the thigh. Both the SAM and the ActivPAL™ are small, easily concealed by clothing and simple to use; features that make them attractive for monitoring PA in both the research and clinical setting. Nevertheless, the capacity of these motion sensors to collect accurate information in people with COPD, who may use a WW to assist with ambulation, is unknown. Further, the capacity of these motion sensors to detect a small increase in PA is unknown. This is particularly important if these motion sensors are used to evaluate the effect of therapies aimed at increasing PA in people with COPD.

The main analysis presented in this chapter has been published (240). However, additional information and data have been added to this chapter (namely the data pertaining to static tasks and a sit to stand activity). These data were not included in the original publication due to space limitations imposed by the journal.

3.2 Methodology

3.2.1 Overall aim

Evaluate the measurement properties of two motion sensors: the SAM and the ActivPAL™.

3.2.2 Research questions

- i. Do the SAM and the ActivPAL™ detect movement when people with COPD perform stationary tasks and during a sit to stand task?

- ii. Are the SAM and the ActiPAL™ accurate and responsive in detecting steps when people with COPD walk at slow and normal pace with and without a WW?

3.2.3 Research hypotheses

The first hypothesis is that both motion sensors will not detect steps when people with COPD perform stationary tasks, namely lying supine, sitting and standing as well as during the transition from sitting to standing.

The second hypothesis is that both the SAM and ActiPAL™ will be accurate and responsive at detecting steps in people with COPD during:

- i. slow and normal walking pace; and
- ii. slow and normal walking pace when using a WW.

3.2.4 Study design

A cross-sectional observational study was undertaken during which data collection for each participant was completed during a single 2-hour session. The study was approved by the following Human Research Ethics Committees: Curtin University (HR 86/2009), Sir Charles Gairdner Hospital (2009-044), Royal Perth Hospital (RA-10/007), Bentley Hospital (S/10/192), and Swan Districts Hospital (Ref no: 032). Written, informed consent was obtained from all participants prior to data collection.

3.2.5 Participants

Participants were recruited from referrals to out-patient pulmonary rehabilitation programs in the Perth metropolitan area.

3.2.5.1 Inclusion and exclusion criteria

Inclusion criteria comprised of a diagnosis of COPD and functional limitation defined as a 6-minute walk distance (6MWD) \leq 450 m prior to rehabilitation. In people with COPD, a 6MWD of $>$ 451 m has been shown to reflect mild functional impairment as it is consistent with a volume of peak rate of oxygen consumption between 20 and 25 ml/kg/min, measured during cardiopulmonary exercise test (241).

Hence, in this study a 6MWD threshold of ≤ 450 m was chosen in order to identify a population of people with COPD with more severe functional impairment. Potential participants with any co-morbidity such as musculoskeletal or neurological conditions that limited mobility were excluded from the study.

3.2.6 Activity monitors

The two motion sensors used in this study were: the SAM and the ActiPAL™. Both motion sensors measure physical activity in terms of steps. The ActiPAL™ also identifies time spent in sedentary activity (sitting and lying), standing and stepping.

3.2.6.1 StepWatch™ Activity Monitor

The SAM is a sealed, waterproof, microprocessor controlled device which responds to time and movement. It is small (20 x 75 x 50 mm) and light (38g) and was attached to the participant's right ankle using a Velcro® strap (Figure 3-1). The SAM has a sampling frequency of 128 Hertz (Hz) and data are available in 1-minute epochs. As it reports the number of steps taken by one leg, the measurement was doubled to calculate the total number of steps taken during a walking task. Prior to data collection, the SAM was initialized for each participant. Specifically, the participant's height (in centimetres) was entered and the settings that pertained to 'range of walking speed' and 'leg motion' were selected as 'moderate' and 'normal', respectively. For each participant, the first 40 steps taken whilst wearing the SAM were observed to ensure that the device was detecting steps, as indicated by a flashing light emitting diode on heel strike (242).

3.2.6.2 ActiPAL™

The ActiPAL™ is a small (7 x 35 x 53 x mm), light (20g) uni-axial piezoresistive accelerometer (Figure 3-2). It was attached to the anterior aspect of the right thigh and held in position using a 10 by 14 cm transparent film dressing (3M Tegaderm™, 3M, St. Paul, Minnesota, US). The ActiPAL™ has a sampling frequency of 10 Hz and data are available in 15-second epochs.

3.2.7 Procedures for data collection

Once written informed consent was obtained, measurements were collected of height and weight. Participants were also asked to rate their level of functional limitation resulting from dyspnea using the Modified Medical Research Council (MMRC) dyspnea grade. The most recent measurements of the volume exhaled during first second of a forced expiration (FEV₁) and forced vital capacity (FVC) as well as 6MWD were extracted from the medical notes. The 6-minute walk test (6MWT) was conducted in accordance to American Thoracic Society guidelines (243). The SAM and ActivPAL™ were then attached to each participant and they completed five tasks, performed in a standardised order. The tasks comprised; lying in supine, sitting and standing, a sit to stand task and four separate constant pace walking tasks.

3.2.7.1 Stationary tasks

Participants were required to complete three stationary tasks, each for 5 minutes, in the following order; supine lying, sitting over the edge of the plinth and upright standing.

3.2.7.2 Sit to stand

Participants were instructed to carry out 12 repetitions of transitioning between sitting and standing at their own pace. A stop watch was used to measure the time taken to complete the task.

3.2.7.3 Walking tasks

All walking tasks were 5 minutes in duration and performed within a 20 m level, enclosed corridor and were separated by 30 minutes of seated rest; a time period previously used to allow cardio-respiratory responses to return to resting values between successive walking-based assessments of exercise capacity in people with COPD (244). The first two walking tasks were undertaken at a speed considered to be ‘slow’ by the participants with the final two walking tasks undertaken at a speed considered to be ‘normal’ by the participants. This method was chosen to allow each participant to walk at an individualised slow and normal pace, which, in contrast to arbitrary walk speeds selected by the investigators, was more likely to be reflective

of daily life (13). The first walk at both speeds was completed without a WW and the second walk at both speeds was completed using a WW.



Figure 3-1: StepWatch™ Activity Monitor



Figure 3-2: ActiPAL™ and the USB docking station.

The process used to ensure that a constant pace was maintained during each walking task has been described elsewhere (13). Briefly, the time taken for each participant to; (i) walk for 40 m at a pace that they considered to be slow and, (ii) walk for 40 m at a pace that they considered to be normal were used to calculate the slow and normal walking speeds, respectively. Thereafter the 20 m corridor was marked at 5 m intervals with orange traffic cones. The speed during each walking task was kept constant by using audio-signals that corresponded to a specific walking speed. That is, each audio-signal emitted a beep corresponding to when the participant needed to pass a cone in order to maintain the speed. The audio signals were made based on various speeds ranging from 25 to 75 m/min (Appendix A). For example, the audio signal corresponding to a speed of 25 m/min emitted a beep every 12 sec. The investigator walked with each participant for the first minute to provide verbal feedback regarding the use of the audio-signals. All participants were encouraged to maintain the pace dictated by the audio-signals, but to adopt a natural walking pattern. During each walking task, for each participant, the investigator counted the number of steps taken over three separate 30-second intervals (i.e. at the beginning of the second, third and fourth minutes). The average of these three samples was used to determine the average step rate, for each participant, for each walking task.

3.3 Data management and analyses

Analyses were performed using the Statistical Package for Social Sciences (SPSS version 17.0; Chicago, Illinois) with probability (p) < 0.05 used to denote statistical significance. The distribution of all data was examined using Shapiro-Wilk Test as well as using frequency histograms to test for normality. Data are expressed as mean±standard deviation (SD) unless otherwise stated. Raw data from the SAM and ActiPAL™ were exported to Microsoft Excel® for further analyses.

3.3.1 Data collected during stationary tasks, sit to stand task and walking tasks

Data collected during each stationary task were reviewed to determine whether either device had recorded movement. Data collected during the transitions from sit to stand were reviewed to determine if steps were detected during the tasks and data from the ActiPAL™ were reviewed to determine the number of changes in posture recorded from sedentary to upright. For all analyses undertaken of data collected

during the walking tasks, data available during complete consecutive minutes only were averaged and converted into step rate.

3.3.2 Accuracy during walking tasks

A repeated measures analysis of variance (ANOVA) was used to examine the effect of WW, walking speed and the interaction between the two, on the difference in step rate measured by the SAM and direct observation. The same procedure was undertaken using data collected from the ActiPAL™. Agreement analyses were undertaken according to the methods described by Bland and Altman (245).

3.3.3 Responsiveness during walking tasks

To determine if the SAM and ActiPAL™ could detect a difference in step rate between walking speeds with and without the WW, a repeated measures ANOVA was used to examine the effect of WW, walking speed and the interaction between the two, on step rate.

3.3.4 Sample size calculation

Prospective sample size calculations were conducted to attain a precision around the estimate of the limit of agreement (LOA) of ≤ 6 steps/min. This value was chosen as earlier work demonstrated that an increase of 12 steps/min during self-selected walking tasks was perceived as the difference between slow and normal paced walking in people with COPD (13). Therefore we speculated that a difference less than half this value would not be perceived as a different walking speed by the average person with COPD. Using data available in the literature, we estimated the SD of the difference between slow and normal paced walking to be 3 steps/min (52 steps/20 minutes) (12). Using the methods described by Bland and Altman (245), a sample size of 20 participants was needed for the 95% confidence interval (CI) around the LOA to span 5 steps/min.

3.4 Results

3.4.1 Baseline characteristics

Twenty-two participants consented to participate in this study. The characteristics of the 20 participants who completed the study are summarised in Table 3-1. Five (25%) participants used a WW in their home environment. Six (32%) of the participants were on ambulatory oxygen.

3.4.2 Data collected during stationary tasks

Neither the SAM nor the ActiPAL™ detected any steps during the stationary tasks for any participant.

3.4.3 Data collected during sit to stand task

The average time taken for the participants to perform 12 repetitions of transitioning from sitting to standing was 45 ± 15 sec. Both the SAM and ActiPAL™ did not detect any steps during this task. The ActiPAL™ recorded this activity as sedentary time for each participant.

3.4.4 Data collected during walking tasks

Data from two (9%) participants were excluded as they were unable to complete the walking tasks without resting and therefore, their walking cadence was not constant during the tasks. All other participants were able to maintain a constant walking speed during each task. Figure 3-3 a-b illustrates the step rate calculated using the three 30-second samples of direct observation for walking tasks undertaken at slow speed and normal speed, respectively.

3.4.4.1 Accuracy of the SAM and ActiPAL™

Regarding data collected using the SAM, the ANOVA demonstrated no interaction (WW x walking speed; $F_{1, 19} = 0.24$; $p = 0.63$), effect of WW ($F_{1, 19} = 0.12$; $p = 0.73$) or walking speed ($F_{1, 19} = 0.03$; $p = 0.86$) on the difference between step rate derived using this device and via direct observation. This indicated that the difference between step rate derived using the SAM and direct observation was similar across

all walking tasks and therefore we grouped data from all four walks in the Bland-Altman analysis (Figure 3-4). The mean difference (i.e. bias) between the step rate derived using the SAM and direct observation was 2 steps/min, with a LOA of 6 steps/min. The upper and lower LOA occurred at 8 (95% CI; 6 to 9) and -4 (95% CI; -5 to -2) steps/min, respectively.

Regarding data collected using the ActiPAL™, there was no interaction (WW x walking speed; $F_{1, 19} = 0.58$; $p = 0.46$) or effect of WW ($F_{1, 19} = 0.01$; $p = 0.91$) on the difference between step rate derived using this device and via direct observation. This indicates that the difference between the step rate derived using the ActiPAL™ and direct observation was not affected by the use of a WW. However, there was a significant effect of walking speed ($F_{1, 19} = 5.75$; $p = 0.03$) on the difference between step rate derived using the ActiPAL™ and direct observation. This indicates that the difference between the step rate derived using the ActiPAL™ and direct observation differed between walking speeds and therefore, separate Bland-Altman plots were prepared for slow and normal walking speeds (Figure 3-5a and 3-5b, respectively). The mean difference (i.e. bias) in step rate derived using the ActiPAL™ and direct observation at slow walking speeds was 7 steps/min with a LOA of 10 steps/min. The upper and lower LOA occurred at 17 (95% CI; 14 to 20) and -4 (95% CI; -7 to -1) steps/min, respectively. The mean difference in step rate derived using the ActiPAL™ and direct observation at normal walking speeds was 4 steps/min with a LOA of 5 steps/min. The upper and lower LOA occurred at 10 (95% CI; 8 to 11) and -1 (95% CI; -3 to 0) steps/min, respectively.

Table 3-1: Characteristics of study participants (n=20; 8 males).

Variable	Mean±SD
Age (years)	73.0±8.5
Height (m)	1.67±0.09
Weight (kg)	69.0±20.2
BMI (kg/m ²)	24.6±6.2
FEV ₁ (L)	0.84±0.30
FEV ₁ (% predicted)#	35±13
FVC (L)	2.17±0.63
FVC (% predicted)#	63±20
FEV ₁ /FVC (%)	40±12
6MWD (m)	338±85
6MWD (% predicted)†	55±14
Slow walking speed (m/min)	34±6
Normal walking speed (m/min)	46±10
MMRC dyspnea grade (0 – 4)*	2.5 (2 – 3)
BODE score*	4.5 (4 – 6)

Data are mean±standard deviation (SD). #, percent predicted based on NHANES (246). †, percent predicted based on formula obtained from Jenkins et al (247).*, median (inter quartile range). BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea & exercise capacity index; FEV₁, volume exhaled during first second of a forced expiration; FVC, forced vital capacity; kg, kilograms; L, litres; m, metres; min, minutes; MMRC, Modified Medical Research Council; % percent; 6MWD, 6-minute walk distance.

Time between participation in the study and most recent measurement of 6-minute walk distance and lung function and was 4±3 and 2±3 months, respectively.

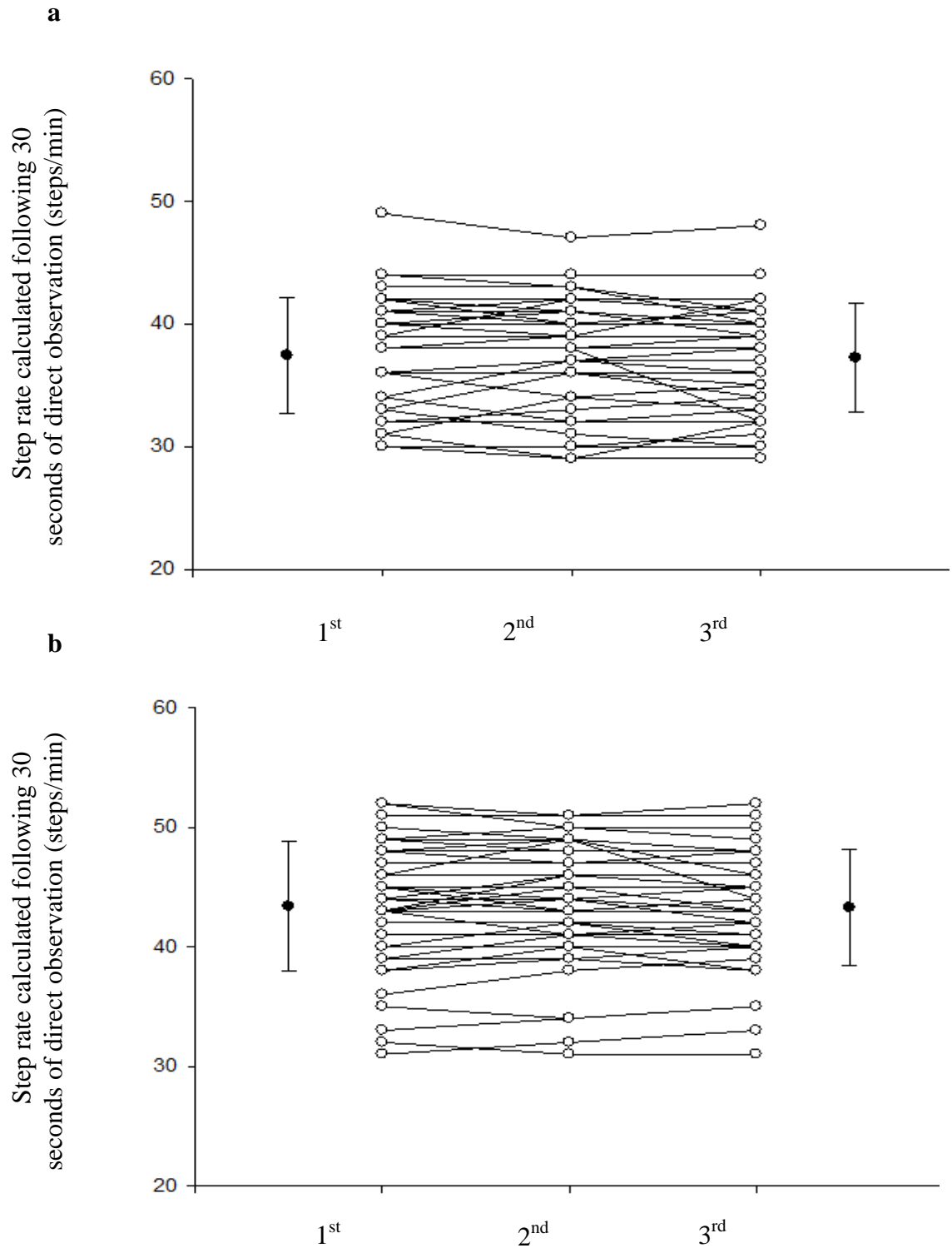


Figure 3-3: Average step rate calculated using the three 30-second samples of direct observation for walking tasks undertaken at slow speed (a) and normal speed (b).

Each participant contributed two lines to Figure 3-3a and 3-3b (i.e. for the walking task performed with and without the wheeled walker). Also shown are the group mean (closed circles) and standard deviation (error bars) for the 1st and 3rd 30-second samples. Note the consistency in step rate over the duration of both the tasks.

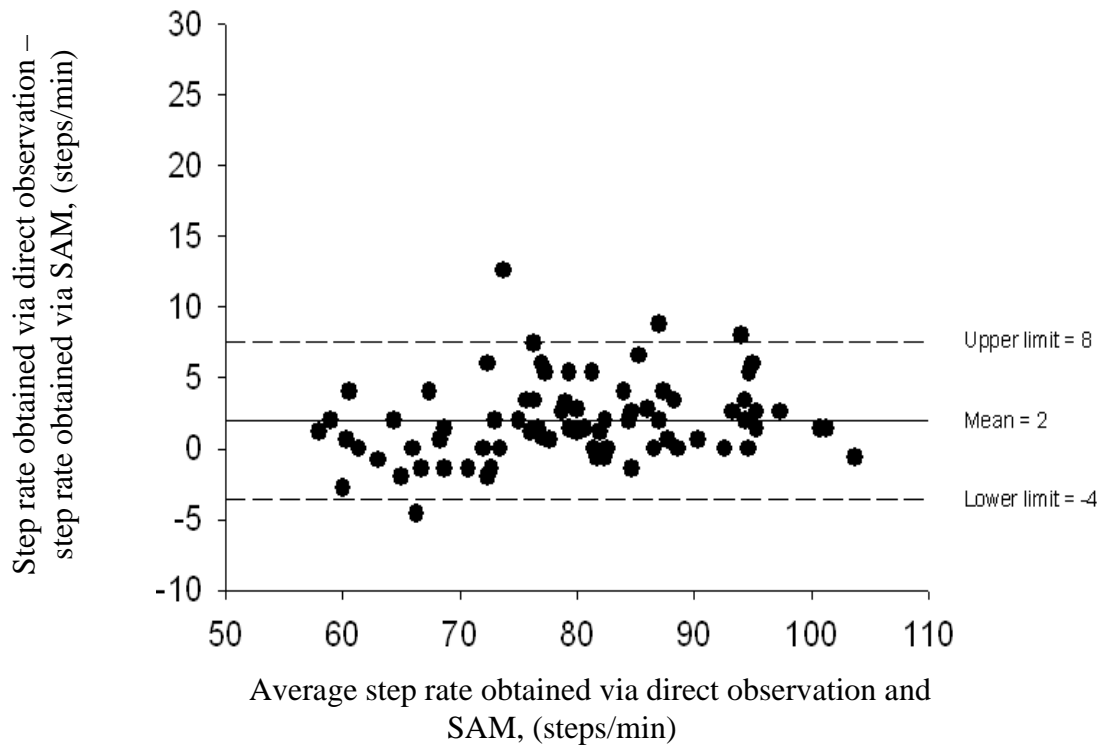


Figure 3-4: Bland-Altman plot for step rate obtained via direct observation and via the StepWatch™ Activity Monitor (SAM).
 Data from all four walking tasks are included.

3.4.4.2 Responsiveness of the StepWatch™ Activity Monitor and ActivPAL™

For data collected using the SAM, there was no interaction (WW x walking speed; $F_{1, 19} = 0.23$; $p = 0.63$) but a significant effect of WW ($F_{1, 19} = 12.39$; $p = 0.02$) and walking speed ($F_{1, 19} = 88.69$; $p < 0.01$) on step rate. This indicates that the SAM was able to detect the difference in step rate associated with changing walking speeds and using a WW. Likewise, for data collected using the ActivPAL™, there was no interaction (WW x walking speed; $F_{1, 19} = 0.01$; $p = 0.93$) but a significant effect of WW ($F_{1, 19} = 12.10$; $p = 0.003$) and walking speed ($F_{1, 19} = 102.86$; $p < 0.001$) on step rate. This indicates that the ActivPAL™ was able to detect differences in step rate associated with changing walking speeds and using a WW. The step rate for each walking task is presented in Table 3-2.

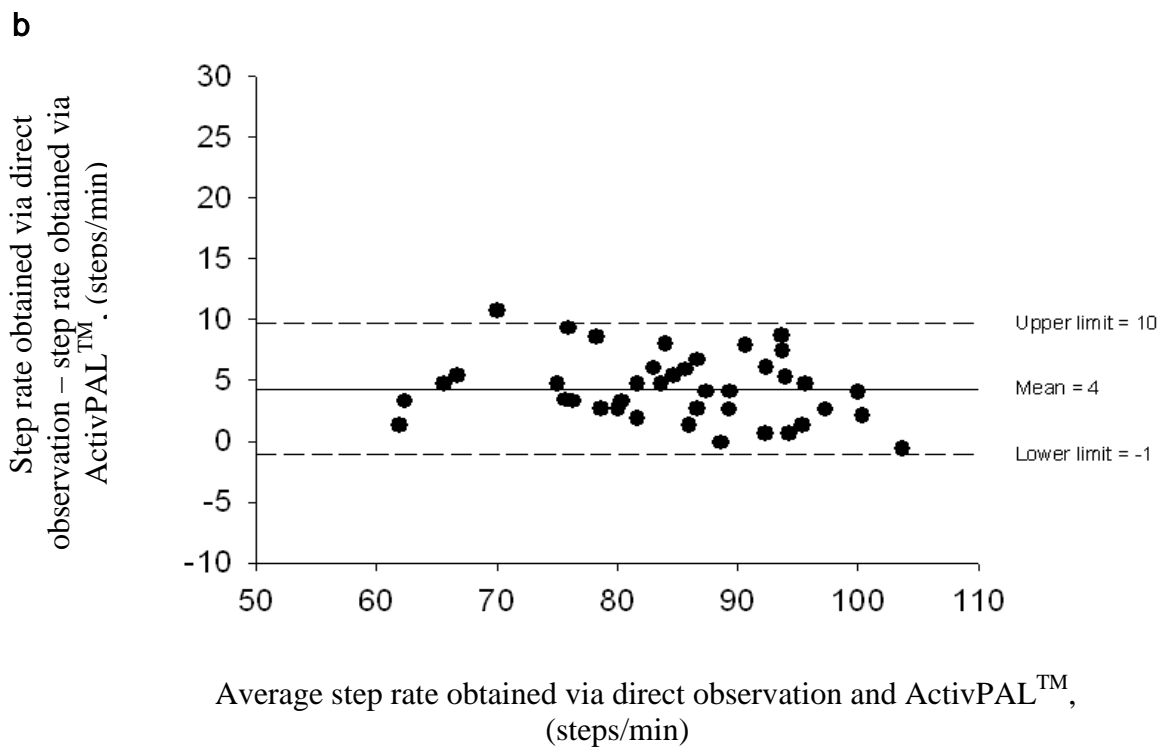
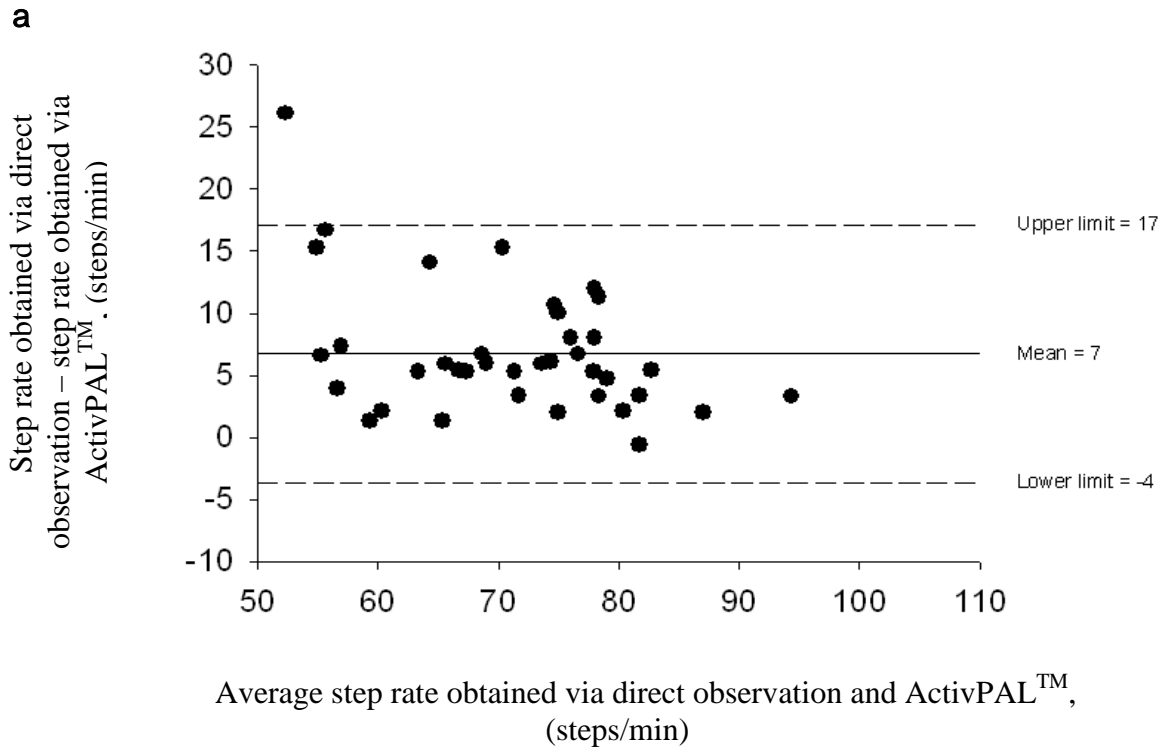


Figure 3-5: Bland-Altman plots for step rate obtained via direct observation and the ActiPAL™ at (a), slow walk speed (with and without wheeled walker) and (b), normal walk speed (with and without wheeled walker).

Table 3-2: Step rates (in steps/min) for all walking tasks.

	Observed	SAM	ActiPAL™
Slow walk*	75±8	73±8	68±11
Normal walk*	85±10	85±10	83±11
Difference (normal-slow)*	12±7	12±6	14±7
Walk without wheeled walker†	83±12	80±11	74±12
Walk with wheeled walker†	79±11	77±10	77±14
Difference (without - with wheeled walker)†	3±3	3±4	3±5

Data are mean±standard deviation. *, includes data collected irrespective of whether a wheeled walker was used. †, includes data collected irrespective of walking speed.

3.5 Discussion

This is the first study to examine the measurement properties of the SAM and ActivPAL™ in people with COPD during stationary tasks, sit to stand as well as at two self-selected walking speeds. Further, this study determined whether or not the use of a WW to assist with ambulation affected the accuracy or responsiveness of these motion sensors. The important findings of this study are; (i) both the SAM and the ActivPAL™ did not detect any movement during the stationary tasks as well as during the 12 repetitions of sit to stand, (ii) the capacity of the SAM to detect steps was similar regardless of walk speed or WW use, (iii) the capacity of the ActivPAL™ to detect steps was affected by walk speed but not WW use and, (iv) both motion sensors were able to detect small changes in step rate.

3.5.1 Accuracy of the motion sensors

Neither the SAM nor the ActivPAL™ recorded steps during the stationary tasks or during the transition from sitting to standing. This is consistent with the SAM only recording steps, which did not occur during these tasks. In contrast, the ActivPAL™ records steps, but also includes time spent being inactive versus active, outcomes related to posture changes. The ActivPAL™ had demonstrated good agreement with counting by direct observation during practice session of sit to stands in rehabilitation in patients with stroke (248, 249). Similarly, an earlier study by Grant et al (137) found the ActivPAL™ to be a reliable device to detect postures and motion in everyday living. That conclusion was based on data showing that the ActivPAL™ accurately detected transitions from sitting to standing while participants were carrying out six random everyday tasks such as making a telephone call, removing rubbish and washing and drying dishes, each task lasting between 2 to 9 minutes (137). However, this was not case in this study as it was not able to detect the task of sit to stand. One possible reason for this was the fact that task of sit to stand was done repetitively in a continuous manner by the participants and the ActivPAL™ records data only at 15-second epochs. Thus it is likely that the participants did not spend sufficient time in the standing position for the ActivPAL™ to detect the new posture. Therefore, the data of this study suggests that the ActivPAL™ was not sensitive to measure transitions between sitting and standing if the new posture was not sustained.

For the walking tasks, the data revealed that the capacity of the SAM to measure step rate was similar at slow and normal walk speeds, regardless of whether or not a WW was used. The mean difference between step rate derived using the SAM and direct observation was 2 steps/min, which is trivial compared with that reported for other commercially-available for motion sensors such as the Minimod, SenseWear armband and Digiwalker pedometer (12, 14). The excellent agreement in step rate derived using the SAM and direct observation extends the findings of Resnick et al (17) who reported a strong correlation between these variables ($r = 0.98$) in a group of elderly people (aged 86 ± 6 years) of whom 22 (73%) used a walking aid to assist with ambulation. Although a strong correlation indicates that these measures were related, Bland-Altman analyses are needed to demonstrate agreement and therefore mean difference (i.e. bias) and LOA were reported. In contrast with the SAM, the data indicate that the capacity of the ActivPAL™ to detect steps was impaired at slow walking with the bias increasing from 4 to 7 steps/min between normal and slow walking speeds respectively. It is likely that the shorter stride lengths associated with walking at slower speeds (250) reduced movement at the thigh and thus impaired the capacity of the ActivPAL™ to detect steps. The shorter stride lengths will reduce movement at the ankle to a lesser extent; a factor that may explain why the SAM, which attaches to the ankle, had a similar capacity to detect steps at both walking speeds (251). In addition to the position of the motion sensors, the difference in the capacity of the SAM and ActivPAL™ to detect steps at the two walking speeds may also reflect the superior sampling frequency of the SAM (128 Hz) compared with the ActivPAL™ (10 Hz).

Although the data indicates that the ActivPAL™ underestimated step rate at slow walk speeds, it is important to note that the walk speed selected by the participants for both the 'normal' (46 ± 10 m/min) and 'slow' (34 ± 6 m/min) walks was considerably slower than that used in other studies. For example, in the study by Langer et al (12), the participant who walked the slowest at 42 m/min was considered an outlier and excluded from the statistical analysis. In this individual, the Minimod underestimated step rate by approximately 39 steps/min, and SenseWear armband underestimated step rate by approximately 56 steps/min (12). The ActivPAL™ which underestimated step rate by 7 and 15 steps/min with the WW and 4 and 26 steps/min without the WW in the two participants who walked the slowest (25

m/min) in this study; a speed considerably slower than the outlier in the study by Langer et al (12), is more favourable than the above monitors. Therefore, although ActiPAL™ does underestimate steps at very slow walking speeds, it seems to outperform other popular, more expensive, commercially-available motion sensors, such as the Minimod and SenseWear armband.

An important and novel finding of this study is that the use of a WW did not affect the capacity of the SAM or the ActiPAL™ to detect step rate. People with COPD who are characterised by a low 6MWD and marked dyspnea on exertion benefit from using a WW both in terms of exercise capacity and reduction in dyspnea (21, 22). Further, there is a high level of satisfaction associated with their use in the community (252). Given the increasing use of WWs by people with COPD, it is important that clinicians and researchers are able to obtain accurate measures of PA in this subgroup. To date, this study is the first to identify two motion sensors that yielded accurate measures of PA in people with COPD who use a WW.

3.5.2 Responsiveness of the motion sensors

For both motion sensors, there was a significant effect of walk speed, suggesting that the SAM and ActiPAL™ could detect the difference in step rate associated with changing from the slow to normal walk speed, regardless of whether the participant was using a WW. The change in step rate between slow and normal walking, calculated via direct observation was 12 ± 7 steps/min; a difference of similar magnitude as detected by the SAM (12 ± 6 steps/min) and ActiPAL™ (14 ± 7 steps/min). A more impressive result is that there was a significant effect of use of a WW, suggesting that the SAM and ActiPAL™ could detect the trivial decrease in step rate associated with changing to use a WW to assist with ambulation, regardless of walk speed. The change in step rate between using and not using the WW, calculated via direct observation was 3 ± 3 steps/min; a difference of similar magnitude as detected by the SAM (3 ± 4 steps/min) and ActiPAL™ (3 ± 5 steps/min). Studies that have examined the measurement properties of motion sensors usually focus on accuracy or validity of the motion sensors. This study extends earlier work (11, 16-19) by confirming the excellent responsiveness of these two motion sensors to detect very small changes in step rate.

3.5.3 Limitations

We examined the measurement properties of the SAM and ActiPAL™ during static tasks (supine lying, sitting and standing), sit to stand activity as well as walking tasks as these are common activities of daily living (9). We did not explore the measurement properties of these motion sensors during other activities, such as cycling and also, did not determine the extent to which these motion sensors may mis-classify movement associated with travelling in a car as steps.

3.6 Conclusions

The stationary tasks and transitions between sit to stand were not detected as motion by either device. Both the SAM and ActiPAL™ underestimated step rates in the participants with COPD, however the difference was very small. Both motion sensors were responsive to small changes in step rate. The SAM was accurate in detecting step rate regardless of walking speed or WW use. In contrast, the accuracy of the ActiPAL™ to detect step rate was affected by walking speed but not WW use. These motion sensors can be used to assess PA in people with COPD, including those who use a walking aid such as a WW.

CHAPTER 4

EFFECT OF USING A WHEELED WALKER ON PHYSICAL ACTIVITY IN INDIVIDUALS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

4.1 Overview

This chapter presents the results of a study that aimed to determine the effects of providing a wheeled walker (WW) to individuals with chronic obstructive pulmonary disease (COPD) on physical activity (PA), health-related quality of life (HRQoL) as well as the fear of falling. A WW, also known as a rollator, is a frame used to assist with walking that has four standard wheels where the front two are on swivel casters. It is equipped with hand brakes, a basket for carrying items and a fold-down seat (Figure 4-3) (21).

Individuals with COPD who are characterised by marked functional limitation due to intolerable dyspnea may benefit from ambulating with a WW (20). In a randomised cross-over study, Solway et al (21) found a significant reduction in dyspnea (1.8 ± 0.2 [mean \pm standard deviation (SD)] unit change) and rest duration recorded (12 ± 6 sec) during a 6-minute walk test (6MWT) when using a WW compared to walking without a WW, even though there was no significant increase in 6-minute walk distance (6MWD). However, in the study by Probst et al (22), individuals with COPD walked a median of 27 m (6%, $p = 0.04$) further during a 6MWT when provided with a WW while experiencing a non-significant reduction in dyspnea at the end of the 6MWT.

The improvements in 6MWD and dyspnea have been demonstrated to be greater in individuals with COPD who have greater functional limitation. Solway et al (21) found that 6MWD significantly increased when a sample of individuals with COPD who walked < 300 m in their 6MWT unaided were provided with a WW (with a WW, $6MWD = 243 \pm 14$ m versus without a WW, $6MWD = 220 \pm 12$ m; $p = 0.02$).

Further, in the individuals with a 6MWD of < 300 m, both dyspnea and rest duration during the 6MWT were further reduced (1.8 ± 0.3 unit change; $p < 0.001$ and 24 ± 12 sec; $p < 0.001$ respectively) when a WW was used (21).

The reasons for the improvements seen when walking with a WW most probably relate to the use of a forward lean position, the capacity to brace the arms on the WW and decreases in the metabolic cost of walking (23, 24). The following paragraphs will elaborate on these possible mechanisms.

In individuals with COPD, hyperinflation of the lungs decreases the length of the diaphragm (23), resulting in impairment in the force-generating capacity of the diaphragm (253). Adopting a forward lean position optimises the pressure-generating capacity of the inspiratory muscles, most likely because it improves the length-tension relationship of the diaphragm (171, 172) and reduces accessory muscle activation (23). This in turn is likely to decrease the level of neuromechanical dissociation, defined as the mismatch between the afferent input from the mechanoreceptors of the respiratory system and the efferent output or motor output to breathe, which is perceived by the individual as a reduction in dyspnea (173).

The arm bracing posture adopted when using a WW has been shown to increase maximum voluntary ventilation (MVV) which may also contribute to the reduction in dyspnea felt when using a WW (22, 174). In the study by Probst et al (22), individuals with COPD significantly increased MVV when they braced their arms on the WW compared to without using a WW. Cavalheri et al (174) found that MVV was 4 L/min higher when individuals with COPD braced their arms on the WW compared to a period without a WW. This increase in MVV implied that the arm bracing posture improved ventilatory capacity. The increased ventilatory capacity associated with arm bracing is most likely due to the increased capacity to use accessory muscles of respiration, namely the serratus anterior, scalenes and sternocleidomastoid (175), which may also contribute to the relief of dyspnea in individuals with COPD when they use a WW. Thus, the arm bracing posture adopted when using a WW may allow individuals with COPD to rely on the accessory muscles to assist in respiration (176).

Besides the forward lean position with the arms braced on the WW, the reduction in dyspnea and improvement in 6MWD when using a WW may be partly due to a reduction in the metabolic cost of walking (22). Hill et al (24) investigated participants with COPD who undertook walking tasks that were 6 minutes in duration at a constant speed with and without a WW, finding a borderline relationship when using a WW between the reduction in dyspnea and the change in energy expenditure (Spearman correlation (r) = 0.50, p = 0.06). That is, the reduction in dyspnea had an association with the reduction in the metabolic cost of walking associated with using a WW. Interestingly, this reduction in the metabolic cost of walking when using a WW was seen in 75% of the individuals (n = 15) in this study who also reported a reduction in dyspnea (24). This implies that the reduction in the metabolic cost of walking was not the sole reason for the reduction of dyspnea when a WW is used (24), and supports the contribution of the physiological benefits of the forward lean position and the arm bracing when a WW is used (177). Further, it is possible that in some individuals with COPD who reported a reduction in dyspnea when using a WW the benefit was related, in part to a placebo effect (i.e. the participants' expectation of benefit) as their dyspnea did not increase despite them demonstrating a greater energy expenditure or minute ventilation (24).

This reduction in dyspnea and improvement in functional capacity when using a WW may enable individuals with COPD to increase their PA. Despite the acute improvements in dyspnea and functional capacity which have been documented in the laboratory setting, no study has evaluated the effects of a WW on daily PA in the community. Further, it is possible that using a WW will decrease the fear of falling and increase confidence when walking. This is particularly important given the evidence demonstrating a reduction in the balance and coordination of individuals with COPD (25-27) which is likely to result, at least in part, from an less active lifestyle (26). To date, only one randomised controlled trial (RCT) was identified that evaluated the impact of using a WW for 8 weeks on HRQoL in individuals with COPD, with no significant benefit demonstrated (178). This could be due to the infrequent use of the WW by the participants in this study by Gupta et al (178).

4.2 Methodology

4.2.1 Overall aim

The aim of this study was to determine the effects of providing a WW for home and community use on a variety of outcome measures for individuals with COPD.

4.2.2 Research questions

- i. Does providing a WW for home and community use increase PA in individuals with COPD?
- ii. Do the clinical characteristics of individuals with COPD influence the effect a WW has on PA?
- iii. Does the use of a WW improve HRQoL and reduce fear of falling?
- iv. What is the average distance covered each day when a WW is used to assist with ambulation?
- v. What are the barriers to using a WW in the home and in the community?

4.2.3 Research hypotheses

The main hypothesis for this study was that individuals with COPD would benefit from the use of a WW in the home and community. Specifically, compared to a 5-week period without a WW, the use of a WW for 5 weeks would result in significant improvements in:

- i. PA;
- ii. HRQoL and;
- iii. Fear of falling.

4.2.4 Study design

A prospective randomised cross-over study was conducted. Individuals with COPD were recruited from pulmonary rehabilitation programs (PRPs) within the Perth metropolitan area, namely, at Sir Charles Gairdner Hospital, Royal Perth Hospital, Bentley Hospital and Swan District Hospital.

4.2.5 Ethical approval

Approval to conduct the study was granted by the Human Research Ethics Committees at Curtin University (HR 86/2009), Sir Charles Gairdner Hospital (2009-044), Royal Perth Hospital (RA-10/007), Bentley Hospital (S/10/192), and Swan District Hospital (Ref no: 032). Written, informed consent was obtained from all participants. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000332224).

4.2.6 Participants

The inclusion criteria were: (i) clinically stable with a medical diagnosis of moderate to severe COPD, (ii) marked functional limitation, which was defined as an unaided 6MWD \leq 450 m before commencement of the PRP and, (iii) deemed suitable for a WW by the physiotherapist(s) responsible for conducting the PRP. The exclusion criteria comprised: (i) prior use of a WW for more than 2 weeks before commencing the PRP and, (ii) any co-morbid condition that limited mobility such as severe arthritis or claudication. The last two inclusion criteria will now be described in more detail.

The threshold of \leq 450 m in an unaided 6MWD to define marked functional limitation was based on earlier work by Starobinet et al (241) who demonstrated that a 6MWD of $>$ 450 m in individuals with COPD corresponded to a peak rate of oxygen consumption of 20 to 25 ml/kg/min, measured during a cardiopulmonary exercise test, which indicated mild functional impairment. Therefore, in this study, a 6MWD threshold of \leq 450 m was chosen in order to identify individuals with COPD of a severity that resulted in more than mild functional limitation.

Factors used by the physiotherapist(s) to deem an individual suitable for a WW included: (i) the need to rest due to dyspnea during their pre-rehabilitation 6MWT, (ii) habitual upper limb bracing either during a 6MWT or supervised walking training, (iii) reporting less dyspnea or walking further when a WW was trialled during supervised walking training and, (iv) being receptive towards the idea of using a WW in their home. As part of usual clinical practice, the physiotherapist(s) responsible for conducting the PRP reviewed patients with COPD during their pre-

rehabilitation assessment and over the first 2 weeks of supervised exercise training to determine their suitability for a WW.

4.2.7 Protocol

All participants completed an 8-week hospital-based PRP. This comprised two supervised exercise classes each week and an individually prescribed home exercise program to complete on an additional 2 or 3 days each week. The rehabilitation program consisted of 20 to 30 minutes of walking training, functional strength training exercises for the lower limbs and endurance training for the upper limbs. To increase familiarity with the WW, all participants were encouraged to use the WW (which weighed 7 kg) during the supervised walking program for 3 to 4 weeks during the PRP. However, the WW was not provided for use at home during participation in the PRP.

During the final 2 weeks of the PRP, two assessment sessions were undertaken in order to: (i) familiarise the participants with wearing the motion sensors that would be used to collect PA data and, (ii) collect descriptive baseline data (i.e. height, weight, spirometry, 6MWD). On completion of the PRP, participants were then randomised to one of two groups using a computer-generated random number sequence. The randomisation sequence was stratified according to the use (or not) of ambulatory oxygen and location of the PRP (i.e. Northern Metropolitan Area Health Service [Sir Charles Gairdner Hospital and Swan District Hospital] or Southern Metropolitan Area Health Service [Royal Perth Hospital and Bentley Hospital]) and concealed using opaque envelopes. Those allocated to Group 1 were provided with a WW for 5 weeks immediately following completion of the PRP but not the next 5 weeks. Participants allocated to Group 2 were not given a WW for the first 5 weeks but were thereafter provided with a WW for the next 5 weeks. The study design is illustrated in Figure 4-1.

On completion of the PRP, the usual practice of the physiotherapists who run the PRPs, namely, to refer participants to maintenance PRPs upon completion of the 8-week program, was undertaken. These maintenance programs offered a weekly exercise class, supervised by a physiotherapist, and were held in a non-medical community facility or a hospital.

Immediately following randomisation, participants allocated to Group 1 received a WW and were provided with standardised instructions regarding its use. They were instructed to use the WW to assist with daily activities that involved walking and to use the WW during the walking component of their home exercise program and maintenance PRP. Participants allocated to Group 2 were encouraged to continue with their home exercise program and attend the maintenance PRP, but were not provided with a WW. Four weeks later, two motion sensors were applied to participants in both groups to measure PA. These motion sensors were applied by a research assistant either as part of a home visit or during a maintenance class by a physiotherapist. Participants were instructed to wear both motion sensors 24 hours a day for 5 consecutive days. At the end of this 5-day period, all participants were visited at home to collect the motion sensors and complete questionnaires pertaining to their HRQoL and fear of falling. During this home visit, Group 1 participants had their WW removed and were encouraged to continue with their home exercise program and attend the maintenance PRP, whereas Group 2 participants were provided with a WW to use for the following 5 weeks and provided with standardised instructions regarding its use (as per Group 1).

Four weeks later, the same motion sensors were applied to participants in both groups either as part of a home visit or during a maintenance class by a physiotherapist. They were instructed to wear both motion sensors 24 hours a day for 5 consecutive days. At the end of this period, a final home visit was made to collect the motion sensors and repeat the questionnaires. Relevant information was provided to those participants who were keen to obtain or purchase a WW at the end of the data collection period.

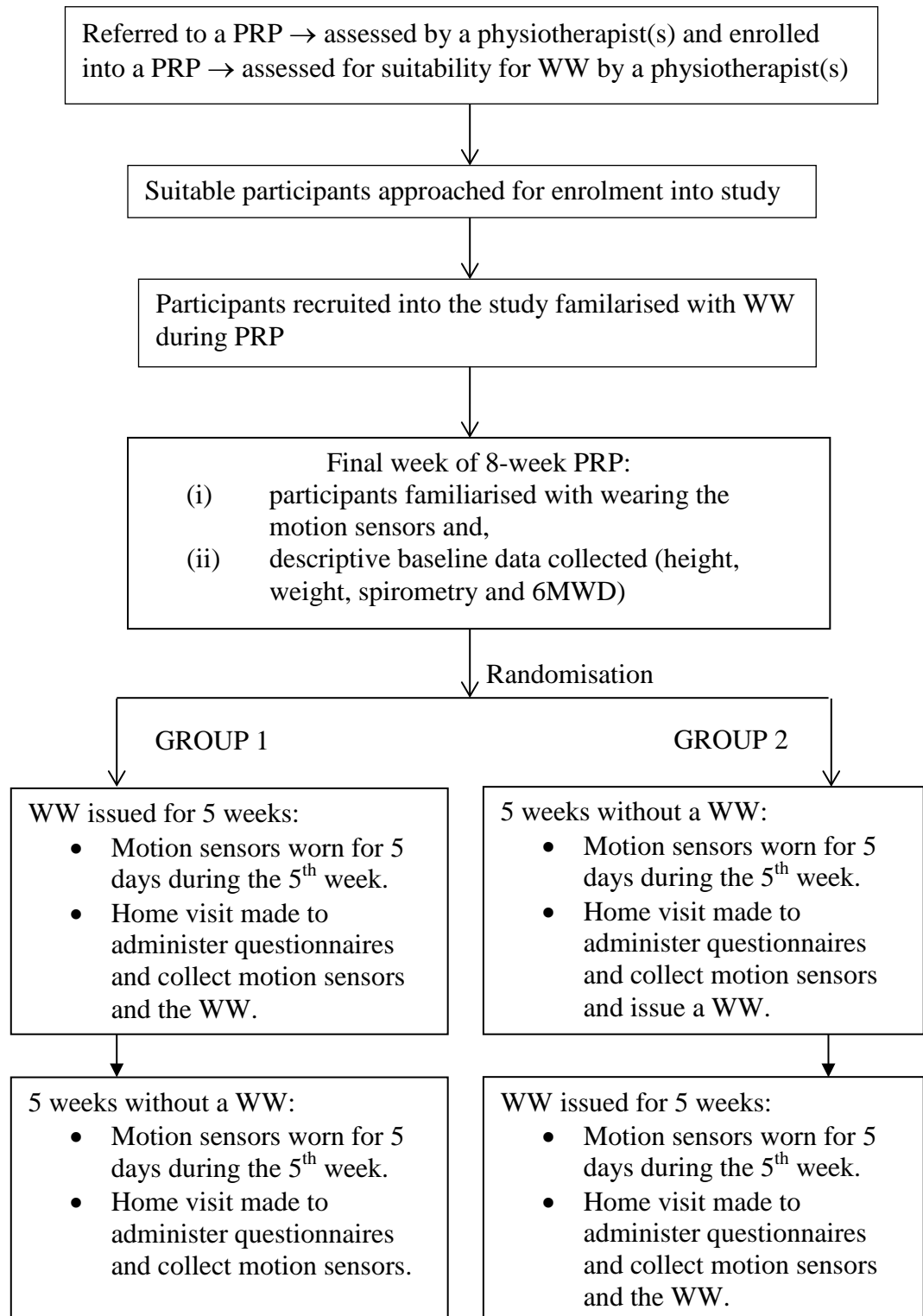


Figure 4-1: Study design

PRP, pulmonary rehabilitation program; WW, wheeled walker; 6MWD, 6-minute walk distance.

4.2.8 Outcome measures

All outcome measures were collected during the home visits by a research assistant, who was unaware of participants' group allocation before the first home visit. It was impossible to blind the research assistant or the participants as the intervention in this study was the provision of a WW. The WW provided were either the Seat Walker Cruiser Deluxe measuring approximately 600 by 275 by 830 mm or the Sprinter Maxi Seat Walker measuring 650 by 330 by 870 mm (Unicare Health, Perth, Western Australia). As this was a cross-over study where participants acted as their own controls, blinding was impossible. The primary outcome measure was PA. The secondary outcome measures were HRQoL, fear of falling, the distance travelled by the WW over the data collection period and barriers to using the WW.

4.2.8.1 Primary outcome measure

Physical activity

Physical activity was measured concurrently using two separate motion sensors: the StepWatch™ Activity Monitor (SAM; OrthocareInnovations, Seattle, Washington, United States [US]) and the ActivPAL™ (PAL Technologies Ltd, Glasgow, Scotland, United Kingdom [UK]) (Figure 4-2). A valid sample of PA was defined as a minimum of 3 days of data from the motion sensors. This definition was based on earlier work demonstrating that individuals with severe COPD showed little variation in daily step counts, thus a minimum of 3 days of PA data were considered sufficient to adequately capture average daily activity (106). Three full days of PA data has been demonstrated to have an acceptable level of reliability (106, 152), defined as an intra-class coefficient (ICC) of ≥ 0.7 (1). Further, individuals with moderate to severe COPD have been shown to have a smaller day-to-day variation in PA compared with their healthy counterparts (106) and earlier work has showed that there was little variability in PA between weekdays and weekends in sedentary individuals with COPD (50). A detailed evaluation of the measurement properties of these motion sensors has been provided in Chapter 3.

The SAM was a sealed, waterproof, microprocessor controlled device that weighed 38 g, and measured 20 by 75 by 50 mm. It was attached to the participant's right ankle using a Velcro® strap. The SAM responded to time, acceleration and position

(16, 254). As the SAM has been shown to have an excellent capacity to accurately record the number of steps, irrespective of walking speed and WW use (240), it was selected as the outcome measure to investigate changes in the number of steps taken. The SAM detected the steps taken by the right leg, with this number doubled to provide the total number of steps taken per day (i.e. taken by both legs). During the calibration procedure undertaken prior to data collection, the participant's height was entered onto the SAM and the settings that pertained to 'range of walking speed' and 'leg motion' were selected as 'moderate' and 'normal' respectively. For each participant, the first 40 steps taken whilst wearing the SAM were observed to ensure that the device was detecting steps accurately, as indicated by a flashing light being emitted from a diode upon heel strike (242). The sampling frequency of the SAM was 128 Hertz (Hz) and data were available in 1 minute epochs. Thresholds for moderate and low intensity walking were defined at > 15 steps/min and ≤ 15 steps/min respectively (131). The SAM was chosen as one of the motion sensor as it has been shown in the study described in Chapter 3 to be accurate for detecting step rate regardless of walking speed or WW use.

The ActivPAL™ weighed 20 g and measured 7 by 35 by 53 mm. It was a uni-axial piezoresistive accelerometer that was attached to the anterior aspect of the right thigh and held in position using a 10 by 14 cm transparent film dressing (3M Tegaderm™, 3M, St. Paul, Minnesota, US). As the ActivPAL™ has been shown to yield an excellent level of agreement (96%) and sensitivity (ranging from 90% to 100%) for the time spent in various postures (walking, standing and sitting) when compared to direct observation (137), the ActivePAL™ device was used to measure the time spent walking, standing and sitting. The sampling frequency of the ActivPAL™ was 10 Hz and data were available in 15-second epochs. The ActivPAL™ was used to complement the SAM in order to quantify the time spent being less active (sitting and lying down) compared to the time spent being active (standing and walking).

Wearing both the SAM and ActivPAL™ motion sensors for a period of 5 consecutive days was considered unlikely to impact on participants' daily routine as these motion sensors are small, light and provided no feedback (255). Further, this was a randomised cross-over study, thus reducing any likelihood the motion sensors might have on participants' daily routine.

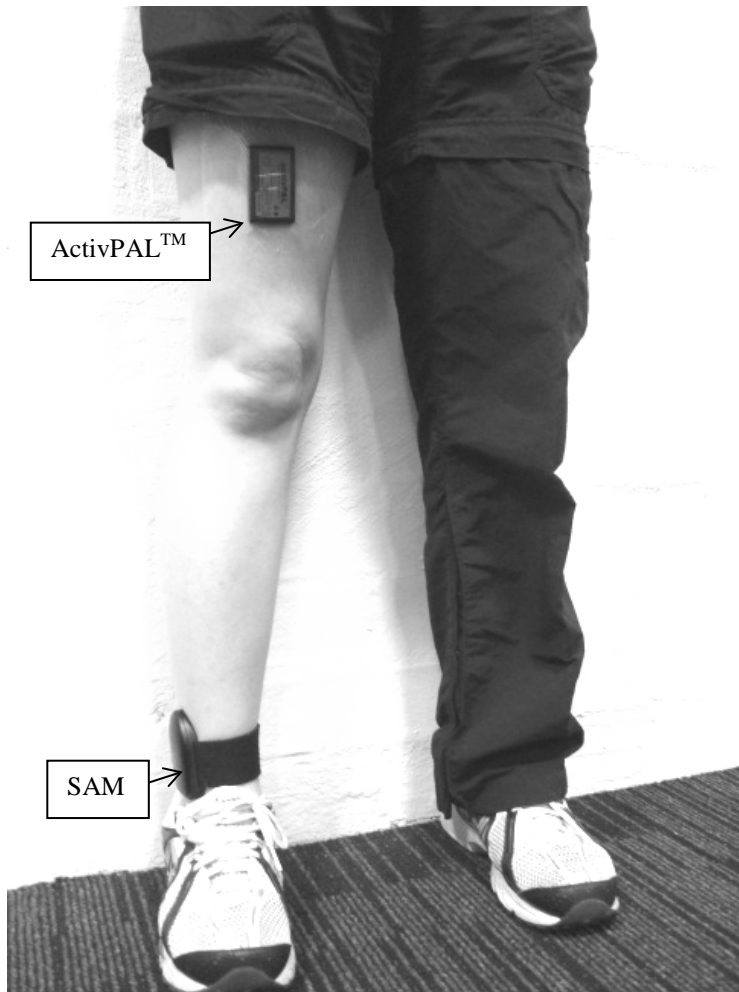


Figure 4-2: A StepWatch™ Activity Monitor (SAM) and an ActivPAL™ device attached to the right leg.

4.2.8.2 Secondary outcomes

Health-related quality of life

Health-related quality of life was measured using the self-administered, individualised version of the Chronic Respiratory Disease Questionnaire (CRDQ) (256). The same five activities chosen to quantify dyspnea during daily life were used at all time points.

Fear of falling

Fear of falling was assessed using the Survey of Activities and Fear of Falling in the Elderly (SAFE) scale (257). This questionnaire has been demonstrated to be valid in elderly populations and has acceptable internal consistency (257-259). This scale assigned scores associated with the fear of falling and activity restriction resulting from a fear of falling for 11 common activities of daily living. A 5-point (0-4) scale was used for each of the 11 activities and the scores were totalled to give a fear of falling score, where a score of > 0 indicated fear of falling (260). Scores ranged from 0 to 44 with higher scores indicating a greater fear of falling. This questionnaire has been shown to be able to differentiate between those with a fear of falling that has resulted in activity restriction and those with a fear of falling with activity (257).

Wheeled walker use and barriers to its use

A magnetic odometer (Fargo Controls, Inc., Eatontown, New Jersey, US) was placed on the rear wheel of the WW to quantify the distance walked using this device (Figure 4-3). This odometer was attached to a lithium-powered, panel-mounted counter that measured 48 by 22 by 45 mm. This odometer device measured the number of revolutions of the wheel, enabling the distance over which the WW was used to be calculated. A similar device has been used previously to measure the distance walked during a 6MWT with a WW in individuals with COPD (21). Participants were asked to record the daily odometer readings in a diary during the 5-week period when they had the WW (Appendix B).

All participants were also asked four standardised closed questions regarding the use of the WW in their daily life at the end of the 5-week period when they had the WW.

These questions were modified from those used as part of an earlier study (252) and pertained to: (i) if they preferred having the WW, (ii) the type of activities that they used the WW for, (iii) the main barriers to using the WW and, (iv) whether the participant felt embarrassed using the WW (Figure 4-4).

4.2.8.3 Descriptive measures

Details were recorded pertaining to age, gender, height, weight, medication and ambulatory oxygen use. The 6MWD measured on completion of the PRP was recorded. The 6MWT was performed along a straight course within a level enclosed corridor in accordance with published guidelines (243). Standardised instructions were given prior to the test. Participants were informed each minute of the time remaining for the test, and were given standard phrases of encouragement. As previous research has shown that individuals with COPD do not demonstrate a change in 6MWD when two tests are performed at the end of an 8-week PRP (261), only one 6MWT was performed at the end of the PRP. Reference values for the 6MWD were calculated using a regression equation published by Jenkins et al (247). Spirometry data were obtained from the medical records. The measures of 6MWD and spirometry were collected on completion of PRP to describe the sample and potentially look for characteristics of those individuals who showed the greatest change in PA. Functional limitation resulting from dyspnea was assessed using the Modified Medical Research Council (MMRC) dyspnea grade (262). The BODE index, a multi-dimensional score that comprises measures of forced expiratory volume in the first second (FEV_1), body mass index, 6MWD and MMRC dyspnea grade was also calculated (263).

4.2.8.4 Healthcare utilisation

During the home visits by a research assistant to collect the motion sensors, participants were asked about changes in their medication and healthcare utilisation (for both respiratory and non-respiratory related problems), such as visits to the family doctor, an emergency department visit or hospital admission during each preceding 5-week time frame. Self-reports of emergency department visits and/or hospitalisations were verified using hospital databases.



Figure 4-3: A wheeled walker with a magnetic odometer attached to a rear wheel.

1. Did you prefer having the wheeled walker to use?

Yes
 No

2. Which activities did you use the wheeled walker for?
(Please check as many as apply):

Activities in the home (e.g. cooking, cleaning, in the bathroom)
 Walking in the home
 Walking outside of the home
 Getting to and from the car
 Walking indoors other than your home (e.g. in shopping centres or in a friend's home or unit)
 Activities outside your home (e.g. grocery shopping or running errands)
 Others – please specify: _____

3. What, if any, were the main barriers to using the wheeled walker? (Please check as many as apply):

Difficult to push
 Unable to use it within the home (e.g. not enough space, too large or bulky)
 Stairs
 Difficulty getting the wheeled walker in and out of the car
 Too heavy
 Didn't use it because I was unwell and not able to walk
 Others – please specify: _____

4. Did you ever feel embarrassed or ashamed using the wheeled walker?

Yes
 No

Figure 4-4: Questionnaire on the use and barriers to using the wheeled walker.

4.3 Data management and analyses

4.3.1 Primary analyses

All analyses were conducted using the Statistical Package for Social Sciences (SPSS version 18.0; Chicago, IL, US) with a probability value (p) ≤ 0.05 used to indicate statistical significance. Data are expressed as mean \pm standard deviation (SD) unless otherwise stated. Raw data from both motion sensors were exported into Excel[®] for further analyses. The assumption of normality was assessed using frequency histograms. Data that did not follow a normal distribution were analysed using non-parametric statistical tests. Baseline characteristics of participants allocated to Group 1 or 2 were compared using independent t-tests and Mann-Whitney U-tests for parametric or non-parametric data respectively. Gender and the use of ambulatory oxygen were compared between groups using Chi-squared analysis. Data are presented as mean \pm SD unless otherwise indicated.

A linear mixed model was used to determine whether or not there was an order effect (i.e. whether group allocation had an impact on PA). The dependent variables were the outcomes measures from the motion sensors, namely, steps/day and time spent walking without a WW. Group allocation was the factor used in the analysis of fixed order effects. In the absence of an order effect, data from Group 1 and Group 2 were combined for the purpose of comparing outcomes between walking with a WW or without a WW. As these data were normally distributed, paired t-tests were used for the comparisons. The effect size was calculated for steps/day by dividing the difference in steps/day with the WW compared to without the WW by the pooled SD of the difference with and without the WW (203).

4.3.2 Secondary analyses

Secondary analyses were undertaken to explore factors that may have impacted on PA when the WW was provided. These factors comprised: (i) MMRC dyspnea grade, (ii) the use of ambulatory oxygen, (iii) 6MWD, (iv) the fear of falling, (v) gender and, (vi) the development of an acute exacerbation. These factors were selected based on data presented in earlier work as follows. A MMRC dyspnea grade of ≥ 3 categorises individuals with COPD who are markedly limited by dyspnea

during daily life (i.e. either needing to rest within 100 yards of walking or those who were too breathless to leave the house (225)). Compared with individuals with less marked limitation, those with an MMRC dyspnea grade of ≥ 3 have greatly reduced PA and thus may derive greater benefit from using a WW (106). The effect of ambulatory oxygen was investigated as the WW used in this study contains a basket that can be used to carry the oxygen cylinder. Hill et al (252) reported that a WW assisted 18 (67%) of the participants in their study who were on ambulatory oxygen to walk outdoors. The effect of 6MWD was explored as Solway et al (21) demonstrated that individuals with an unaided 6MWD of < 300 m had a greater increase in 6MWD when a WW was used compared with those who had a 6MWD of > 300 m (21). Regarding the fear of falling, a survey conducted on 266 elderly individuals found 78% of those who expressed a fear of falling curtailed their activities (264) and Solway et al (21) demonstrated that $> 50\%$ of the individuals with COPD felt safer when using a WW during the 6MWT. Therefore, using a WW may reduce the fear of falling and thus facilitate PA in individuals with COPD. Finally, the effect of gender on PA while using the WW was investigated as an earlier study that evaluated the effects of providing a WW for use in the home and community on HRQoL recruited slightly more women (58%) than men (178), suggesting that women may be more willing to participate in a study involving the use of a WW.

In light of the results of these earlier studies, the magnitude of change in PA associated with WW use was compared between participants grouped as follows: (i) MMRC dyspnea grade 2 compared to 3 and 4, (ii) use (or not) of ambulatory oxygen, (iii) 6MWD < 300 m compared to ≥ 300 m, (iv) a fear of falling (score > 0) compared to no fear of falling (score = 0) and, (v) males compared to females. Given the limited sample sizes available for these analyses, they were undertaken using Mann-Whitney U tests.

4.3.2.1 Sample size

Sample size calculations were performed using data from a previous study of PA in individuals with COPD (9). A large population-based cohort study ($n = 2,386$) showed that a higher level of PA, equivalent to approximately ≥ 2 hours a week or

≥ 17 minutes a day, was associated with a 30 to 40% reduction in the risk of hospital admission and all-cause mortality in individuals with COPD (9). Using these data, a sample size of 19 participants was required in order to detect a difference in the average time spent walking each day with a WW of 17 minutes with a SD of 34 minutes ($\alpha = 0.05$ and $1 - \beta = 0.8$) (263).

4.4 Results

4.4.1 Baseline characteristics

Thirty-one individuals with COPD, who met the study criteria, were approached regarding participation. Of these, 12 (39%) declined to participate. A total of 19 (61%) participants were recruited and randomised. Of these 19 participants, six (32%) were recruited from Sir Charles Gairdner Hospital, 11 (58%) from Bentley Hospital and one (5%) each from Royal Perth Hospital and Swan District Hospital. Baseline characteristics of the participants are summarised in Table 4-1. The majority of participants ($n = 16$; 84%) had severe or very severe airflow limitation (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade III [$n = 6$] or IV [$n = 10$] (56)) and markedly reduced 6MWD [243 ± 85 m; 39 ± 14 % predicted (247)]. Five (26%) participants required ambulatory oxygen and used the WW to transport their oxygen cylinder during supervised training and during the 5 weeks when allocated a WW at home. On completion of the PRP, 16 (84%) participants attended maintenance exercise classes once a week during the study period. The other three (16%) participants declined a referral to a maintenance class stating they preferred to continue with their exercises at home. Six (32%) participants had an exacerbation at some stage during their participation in the study: two (11%) of these participants had an exacerbation during the period when a WW was available and four (21%) had an exacerbation during the period when a WW was not available. These exacerbations were managed at home with antibiotic medications without the need for hospitalisation. The inclusion of those who had an exacerbation during the study period provides a more realistic estimate of the effect, given that many exacerbate with moderate-to-severe disease (265). One (5%) of the participants was hospitalised for 2 days for a gastroenterological condition during the period without a WW and removed the ActivPAL™, therefore his data were not included in the

analysis pertaining to ActivPAL™. There were no significant differences in the baseline characteristics between participants allocated to Group 1 compared to Group 2.

Table 4-1: Characteristics of the 19 participants.

	Group 1 (n=9)	Group 2 (n=10)	Total (n=19)
Gender, n	5M / 4F	6M / 4F	11M / 8F
Age (years)	75±6	70±9	72±8
BMI (kg/m ²)	25.1±5.2	25.0±5.8	25.0±5.4
Smoking (pack years)	66±90	47±27	56±64
MMRC dyspnea grade (0 – 4)	3 (2 to 3)	3 (2 to 4)	3 (2 to 4)
BODE index (0 – 10)	6 (3 to 8)	6 (3 to 8)	5(3 to 8)
Number using ambulatory O ₂	4	1	5
Pulmonary Function			
FEV ₁ (L)	0.88±0.35	1.06±0.52	0.98±0.44
FEV ₁ (% predicted)*	37±17	40±21	38±19
FVC (L)	2.12±0.69	2.41±0.71	2.27±0.69
FVC (% predicted)*	65±24	65±17	65±20
FEV ₁ /FVC ratio	0.42±0.13	0.43±0.12	0.43±0.12
6-Minute Walk Test			
6MWD (m)	238±96	248±78	243±85
% predicted 6MWD†	39±16	39±12	39±14
Peak dyspnea	4 (3 to 8)	4 (2 to 6)	4 (2 to 8)
Peak heart rate (bpm)	102±20	99±21	101±20
Nadir oxygen saturation (%)	83±3	89±4	86±5
Number who rested during test	9	9	18
Number of rests	2 (1 to 2)	2 (1 to 2)	2 (1 to 2)

Data are mean±standard deviation, median (interquartile range). *Predicted values based on National Health and Nutrition Examination Survey (NHANES) data (246). †Percent predicted based on regression equation published by Jenkins et al (247). BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity index; bpm, beats per minute; F, female; FEV₁, volume exhaled during first second of a forced expiration; FVC, forced vital capacity; kg, kilograms; L, litres; M, male; m, metres; MMRC, Modified Medical Research Council; n, number of participants; O₂, oxygen; %, percentage; 6MWD, 6-minute walk distance.

4.4.2 Effect of a wheeled walker on physical activity

The following sections provide data pertaining to the effect of a WW on PA measured using the SAM and the ActivPAL™. Only data from the days when the SAM and the ActivPAL™ were worn for at least 99% of the time were included in the analyses. For the SAM and ActivPAL™ data, no order effect was found ($F_{1, 16} = 3.11$; $p = 0.10$ and $F_{1, 14} = 2.00$; $p = 0.18$, respectively), thus data from both groups were combined for the analyses.

4.4.2.1 Physical activity measured using the StepWatch™ Activity Monitor

Fourteen (74%) of the 19 participants wore the SAM for at least 3 days during the 5th week of each 5-week period. Of these 14 participants with valid PA data, four participants had an exacerbation or were hospitalised during the study period.

Table 4-2 shows data for the mean number of steps/day and the time spent walking at low and moderate intensities.

Compared with the period when the WW was not available, the mean number of steps taken daily significantly increased by $732 \pm 1,027$ steps ($p < 0.02$) when the WW was available. This change was equivalent to an increase of $26 \pm 36\%$ compared with data collected when the WW was not available. The effect size for the change in steps taken daily was 0.2. The mean time spent walking at a moderate intensity increased by 9 ± 13 min/day ($p < 0.02$) when the WW was available. This change was equivalent to an increase of $55 \pm 90\%$ compared with data collected when the WW was not available. The mean time spent walking at a low intensity increased by 18 ± 36 min/day, which, whilst not significant, showed a statistical trend ($p = 0.08$).

The magnitude of change in the mean number of steps/day and the time spent walking at low and moderate intensities was greater when the four participants who had an exacerbation or were hospitalized during the study period were removed in the subsequent analyses. Compared with the period when the WW was not available, the mean number of steps taken daily increased by $1,083 \pm 857$ steps ($p = 0.003$) when the WW was available. This change was equivalent to an increase of $34 \pm 33\%$. The effect size determined was 0.26. The mean time spent walking at a moderate intensity increased by 13 ± 12 min/day ($p = 0.006$). This change was equivalent to an

increase of $47\pm 43\%$ compared with measures collected when the WW was not available. There was an increase of 25 ± 36 min/day in the mean time spent each day walking at a low intensity ($p = 0.06$).

Table 4-2: Physical activity measured using the SAM with and without a wheeled walker for the 14 participants with valid data.

	Without WW	With WW	With WW-Without WW		p value
				95% CI	
Number of days the SAM was worn	4.7±0.6	4.9±0.4	0.1±0.8	-0.3 to 0.6	0.50
Number of hours (per day) the SAM was worn	24.0±0.0	24.0±0.0	0.0±0.0	NA	NA
Steps/day	4,043±3,463	4,775±3,771	732±1,027	139 to 1,325	0.02
Time walking at moderate intensity (min/day)	40±43	49±49	9±13	1 to 17	0.02
Time walking at low intensity (min/day)	156±51	175±62	18±36	-3 to 39	0.08

Data are mean±standard deviation. Probability (p) values pertain to comparisons of outcomes with a WW to without a WW. Moderate intensity walking was defined as > 15 steps/min. Low intensity walking was defined as ≤ 15 steps/min. CI, confidence interval; min, minutes; NA, not applicable; SAM, StepWatch™ activity monitor; WW, wheeled walker.

4.4.2.2 Physical activity measured using the ActivPAL™

Sixteen (84%) participants wore the ActivPAL™ for at least 3 days during the 5th week of each 5-week period. Of these 16 participants with valid PA data, five participants had an exacerbation during the study period. Table 4-3 shows data for the mean time spent walking, standing as well as sitting and lying down.

Compared with the period when the WW was not available, there was a trend for the mean time spent walking each day to increase by 7 ± 16 min/day when the WW was available ($p = 0.09$). This trend was equivalent to an increase of $8\pm 40\%$ compared with measures collected when the WW was not available. The difference in mean time spent standing each day when the WW was available was 9 ± 25 min/day. This difference was equivalent to $12\pm 38\%$ compared with measures collected when the WW was not available, but was not statistically significant ($p = 0.18$). The mean time spent sitting and lying down when the WW was not available did not differ from that measured when the WW was available ($p = 0.11$).

The magnitude of change in the mean time spent walking, standing as well as sitting and lying down was greater when data from the five participants who had an exacerbation during the study period were removed from the analyses. Compared with the period when the WW was not available, there was a trend for time spent walking each day to increase by 10 ± 17 min/day when the WW was available ($p = 0.07$). This trend was equivalent to an increase of $14\pm 38\%$ compared with measures collected when the WW was not available. The difference in mean time spent standing each day when the WW was available was 13 ± 27 min/day. This difference was equivalent to a change of $20\pm 44\%$ compared with measures collected when the WW was not available, but was not statistically significant ($p = 0.15$). The mean time spent sitting and lying down when the WW was available decreased by 23 ± 34 min/day when compared to measures made when the WW was not available, just failing to reach statistical significance ($p = 0.05$).

Table 4-3: Physical activity measured using the ActivPAL™ with and without a wheeled walker for the 16 participants with valid data.

	Without WW	With WW	With WW-Without WW	p value	
			95% CI		
Number of days the ActivPAL™ was worn	4.9±0.3	5.0±0.0	0.1±0.3	-0.1 to 0.2	0.33
Number of hours (per day) the ActivPAL™ was worn	24.0±0.1	24.0±0.0	0.0±0.1	0.0 to 0.01	0.14
Time spent walking (min/day)	37±32	44±37	7±16	-1 to 16	0.09
Time spent standing (min/day)	189±151	180±144	9±25	-4 to 22	0.18
Time spent sitting and lying down (min/day)	1,222±164	1,207±180	-15±35	-34 to 4	0.11

Data are mean±standard deviation. Probability (p) values pertain to comparisons of outcomes with a WW to without a WW. CI, confidence interval; min, minutes; p, probability; WW, wheeled walker.

4.4.2.3 Secondary analysis of the participants grouped according to clinical characteristics that may have influenced the effect a wheeled walker has on physical activity

The results of the secondary analyses that investigated the effect of various clinical characteristics on participants' PA response to using a WW are presented in Table 4-4. Fourteen (74%) participants had valid data for ≥ 3 days for these analyses. Of the five factors investigated, functional limitation due to dyspnea (i.e. MMRC dyspnea grade) was the only factor which appeared to significantly influence the effect a WW had on the number of steps taken each day. Specifically, when the WW was available, participants with modest functional limitation due to dyspnea (i.e. MMRC dyspnea grade ≤ 2) decreased the number of steps taken each day by 724 ± 451 whereas those participants with more marked functional limitation due to dyspnea (i.e. MMRC dyspnea grade ≥ 3) increased the number of steps taken each day by $1,129 \pm 722$. The difference in steps taken per day between these two groups of participants (MMRC dyspnea grade ≤ 2 compared to MMRC dyspnea grade ≥ 3) was significant ($p = 0.01$).

4.4.3 Distance covered by the wheeled walker use

Based on the odometer readings written by participants on their diary cards during the 5-week period the WW was provided, the WW was used by every participant at least three times a week and the mean distance recorded on the odometer was $4,206 \pm 3,346$ m/week. During the 5-day period during which the motion sensors were worn, the mean distance recorded on the odometer attached to the WW was 958 ± 805 m/day (95% confidence interval [CI]; 529 to 1,387 m/day).

Table 4-4: Steps taken per day with participants grouped according to clinical characteristics.

	Without WW (steps/day)	With WW (steps/day)	With WW- Without WW (steps/day)	p value between groups
MMRC dyspnea grade = 2 (n = 3)	3,019 (-)	2,507 (-)	-893 (-)	0.01
MMRC dyspnea grade = 3 & 4 (n = 11)	3,444 (2,338)	4,202 (3,573)	928 (1,049)	
No oxygen (n = 10)	3,082 (2,531)	3,290 (3,318)	608 (1,471)	0.89
On oxygen (n = 4)	3,462 (9,282)	4,400 (11,077)	938 (1,795)	
6MWD > 300m (n = 5)	3,444 (1,894)	4,202 (3,252)	722 (1,672)	0.95
6MWD < 300m (n = 9)	2,720 (2,724)	3,193 (3,507)	655 (1,405)	
No fear of falling (n = 8)	3,308 (1,903)	4,048 (2,593)	938 (1,063)	0.25
Fear of falling (n = 6)	3,470 (2,553)	3,213 (4,671)	465 (2,304)	
Gender (male) (n = 8)	3,765 (4,361)	3,795 (4,277)	791 (846)	0.90
Gender (female) (n = 6)	3,095 (856)	3,466 (3,286)	546 (2,517)	

Data are median (interquartile range). (-) indicates that interquartile range was not determined due to small samples, i.e. $n \leq 3$.

MMRC, Modified Medical Research Council; p, probability; WW, wheeled walker; 6MWD, 6-minute walk distance.

4.4.4 Effect of a wheeled walker on health-related quality of life

Eighteen (95%) of the 19 participants completed the CRDQ at the end of each 5-week period. Compared with the period when the WW was not available, the magnitude of change in all domains of CRDQ when the WW was available did not reach statistical significance (Table 4-5). The magnitude of change associated with using a WW was also below the threshold for the minimal clinically important difference of 0.5 points per item determined for the domains of the CRDQ (41).

4.4.5 Effect of a wheeled walker on fear of falling

The SAFE scale only classifies individuals as fearful versus non-fearful. Nine (47%) of the 19 participants expressed a fear of falling (i.e. scored > 0 on the SAFE scale). The use of a WW reduced this fear in seven of these nine participants (78%). Amongst these seven participants who reported a reduction in the fear of falling, using the WW conferred gains in each domain of the CRDQ that exceeded the minimal clinically important difference. Specifically, compared with measures collected when the WW was not available, the domains of dyspnea, fatigue, emotional function and mastery improved by 1.1 ± 1.3 , 0.5 ± 1.6 , 0.5 ± 1.0 and 0.6 ± 1.3 points per item respectively when the WW was available. However, none of these improvements were statistically significant. Two (11%) of the 19 participants reported activity restriction due to a fear of falling, but this fear was absent during the period when the WW was available.

4.4.6 Barriers towards the use of a wheeled walker

Table 4-6 lists the reported barriers to using a WW. Five (45%) of the 11 males and five (63%) of the eight females found that lifting a WW in and out of the car was the greatest barrier. Three (16%) participants (two males and one female) reported that they felt embarrassed using a WW.

Table 4-5: Health-related quality of life with and without a wheeled walker for the 18 participants.

CRDQ domains	Without WW	With WW	With WW-Without WW		p value
			Mean±SD	95% CI	
Dyspnea	3.0±0.8	3.4±1.3	0.4±1.1	-0.1 to 0.9	0.13
Fatigue	3.7±1.5	4.1±1.3	0.4±1.3	-0.3 to 1.0	0.25
Emotional function	5.1±1.1	5.2±1.1	0.1±1.0	-0.3 to 0.6	0.58
Mastery	4.7±1.5	5.0±1.3	0.3±1.0	-0.2 to 0.8	0.23
Total score	4.2±1.0	4.5±0.9	0.3±0.9	-0.2 to 0.7	0.21

Data are mean±standard deviation and expressed as points per item. Probability (p) values are presented for the comparison for CRDQ domains with a WW to without a WW. CI, confidence interval; HRQoL, health-related quality of life; WW, wheeled walker.

Table 4-6: Reported barriers towards the use of a wheeled walker.

Barriers	Number (%) of participants
Difficulty getting WW in and out of the car	10 (53)
Unable to use at home due to space constraints	6 (32)
Preferred using a trolley at the shops	3 (16)
Loss of independence	1 (5)

WW, wheeled walker.

4.5 Discussion

This is the first study to evaluate the effect of a WW on PA in selected individuals with moderate to severe COPD. The most important finding of this study was that, in this population, having a WW available for use at home and in the community conferred a significant increase in the number of steps taken per day as well as the time spent walking at a moderate intensity. However, the use of the WW did not significantly impact on HRQoL as assessed using the CRDQ. This study also demonstrated that most of the participants who expressed a fear of falling found that using a WW reduced this fear. The main barrier for the use of a WW among the participants was lifting the WW in and out of the car.

In this study, outcomes of PA were measured in several ways, including steps, and time spent walking, standing as well as sitting and lying down. The significant increase in the mean number of steps taken each day when a WW was provided, despite no significant change in the mean time spent walking, indicated that the increase in steps/day was likely the result of an increased pace of walking. In a published article on the measurement properties of the two motion sensors used in this study (Chapter 3), walking with a WW reduced the number of steps taken significantly as compared to walking unaided (240). Thus, a decrease in stride length when walking with a WW was unlikely to explain the increase in steps taken daily.

The effect size quantifies the effectiveness of the use of a WW. In this study, the effect size determined for steps/day was 0.20, which is considered small (203). This effect size remained small (0.26) when data from those participants who had an exacerbation during the study period were excluded from the analyses. This finding of a change in the mean number of steps taken each day when using a WW is particularly notable given that previous studies of interventions aimed at increasing PA in individuals with COPD have demonstrated little or no benefit. For example, one study found that providing ambulatory oxygen for use in the home had no significant impact on PA despite a gradual increase in oxygen usage over an 8-week period (162). Furthermore, a meta-analysis on the effect of supervised exercise training programs in individuals with COPD, lasting between 6 weeks and 6 months, found only a trivial improvement in PA (effect size of 0.12) equivalent to an increase

of approximately 5 minutes of walking time per day (55). In this meta-analysis, providing supervised exercise training at least three times a week for a minimum of 8 weeks and extending the intervention period for those who had an exacerbation, were suggested to increase the likelihood of demonstrating a positive effect on PA (55). However, there were no published RCTs in this meta-analysis (55). The study by de Blok et al (31), which had a 9-week comprehensive PRP as an intervention, was the only randomised trial to demonstrate an actual effect size and the reported improvement of 673 steps/day is similar to the results of the present study. That is, providing a device like a WW over a short period of 5 weeks was as effective as that of a 9-week comprehensive PRP that required a considerable level of commitment and personal investment.

The only other intervention that has significantly increased PA in individuals with COPD is lung transplantation. In a cross-sectional study by Bossenbroek et al (166), lung transplant recipients were significantly more active compared to lung transplant candidates. Langer et al (167) found that the participants who did not participate in a supervised exercise training 3 months after lung transplantation, increased the number of daily steps by 750; a change of similar magnitude to that found in this study. However, lung transplantation is a costly, risky invasive surgical procedure that is available for only a minority of individuals with end stage COPD (266). In comparison, a WW is inexpensive and risk free, thus providing a WW that resulted in a similar change in daily steps as lung transplantation would be an alternative to improve PA in the majority of individuals with COPD with significant functional limitation due to dyspnea. Nevertheless, this comparison should be guarded as lung transplantation candidates had end stage COPD, unlike the participants in this study who were categorised as having moderate or severe COPD.

In the secondary analyses, the only factor which appeared to influence the effect a WW had on the magnitude of change in PA was the extent of functional limitation due to dyspnea. Participants with a MMRC dyspnea grade ≥ 3 increased their steps/day significantly more than those with a MMRC dyspnea grade 2. This improvement observed in those participants with a MMRC dyspnea grade ≥ 3 is important as Watz et al (106) demonstrated a progressive reduction in PA with increasing MMRC dyspnea grade in individuals with COPD. The reasons why

individuals with greater functional limitation due to dyspnea appeared more likely to increase the number of steps taken per day when using a WW may be due to the physiological benefits of the forward lean with arm bracing position as well as the reduction in metabolic cost of walking with a WW (23, 24). The fact that the WW is equipped with a seat allowing participants to have a seated rest when required (as in those individuals with COPD who graded themselves as MMRC dyspnea grade ≥ 3) might also have explained the ability of participants to walk further, but the number of seated rests taken was not able to be measured in this study. Thus, an individual's need for a rest due to intolerable dyspnea, after walking for only a few minutes, may be an important criterion for physiotherapists to consider when deciding whether to recommend a WW to individuals with COPD with the aim of increasing PA. This finding is supported by the study by Solway et al (21) where the need to rest during an unaided 6MWT was a significant predictor of improved 6MWD and perception of dyspnea when a WW was used.

The three participants with a MMRC dyspnea grade 2 had a reduction in mean steps/day when a WW was provided. This result probably reflects that two of the three participants (67%) experienced an acute exacerbation of their COPD during the WW 5-week period. In the primary analysis, the magnitude of change in PA was greater when the participants who had an exacerbation were removed from the analysis. Given that exacerbations have been shown to reduce daily activity in individuals with COPD, both during the exacerbation and after recovery (36), this finding was unsurprising.

We found that the use of a WW had no significant impact on the domains of the CRDQ. This is consistent with the findings of Gupta et al (178). However, Gupta et al (178) found a higher score in the mastery domain of the CRDQ in those who used the WW at least three times a week during their 8-week study period compared to those who used the WW infrequently (5.2 ± 0.8 versus 4.7 ± 0.6 points per item, $p = 0.014$). Based on their activity diary, the participants in the present study used the WW frequently (at least three times a week). Thus, while frequency of use in the current study was acceptable, it is possible that the 5-week study period might have been too short to register an improvement of HRQoL with the use of a WW. Sandland et al (162) found in an 8-week RCT investigating the provision of

ambulatory oxygen following 7 weeks of rehabilitation, no significant change in CRDQ. This suggests that participants may require more time to realise any benefit in HRQoL following interventions that require no effort from them, such as the provision of ambulatory oxygen (162), or in this study, a WW.

In this study, the majority of the participants who expressed a fear of falling found the use of the WW reduced this fear. However, no change was observed in PA in these individuals when provided with a WW. This implies that although the fear of falling was reduced when using a WW, this did not necessarily empower individuals with COPD to be more active. The issue of falls is important in this population, as falls have negative consequences for older adults such as activity avoidance, fractures and even death (267). Individuals with COPD are at increased risk of falls for several reasons including muscle weakness, multiple medications and reduced PA (26). Furthermore, individuals with COPD have a higher prevalence of osteoporosis than those without COPD (268), increasing their risk of fall-related fractures (25). The fear of falling has been shown to result in a loss of autonomy and thus limit activity, which in turn can reduce quality of life (269). A study by Beauchamp et al (270) demonstrated that reduced confidence in performing activities without losing balance was a predictor of falls risk in individuals with COPD. The present study demonstrated that the use of a WW reduced the fear of falling in most individuals with COPD. It is likely that it also improved balance confidence and might play a role in reducing falls. Thus, although it is possible that the use of a WW reduced falls risk in these study sample of individuals with COPD, the impact of this reduced falls risk on PA was not significant.

In this study, only three (16%) participants felt embarrassed using a WW during their daily life. This percentage is lower than that reported in earlier work where 19% to 48% of participants felt embarrassed about using a WW (252, 271). Embarrassment using the WW appeared to be related to it being viewed as a visual indication of disability and aging (271). The fact that participants in the present study underwent a period of familiarisation with the WW during supervised walking training may have contributed to the low number of participants reporting that they felt embarrassed using a WW.

Barriers to using the WW in the current study included difficulty getting the WW into and out of the car and an inability to use it home at due to space constraints. These findings are similar to those reported previously (252). Specifically, in the study by Hill et al (252), 15 (56%) individuals reported difficulty moving the WW into and out of the car independently. These barriers could be overcome by reducing the weight of the WW using light weight yet durable materials and having smaller wheels.

4.5.1 Implications

Providing a WW to suitable individuals with COPD and familiarising them with the use of the WW during supervised walking training as part of a PRP has the potential to increase the number of steps taken each day and the time spent walking at a moderate intensity. Given these results, using a WW during the walking training component of a PRP may enable some individuals with COPD to increase their walking pace and might therefore be a useful training adjunct, particularly in those with the marked functional limitation due to dyspnea.

4.5.2 Limitations

The major limitations of this study related to the small sample size for some of the analyses and the fact that the participants in this study were highly selected. A larger sample size of a broader spectrum of COPD severity would have been beneficial. However, the sample size was sufficient to demonstrate a significant difference in steps taken per day when the WW was available. Despite the increase in the number of average daily steps taken, there was no change in time spent in sedentary behavior, namely time spent supine, sitting or standing. This suggests that additional strategies are required to reduce sedentary behavior. Although the participants were highly selected, they were representative of individuals with COPD who undergo pulmonary rehabilitation. The duration of 5 weeks to establish the effect of a WW on HRQoL may have been insufficient.

4.6 Conclusion

To date, this is the only study to show an increase in the number of steps taken per day and the time spent walking at a moderate intensity when a WW was provided to selected individuals with COPD who had used it previously during supervised exercise training. The use of a WW had no significant impact on HRQoL, a finding which may be attributed to the short duration of 5 weeks where the participants had a WW. The main barrier towards the use of a WW was difficulty lifting the WW into and out of the car.

CHAPTER 5

WALKING AND FEEDBACK TRAINING (WAFT)**5.1 Overview**

This chapter summarises the data pertaining to a multi-centre randomised controlled trial (RCT) of an 8-week ground walking training program conducted in Sydney, New South Wales and Perth, Western Australia. The methodology employed in the trial is described in detail within this chapter. The reporting of outcome data is restricted to those variables which are relevant to the doctoral program of research presented in this thesis. The data reported in this chapter are further analysed in the following chapter to determine the minimal detectable difference (MDD) for endurance shuttle walk test (ESWT) performance (Chapter 6).

Pulmonary rehabilitation has been shown to be effective in increasing exercise capacity, improving health-related quality of life (HRQoL) and reducing hospital admissions in individuals with chronic obstructive pulmonary disease (COPD) (5). In pulmonary rehabilitation, exercise training is of paramount importance (5). The lower limb muscles in individuals with COPD are weak and metabolically inefficient (28), thus endurance exercise of the leg muscles, such as walking (ground-based or treadmill) and stationary cycling is an essential component of exercise training during pulmonary rehabilitation (5). Walking training is particularly suitable as a method of exercise training for individuals with COPD as it is an activity that is part of their daily lives (29), inexpensive as no specialised equipment is required, serves as a form of transport and protects against mobility loss in older adults (30).

Walking exercise has been recommended to be incorporated into the exercise training component of pulmonary rehabilitation (5). There are only six randomised studies that examined the effectiveness of ground walking training as the sole training modality in individuals with COPD (40, 192, 272-274).

In the first randomised study, one of the intervention group was doing solely 20 minutes of ground walking training in which the intensity was not specified, yet

reported a significant improvement in 6-minute walk distance (6MWD) of 122 m after 8 weeks of training (40). The second randomised study prescribed the intensity of ground walking training at 70% of the maximum speed attained on the incremental shuttle walk test (ISWT), demonstrated no change in incremental shuttle walk distance (ISWD) after 12 weeks of training (272). In these two studies, the walking training was unsupervised. The third study that prescribed unsupervised ground walking at an intensity of approximately 3 to 4 km/h demonstrated no significant change in peak rate of oxygen consumption (VO_{2peak}) after 8 weeks (273). The fourth study randomised participants after recovery from an exacerbation of COPD to supervised walking training or a control arm (192). The walking training group covered 125% of their best 6MWD performed on a treadmill in a 15 minute period three times a day and improved their 6-minute walk distance (6MWD) at the 3- and 6-month assessment (192). The fifth study had participants walking at 80% of their estimated VO_{2peak} derived from the ISWD. The group who undertook walking training paced by music installed on a cell phone showed a significant improvement in their ISWD at 8-week period compared to the group who undertook walking training without pacing (274). In the sixth study, the participants randomised to ground walking at an intensity of 75% of the peak walking speed achieved in the ISWT improved ESWT performance to a greater extent than occurred in a group randomised to supervised cycling training (39).

Of the above studies that have examined ground walking training as the sole training modality in individuals with COPD, one used a very small sample size ($n = 6$) (40), and in four studies, the training was unsupervised so the exercise intensity was not controlled (192, 272-274). Although the last study (39) included supervised walking training, it had a small sample of participants in the walking training group ($n = 17$) and the cycling training group ($n = 15$) to compare.

Despite the strong evidence that supervised exercise training reduces dyspnea and fatigue (5, 6), increases exercise capacity as well as improves HRQoL (5-7), the impact on physical activity (PA) seems modest. Exercise training is muscle and activity specific. Walking training has been shown to improve outcomes in field walking tests to a greater extent than cycling training (39) and upper limb training (40). Thus, it is possible that walking as a sole modality of exercise training may

confer greater gains in daily PA than other exercise modalities such as cycling as walking is an integral part of daily life for individuals with COPD (9).

In summary, there is little evidence that supervised, individually tailored ground walking training alone, in which the exercise intensity is progressed with the aim of achieving optimal training responses, is effective at improving exercise capacity and PA in individuals with COPD. This gap in evidence is important to address as, if found to be effective, a walking program has the advantage that it is low cost and requires few resources. This in turn would support the widespread establishment of walking training programs, particularly in rural and remote areas, as well as in programs run in metropolitan areas. This would potentially provide a large number of individuals with COPD access to such programs, which could be conducted independent of expensive exercise equipment.

The current study was part of a multi-centre trial conducted in Sydney, New South Wales and Perth, Western Australia, examining the effect of supervised ground walking training on the exercise capacity and HRQoL of individuals with COPD. The study had two primary aims. The first aim was to evaluate the effect of short-term, supervised, individually tailored, ground walking training compared to usual care in individuals with COPD, on exercise capacity and HRQoL. The second aim was to evaluate whether, after the short-term walking training, the use of feedback, progressive goal setting and participant support during a program of long-term home-based walking training could maintain any gains conferred in exercise capacity and HRQoL compared to simple instructions about maintaining regular exercise. The findings of this study in relation to these two aims forms the basis of a thesis by a PhD student enrolled at the University of Sydney. The remainder of this chapter summarises the findings of the study that are relevant to the doctoral program of research presented in this thesis; namely, the impact of a short-term, supervised, individually tailored, ground walking training as a sole exercise modality on ESWT performance and PA in individuals with COPD.

5.2 Methodology

5.2.1 Overall aim

The aim of this study was to examine the magnitude of change in clinical outcomes such as functional exercise capacity and PA after a short-term, supervised, individually tailored, ground walking training program in individuals with COPD.

5.2.2 Research questions

- i. Does an 8-week supervised, individually tailored, ground walking training program change ESWT performance in individuals with COPD?
- ii. Does an 8-week supervised, individually tailored, ground walking training program change PA in individuals with COPD?

5.2.3 Research hypotheses

In individuals with COPD, functional exercise capacity, namely ESWT performance, as well as PA will improve after participating in an 8-week supervised, individually tailored, ground walking training program.

5.2.4 Study design

A prospective, single-blind, RCT was undertaken with participants randomised into one of three groups: a walking training group (WG), a walking training with post-training feedback group (WFG) and a usual care group. Both the WG and WFG underwent an identical ground walking training intervention over an 8-week period. All participants were recruited from Sydney or the Perth metropolitan area. After the 8-week period, the participants in both the WG and WFG were followed up over a 12-month period. The participants in the WG were provided with written instructions to walk 45 minutes on at least 3 days a week and a weekly diary to record the duration of each walk. The participants in the WFG received biofeedback in the form of a pedometer and regular phone calls to set goals and provide support, in addition to the same written instructions and weekly diary to record the steps taken during each walk. However, this long term study form the basis of a thesis by the PhD student enrolled at the University of Sydney and will not be included in this thesis.

5.2.5 Ethical approval

In Sydney, approval to conduct the study was granted by the Human Research Ethics Committees of the University of Sydney (2012/523), Royal Prince Alfred Hospital (HREC 09/RPAH/31), Manly Hospital (1008-306M), Concord Hospital (09/CRGH/70), Hornsby Hospital (0907-192M) and Prince of Wales Hospital (09-G-055). In Perth, approval to conduct the study was granted by the Human Research Ethics Committees of Curtin University (HR 50/2009), Sir Charles Gairdner Hospital (2009-026), Bentley Hospital (S/10/320) and Royal Perth Hospital (RA-10/010). Written, informed consent was obtained from all participants. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000472279).

5.2.6 Participants

All participants were recruited from patients who had been referred to the pulmonary rehabilitation programs (PRP) in Sydney and Perth. The inclusion criteria comprised aged > 40 years, medical diagnosis of COPD and a smoking history of ≥ 10 pack-years. The number of pack years was defined as the number of cigarettes smoked per day divided by 20, then multiplied by the number of years that the participant had smoked (58). Exclusion criteria comprised: (i) musculoskeletal, cardiovascular or neurological conditions likely to adversely affect performance during assessments or training, (ii) participation in supervised exercise training within the last 12 months, (iii) prescription of long term oxygen therapy or ambulatory oxygen during exercise training, (iv) inability to maintain an oxygen saturation > 83% during the ESWT and, (v) body mass index > 35 kg/m².

Participants were randomly allocated to groups using a computer-generated random number sequence with stratification for: (i) location (Sydney or Perth) and hospital, (ii) total score obtained on the Saint George's Respiratory Questionnaire (SGRQ) (score < 45 or ≥ 45), (iii) disability level based on 6MWD ($\leq 70\%$ or > 70% predicted normal value [(247)]) and, (iv) severity of COPD (volume exhaled during the first second of a forced expiration [FEV₁] < 40% or $\geq 40\%$ predicted normal value) (246).

All participants had their medical management optimised at baseline in accordance with the COPD-X Plan (275). This included a COPD action plan with the aim of educating participants about managing their condition when stable and during an exacerbation (275). Participants randomised to the usual care group did not perform any exercise training and were not given any instructions regarding exercise. At the end of the 8-week period these participants were offered the standard PRP, at which point their involvement in the study ceased.

5.2.7 Walking training

The initial training intensity prescribed was equivalent to 80% of the average walking speed achieved during the better of two 6-minute walk tests (6MWTs) (169, 276). The 6MWT represents a maximal or near maximal symptom-limited test in individuals with moderate to severe COPD (277, 278), thus data from the 6MWT can be used to prescribe the intensity for walking training (169). This prescription was consistent with evidence-based guidelines (5) which recommend that exercise training, in order to achieve an adequate training stimulus, should be performed at a high-intensity, at least three times a week for 20 to 60 minutes per session (279), at an intensity exceeding 60% of peak exercise capacity (6). The training intensity used in this study was appropriate for individuals with COPD (169) and has demonstrated efficacy as measured by an improvement in 6MWD and HRQoL (276, 280). Across the training sites, the walking program took place on flat walking tracks that ranged in lengths from 26 to 100 m. Each participant was given an individualised goal representing the number of track lengths to complete for a set duration (Appendix C) (280). The track length was consistent for each individual.

The 8-week exercise program consisted of either three supervised sessions a week, or two supervised sessions and one unsupervised exercise session a week for individuals who were unable to commit to travelling to the hospital three times a week for supervised training. This resulted in a maximum of 24 training sessions (supervised and unsupervised). The unsupervised sessions were recorded in a diary. This number of exercise sessions has been shown to be sufficient to confer a benefit in HRQoL and 6MWD (281) for most patients with moderate to severe COPD

(Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade II –IV, (56)) and dyspnea (Modified Medical Research Council [MMRC] dyspnea grade 2-4).

In the event of a respiratory exacerbation, training was postponed until the participant was clinically stable (275). An exacerbation was defined as a sustained worsening of the patient's symptoms from his or her usual stable state that was beyond normal day-to-day variations, was acute in onset and necessitated a change in regular medication (282). If participants had an exacerbation or were unwell, the training period was extended to a maximum of 10 weeks to allow participants to complete a minimum of 16 sessions (supervised and unsupervised).

Participants were permitted to take short rests during walking training in the event of intolerable symptoms. The total exercise time (excluding rests) was 30 minutes at the commencement of walking training. This was progressed by increasing the distance walked during training by increasing the duration of exercise by 5 minutes after every sixth session to a maximum of 45 minutes by session 19. A constant walking pace was maintained during each walking training session. During walking training, a rating of three (moderate breathlessness) to four (somewhat severe) on the modified Borg scale for dyspnea (283) was used to titrate exercise intensity. Once the required duration was reached, if symptoms permitted, the intensity of exercise was increased by increasing walking speed or, if walking speed became limited by stride length, progression was achieved by adding weights in 2 kg increments worn on a waist belt.

Percutaneous oxygen saturation and pulse rate were measured before and after walking training using a hand-held pulse oximeter (Respironics/Novamatrix 513, Murrysville, Pennsylvania, United States [US] or RAD-5v, Masimo Corp, Irvine, California, US). Ratings of perceived dyspnea (283), perceived exertion and leg fatigue (284) on a scale of 0 to 10, were recorded at the conclusion of each training session.

5.2.8 Outcome measures

In all participants, the outcome measures were assessed before and immediately after the 8-week intervention period. All assessments following the intervention period

were performed by a research assistant who was blinded to the participant's group allocation. Participants were instructed not to reveal their group allocation to the research assistant.

The sequence of exercise testing and administration of questionnaires is shown in Figure 5-1. Both before and after the intervention period, assessments were completed over 2 days separated by at least 24 hours. In total, three exercise tests and four questionnaires were completed (Figure 5-1). On the first day of assessment, the participant's medical history (including smoking history) was recorded, and height, weight and spirometry (EasyOne Plus, new Diagnostic Designs Medical Technologies Inc., Andover, Massachusetts, US) were measured. Both before and after the 8-week intervention period, a SenseWear armband (BodyMedia Inc., Pittsburgh, Pennsylvania, US) was given to all participants on the second day of testing with instructions to wear the armband for 7 complete days.

5.2.8.1 Exercise capacity

Three field walking tests, namely the ISWT, ESWT and 6MWT were used to measure exercise capacity. Each of these field walking tests was repeated twice (Figure 5-1). These tests are responsive to change following exercise training in individuals with COPD (7, 44, 285). During the walking tests, percutaneous oxygen saturation using a hand-held pulse oximeter with a finger probe (Respironics/Novamatrix 513, Murrysville, Pennsylvania, US or RAD-5v, Masimo Corp, Irvine, California, US) and heart rate (Polar a1 heart rate monitor; ©Polar Electro, Kempele, Finland) was continuously monitored. The ISWT was performed over a 10 m course and externally paced with walking speed increasing every minute (286). The ESWT was performed on the same track as the ISWT at a speed equivalent to 85% of the participant's VO_{2peak} estimated from the distance walked during best of two ISWTs (287). The 6MWT was performed in accordance with published guidelines (243), but modified to include standardised encouragement every 15 sec during rests (288). Dyspnea was measured using the modified Borg scale before each walking test (283). At the end of each walking test, dyspnea, rating of perceived exertion and leg fatigue (284) on a scale of 0 to 10 were recorded. Data from the best test (i.e. maximum distance walked) were used in the analyses. Each

test was separated by a 30-minute rest period to allow recovery from dyspnea and fatigue elicited from the previous test (169, 243).

Within this chapter, only data relating to the change in ESWT and PA are reported in detail. The rationale for selecting the ESWT as the primary outcome measure is provided in the following paragraph.

Endurance shuttle walk test

The ESWT is an externally paced, constant workload field walking test that has been shown to be more responsiveness than other field-based assessments of exercise capacity (285, 287). The ESWT is performed over a 10 m course (287). Participants were instructed to walk around two cones, positioned 0.5 m from each end, following the speed dictated by an audio signal. The ESWT was performed at a walking speed equivalent to 85% of the participant's VO_{2peak} . This VO_{2peak} was predicted from the distance walked during best of two ISWTs, using the equation: $4.19 + (0.025 \times ISWD)$ (287). The walking speed and level for the ESWT that corresponded to 85% of the predicted VO_{2peak} was determined using a graph of the relationship between predicted VO_{2peak} (ml/min/kg) and ESWT walking speed (km/h). The ESWT has a total of 16 levels, each relating to a specific walking speed, ranging from 1.78 km/hr to 6 km/hr. Dyspnea (modified Borg scale) (283) and rating of perceived exertion (284) on a scale of 0 to 10 were recorded at the end of each minute during the test. The ESWT was terminated if participants were not able to keep up with the speed after being given a warning to keep pace when they were behind the speed for the first time (e.g. due to dyspnea or leg fatigue). Each participant performed two ESWTs which were performed on separate days as two ESWTs performed on the same day has demonstrated little variability (289), which could be due to fatigue or boredom with the test. As the ESWT was the last walking test conducted on the first day of testing, having the ESWT as the first walking test on a separate day could negate fatigue, boredom or learning effect. The ESWT has a pre-determined maximum duration of 20 minutes (287). A study by Revill et al (287) found that seven (30%) of their 21 participants walked for more than 17 minutes on the ESWT at their baseline assessment prior to pulmonary rehabilitation. Further, in another study, six (35%) participants with COPD reached the 20-minute completion time of

the ESWT at the end of a walking training program (39). Thus, in an attempt to avoid a ‘ceiling effect’ (i.e. participants reaching the 20-minute maximum post-training), any participant who, at baseline, was able to complete more than 5 minutes on the ESWT and expressed that this pace was comfortable and had the ability to continue walking, had their ESWT intensity increased to the next level. The higher level or the faster speed of the ESWT was selected for post intervention ESWT.

5.2.8.2 Health-related quality of life

The SGRQ and interviewer-administered Chronic Respiratory Disease Questionnaire (CRDQ) with an individualised dyspnea domain were used to measure HRQoL. In the individualised dyspnea domain of the CRDQ, the participants were asked at baseline to elicit the five most important activities during which they had experienced dyspnea in the past weeks and these activities were used during the administration of CRDQ post intervention period. The SGRQ measures symptoms, activities and impact (214), while the CRDQ measures dyspnea, fatigue, emotional functioning and mastery (213). Both have been shown to be valid, reliable and responsive to changes following exercise training in participants with COPD (290, 291). The changes in HRQoL outcomes following the intervention period are not reported in this chapter as they are not related to the aims of this thesis.

5.2.8.3 Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (292). Scores range from 0 (no anxiety or depression) to 21 (maximum score for anxiety or depression) (293). The HADS has been shown to be responsive to exercise interventions in individuals with COPD (218). The changes in HADS scores following the intervention period are not reported in this chapter as they are not related to the aims of this thesis.

5.2.8.4 General self-efficacy

Self-efficacy was measured using a validated General Self-efficacy Scale (GSES-12). This consisted of 12 items, subdivided into initiative, effort and persistence subscales (294). Scores range from 3 to 15 for the initiative subscale, 5 to

25 for the effort subscale and 4 to 20 for the persistence subscale; with higher scores indicating greater self-efficacy (295). The changes in GSES-12 scores following the intervention period are not reported in this chapter as they are not related to the aims of this thesis.

5.2.8.5 Physical activity

Daily PA was measured using the SenseWear armband (version Pro 3). The rationale for selecting PA as the secondary outcome measure was to determine whether supervised ground walking training could result in an increase in activity compared to usual care.

Participants wore the SenseWear armband (Figure 5-2) on the bulk of the triceps brachii muscle of the right arm over 9 days, however, the data collected during the first and last day were excluded as measures were not available over a full 24 hour period (148). The SenseWear armband measures 2.4 by 8.8 by 5.6 cm, weighs 82 g (135), and is a portable metabolic monitor that integrates bi-axial accelerometry with non-invasive physiologic sensors that detect galvanic skin resistance, heat flux, body temperature and near body ambient temperature (138). The SenseWear armband has been shown to provide accurate data when measuring energy expenditure in individuals with COPD, while undertaking five tasks comprising supine lying, sitting, standing and walking at two different speeds (13). The SenseWear armband has also been shown to be able to detect small changes in average energy expenditure resulting from a moderate increase in average walking speed of 14 m/min (13). Studies pertaining to the use of the SenseWear armband have been reviewed in Chapter 2 (part 2). The SenseWear armband, being a multi-sensor motion device, is able to estimate energy expenditure across a spectrum of activities of daily living compared to a uni-axial motion sensor such as the ActivPALTM or a step counter such as the StepWatchTM Activity Monitor. Data provided by the SenseWear armband comprised total energy expenditure (TEE) in kilocalories, steps per day and active energy expenditure (AEE) in kilocalories (kcal). Only data from days when the SenseWear armband was worn for at least 85% of the time were included in the analyses.

A position statement by American College of Sports Medicine (ACSM) defined moderate intensity activity for adults aged ≥ 65 years as requiring between 3.2 to 4.7 metabolic equivalents (METs) (99). Thus, in this study, PA above 3 METs was used as a cut-off point to define AEE for individuals with COPD.

<p>Sequence of tests and questionnaires conducted on 1st day:</p> <ol style="list-style-type: none"> 1. ISWT 1st test 2. HADS 3. GRC scale for walking ability and activity level* 4. ISWT 2nd test 5. SGRQ 6. ESWT 1st test 	<p>Sequence of tests and questionnaires conducted on 2nd day:</p> <ol style="list-style-type: none"> 1. ESWT 2nd test 2. CRDQ 3. 6MWT 1st test 4. GSES 5. 6MWT 2nd test
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Figure 5-1: Sequence of walking tests and questionnaires on the two separate days pre and post 8-week period.

* This questionnaire was only given at the end of the 8-week period.

CRDQ, Chronic Respiratory Disease Questionnaire; ESWT, endurance shuttle walk test; GSES, General Self-efficacy Scale; GRC, Global Rating of Change; HADS, Hospital Anxiety and Depression Scale; ISWT, incremental shuttle walk test; SGRQ, Saint George's Respiratory Questionnaire; 6MWT, 6-minute walk test.



Figure 5-2: SenseWear armband worn on the right arm.

5.2.8.6 Global rating of change

A global rating of change (GRC) scale was used for participants to rate if they had improved or worsened in their walking ability (Appendix D) and PA (Appendix E) over time (45). This was administered after the 8-week intervention period to all participants.

For walking ability, participants were asked “Since you started this research program, has there been any change in your walking ability?” Participants were then asked to indicate if their walking ability had ‘improved’, ‘worsened’ or ‘stayed the same’. For PA, participants were asked “Since you started this research program, has there been any change in how active you are in your daily life?” Participants were then asked to indicate if their PA had ‘increased’, ‘decreased’ or ‘stayed the same’. If the response was ‘improved’ or ‘worsened’ and ‘increased’ or ‘decreased’, they were required to rate the degree of change on a 7-point Likert scale. The degree of change ranged from: 1 - almost the same or hardly any change at all, 2 - a little change; 3 - somewhat change, 4 – moderate change, 5 - a good deal change, 6 - a great deal change and 7 - a very great deal change.

5.2.8.7 Descriptive measures

Details pertaining to age, gender, height, weight, smoking history and current medication were recorded. Spirometry was measured before and after the 8-week intervention period. The number of respiratory-related hospital admissions in the previous 12 months was also recorded at baseline.

5.3 Data management and analyses

All analyses were carried out using the Statistical Package for Social Sciences (SPSS version 18.0; Chicago, IL, US) with a probability value (p) ≤ 0.05 used to indicate statistical significance. Data are expressed as mean \pm standard deviation (SD) unless otherwise stated. The assumption of normality was assessed using frequency histograms. Data that did not follow a normal distribution were analysed using non-parametric statistical tests. The primary analysis compared outcomes in the training groups with the usual care group. Analysis of covariance (ANCOVA) was conducted

for the between-group comparisons with baseline values as the covariate to account for selection bias. Intention-to-treat analyses were conducted regardless of the participants' attendances of the exercise sessions with no imputation of missing values.

As not every participant wore the SenseWear armband for at least 85% of the time for 7 whole days, an analysis was undertaken to determine the minimum number of days of PA data required to provide a valid representation of the PA of the participants to account for missing data. The variability in outcome measures of PA has been shown to increase with reduced severity of COPD (106) and 3 to 5 days of accelerometer monitoring is recommended to obtain a reliable measure of PA (148). In order to assess whether 3 or 5 days of SenseWear data were required to provide valid data representation for PA, a list of random numbers (ranging from 1 to 7) was generated using Random.org and this list was used to select 3 random days and 5 random days of PA data in order to compare if there was any significant difference in TEE, steps per day and AEE > 3 METs using paired t-tests. Similarly, testing was conducted to compare any 2 random weekdays to 2 weekend days.

5.3.1 Sample size

A sample size calculation revealed that 132 participants were required to provide 80% power to detect a minimum 10 point difference in the mean total CRDQ score between the short-term supervised walking training groups (n = 88) and the usual care group (n = 44) (after adjusting for group size imbalance). This calculation assumed a standard deviation (SD) of 17 points as previously reported (117). This number was increased from 132 to 159 to allow for 20% loss to follow-up.

5.4 Results

The baseline characteristics (including results of the three walking tests and scores from the four questionnaires) of all participants are summarised in this section. The data pertaining to the impact of a short-term, supervised, individually tailored, ground walking training program as the sole exercise modality on ESWT performance and PA in individuals with COPD are presented in the following sections.

5.4.1 Participants

A total of 399 individuals with COPD were screened of whom 256 were excluded as they did not meet the inclusion criteria or refused to participate in the study. A total of 143 participants were recruited from patients who had been referred to the PRPs in Sydney (86 participants) and Perth (57 participants). A flow diagram illustrating the recruitment of participants to this study and their follow-up is presented in Figure 5-3. The number of participants randomised to the walking training groups (WG and WFG) was 95 and 48 participants were randomised to the usual care group. A total of 45 (47%) participants in the walking training groups and 28 (58%) participants in the usual care group had a respiratory-related hospital admission in the 12 months prior to the intervention period. In the walking training groups, 50 (53%) participants attended supervised exercise training three times per week and 17 (18%) participants attended supervised exercise training twice a week for 10 weeks. A total of 20 (21%) participants attended two supervised sessions each week and completed one unsupervised exercise session each week.

5.4.2 Baseline characteristics

Baseline characteristics of the participants are summarised in Table 5-1. The 143 participants were aged 69 ± 8 years and comprised 84 (59%) males and 59 females (41%). There was no significant difference in baseline characteristics between the walking training group and the usual care group. At baseline, 36 (25%) of the 143 participants performed a second ESWT at a faster speed.

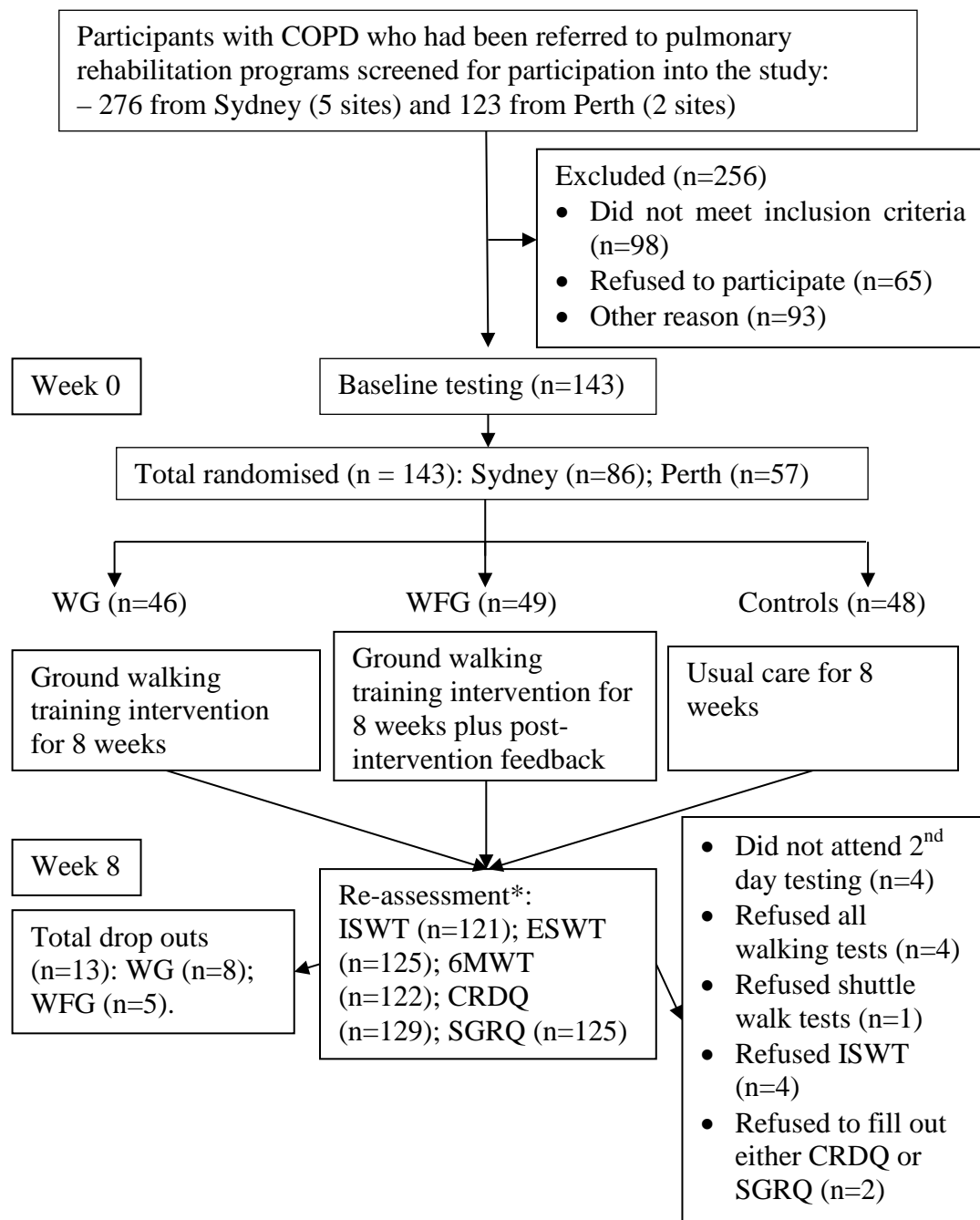


Figure 5-3: Flow diagram of participants through the study.

* The re-assessments may not have included all three walking tests and four questionnaires that were conducted at baseline. COPD, chronic obstructive pulmonary disease; CRDQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; ISWT, incremental shuttle walk test; SGRQ, Saint George's Respiratory Questionnaire; WAFT, walking and feedback training; WFG, walking training with post-training feedback group; WG, walking training group; 6MWT, 6-minute walk test.

Table 5-1: Baseline characteristics of the participants.

Demographic data	Walking training groups (n=95)	Usual care group (n=48)	Total (n=143)
Gender, n (%)	56M (59%) / 39F (41%)	28M (58%) / 20F (42%)	84M (59%) / 59F (41%)
Age (years)	69±8	68±9	69±8
BMI (kg/m ²)	25.3±4.6	27.3±6.0	26.0±5.2
Smoking (pack-years)	49±29	49±42	49±34
MMRC dyspnea grade	1 (1 to 2)	2 (1 to 2)	1 (1 to 2)
Grade 0, n (%)	6 (6%)	4 (8%)	10 (7%)
Grade 1, n (%)	46 (49%)	18 (38%)	64 (45%)
Grade 2, n (%)	25 (26%)	19 (40%)	44 (31%)
Grade 3, n (%)	18 (19%)	6 (12%)	24 (17%)
Grade 4, n (%)	0	1 (2%)	1 (<1%)
BODE index	3 (2 to 4)	3 (1 to 4)	3 (2 to 4)
Pulmonary Function			
FEV ₁ (L)	1.13±0.42	1.19±0.47	1.15±0.44
FEV ₁ (% predicted)*	43±15	43±15	43±15
FVC (L)	2.71±0.84	2.76±0.83	2.73±0.84
FVC (% predicted)*	76±17	75±18	75±18
FEV ₁ /FVC ratio	0.43±0.14	0.43±0.12	0.43±0.13
Walking Tests			
ISWD (m)	316±109	328±120	320±112
ESWT speed (m/s)	4.4±0.8	4.4±0.9	4.4±0.8
ESWT distance (m)	395±306	373±253	388±289
ESWT time (sec)	310±198	292±167	304±187
6MWD (m)	462±83	464±95	463±87
6MWD % predicted	74±13	74±14	74±13

Table 5-1: Continued

Chronic Respiratory Disease Questionnaire#	Walking training groups (n=94)	Usual care group (n=48)	Total (n=142)
Dyspnea	3.5±1.1	3.6±1.0	3.6±1.1
Fatigue	4.2±1.3	4.2±1.1	4.2±1.2
Emotional function	4.9±1.3	4.9±1.2	4.9±1.3
Mastery	5.2±1.3	5.1±1.2	5.2±1.3
Total score	4.5±1.0	4.5±0.9	4.5±1.0
Saint George's Respiratory Questionnaire			
Symptoms	55.8±22.1	60.8±22.5	57.5±22.3
Activity	63.6±19.6	64.3±20.2	63.8±19.7
Impact	33.1±18.0	32.4±16.6	32.9±17.5
Total score	46.5±17.1	46.7±15.9	46.6±16.6
Hospital Anxiety and Depression Scale			
Anxiety	7±4	6±4	6±4
Depression	5±4	5±3	5±4
General Self-efficacy Scale			
	Walking training groups (n=93)	Usual care group (n=45)	Total (n=138)
Initiative	12±3	11±3	11±3
Effort	19±4	20±3	19±4
Persistence	15±3	15±3	15±3
Total score	46±9	45±7	46±8

Data are mean±standard deviation or median (interquartile range). *predicted values based on NHANES (246). # scores expressed as points per item.

BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity index; ESWT, endurance shuttle walk test; F, female; FEV₁, volume exhaled during first second of a forced expiration; FVC, forced vital capacity; ISWD, incremental shuttle walk distance; kg, kilograms; L, litres; M, male; m, meters; MMRC, Modified Medical Research Council (grade 0 to 4); n, number of participants; sec, seconds; %, percentage; 6MWD, 6-minute walk distance.

5.4.3 Primary outcome: change in exercise capacity after walking training program

The ESWT was completed both before and after the 8-week intervention period by 78 (82%) participants randomised to the walking training groups (WG and WFG) and 47 (98%) participants in the usual care group. The duration and distance achieved in the ESWT significantly increased for participants in the walking training groups after the 8-week period (Table 5-2) by 245 ± 313 sec and 289 ± 376 m respectively, representing an improvement of 92 ± 148 %. In contrast, the duration and distance achieved in the ESWT for the usual care group did not change significantly over time (38 ± 229 sec and 54 ± 325 m respectively; representing a difference of 34 ± 102 %) (Table 5-2). In total, 18 participants reached the 20-minute limit of the ESWT (walking training groups [n=16; 17%] and usual care group [n=2; 4%]) at the follow-up assessment.

Of the 78 participants in the walking training groups, 69 (88%) completed the GRC scale for walking ability after the intervention period and 40 (85%) of the 47 participants in the usual care group completed the GRC scale for walking ability after the 8-week control period (Table 5-3). The median score from the GRC scale for the walking group was 4 (i.e. moderately better) whereas the median score from the GRC scale for the usual care group was 0 (i.e. no change). Based on the GRC ratings provided by the participants after the 8-week period, none of the participants who completed the walking training reported deterioration in their walking ability.

Table 5-2: Endurance shuttle walk test performance for the walking training groups versus the usual care group.

	Walking training groups						Usual care group						Mean difference (95% CI) between groups*	p value*
	n	Baseline	Week 8	Change	95% CI	p value	n	Baseline	Week 8	Change	95% CI	p value		
ESWT (sec)	78	330±208	574±389	245±313	174 to 315	<0.001	47	294±168	333±227	38±229	-29 to 106	0.26	208 (104 to 313)	<0.001
ESWT (m)	78	422±324	710±504	289±376	204 to 373	<0.001	47	378±253	432±362	54±325	-42 to 149	0.26	237 (106 to 369)	0.001
End test HR (bpm)	77 [#]	115±17	114±16	-1±13	-4 to 2	0.60	47	122±16	120±16	-2±14	-6 to 2	0.30	-1 (-6 to 4)	0.587
End test SpO ₂ (%)	77 [#]	89±5	88±5	-1.1±4.5	-2.2 to -0.1	0.03	46 [#]	89±5	89±4	0.5±4.2	-0.8 to 1.8	0.43	1.6 (0.0 to 3.3)	0.047
End test dyspnea	77 [#]	5.1±2.1	5.3±2.0	0.2±1.9	-0.3 to 0.6	0.44	47	4.9±1.9	5.4±1.8	0.5±2.0	-0.1 to 1.1	0.12	0.3 (-0.4 to 1.0)	0.407
End test leg fatigue	77 [#]	2.7±2.5	3.4±2.6	0.8±2.1	0.3 to 1.2	0.002	46 [#]	3.0±2.3	3.7±2.7	0.7±2.0	0.1 to 1.3	0.03	-0.1 (-0.9 To 0.7)	0.820
End test RPE	77 [#]	5.3±2.3	5.4±2.1	0.1±2.1	-0.3 to 0.6	0.59	46 [#]	5.1±2.1	5.7±1.8	0.6±2.2	-0.1 to 1.3	0.07	0.5 (-0.3 to 1.3)	0.243

Data are mean±standard deviation or median (interquartile range). * p (probability) values are given for the comparison of ESWT performance between the walking training groups and the usual care group. [#]Some of the participants at baseline were not able to have their heart rate or percutaneous oxygen saturation detected by the heart rate monitor or pulse oximeter at the end of the ESWT or were not able to provide a rating for dyspnea or leg fatigue at the end of the ESWT. bpm, beats per minute; CI, confidence interval; ESWT, endurance shuttle walk test; HR, heart rate; m, metres; n, number of participants; RPE, rating of perceived exertion; sec, seconds; SpO₂, percutaneous oxygen saturation; %, percent.

Table 5-3: Number of participants who rated their walking ability on each point of the global rating of change scale.

GRC scale for walking ability	GRC categories	Walking training groups (n=69)	Usual care group (n=40)
-7	A very great deal worse	0	0
-6	A great deal worse	0	0
-5	A good deal worse	0	3 (7.5%)
-4	Moderately worse	0	2 (5%)
-3	Somewhat worse	0	0
-2	A little worse	0	1 (2.5%)
-1	Almost the same, hardly any worse at all	0	0
0	No change	6 (8.7%)	19 (47.5%)
1	Almost the same, hardly any better at all	2 (3%)	0
2	A little better	9 (13%)	2 (5%)
3	Somewhat better	10 (14.5%)	5 (12.5%)
4	Moderately better	15 (21.7%)	4 (10%)
5	A good deal better	21 (30.4%)	2 (5%)
6	A great deal better	5 (7.2%)	2 (5%)
7	A very great deal better	1 (1.5%)	0

GRC, global rating of change; n, number of participants.

5.4.4 Secondary outcome: change in physical activity after walking training program

Physical activity data of 129 participants were reviewed to determine the minimum number of days of PA data required for analysis. Of these, 115 (89%) participants had at least 5 days of valid PA data. Physical activity outcomes, namely TEE, steps per day and time spent at AEE > 3 METs were analysed. There was no significant difference in PA outcomes over any 3 random days compared to any 5 random days ($p > 0.1$). A total of 114 (88%) participants had valid PA data over 2 weekend days, and no significant difference was found in PA over 2 random weekdays compared to 2 weekend days ($p > 0.2$) (Table 5-4). A minimum of 3 days of PA data was accepted as a valid sample for the analyses on the effects of the walking training on PA in this study. Thus, participants with ≥ 3 days of PA data were analysed.

A total of 61 (64%) participants in the walking training groups and 38 (79%) participants in the usual care group had at least 3 days of valid PA data before and after the 8-week intervention period, during which the SenseWear armband had been worn for at least 85% of each day. Over time, the walking training groups and usual care group showed a non-significant increase in PA in the form of TEE, AEE and total steps taken per day (Table 5-5).

Of the 61 participants in the walking training groups with valid PA data, 53 (56%) participants completed the GRC scale for PA after the 8-week training period (Table 5-6). Of the 38 participants in the usual care group with valid PA data, 34 (71%) participants completed the GRC scale for PA after the 8-week control period (Table 5-6). The median score from the GRC scale for the walking group was 3 (somewhat increased) whereas the median score from the GRC scale for the usual care group was 0 (no change). None of the participants who completed the walking training reported a decrease in activity levels.

Table 5-4: Comparison between different number of days as well as between weekdays and weekend days of outcomes in PA.

PA variable	n	3 days	5 days	Difference	p value	n	2 weekdays	2 weekend days	Difference	p value
TEE (kcal)	115	2,085±426	2,091±414	6±90	0.48	114	2,074±406	2,064±426	10±199	0.59
Steps/day	115	5,080±2,818	5,108±2,839	28±820	0.72	114	4,963±2,873	4,756±2,986	208±1,881	0.24
AEE ≥ 3 METs (kcal)	115	213±164	227±166	13±88	0.11	114	205±183	205±158	0.1±158	0.99
Duration ≥ 3 METs (min)	115	47±34	50±37	3±20	0.13	114	47±37	46±41	0.1±34	0.97

Data are baseline PA, presented as mean±standard deviation. AEE, active energy expenditure; kcal, kilocalories; METs, metabolic equivalents; min, minutes; n, number of participants; p, probability; PA, physical activity; TEE, total energy expenditure.

Table 5-5: Physical activity outcomes for the walking training groups versus the usual care group.

	Walking training groups (n = 61)					Usual care group (n = 38)					Mean difference (95% CI) between groups	p* value
	Baseline	Week 8	Change	95% CI	p value	Baseline	Week 8	Change	95% CI	p value		
TEE (kcal)	2,067±411	2,083±435	16±132	-18 to 50	0.35	2,178±446	2,205±476	28±160	-25 to 80	0.29	11 (-71 to 49)	0.72
Steps/day	5,363±2,087	5,767±3,504	404±1,608	-8 to 816	0.05	4,662±2,306	4,930±2,491	268±1,616	-263 to 799	0.31	113 (-557 to 782)	0.74
AEE ≥ 3 METs (kcal)	234±207	262±251	28±134	-6 to 62	0.11	217±186	247±226	29±124	-11 to 70	0.15	1 (-55 to 52)	0.96
Duration ≥ 3 METs (min)	54±44	60±55	6±31	-2 to 14	0.13	46±41	52±51	6±27	-3 to 15	0.16	0 (-12 to 12)	0.96

Data are mean±standard deviation. *p (probability) value represents between-group comparisons. AEE, active energy expenditure; CI, confidence interval; kcal, kilocalories; METs, metabolic equivalents; min, minutes; n, number of participants; TEE, total energy expenditure.

Table 5-6: Number of participants who rated their physical activity levels on each point of the global rating of change scale.

GRC scale for physical activity	GRC categories	Walking training groups (n=53)	Usual care group (n=34)
-7	A very great deal decreased	0	0
-6	A great deal decreased	0	0
-5	A good deal decreased	0	1 (2.9%)
-4	Moderately decreased	0	1 (2.9%)
-3	Somewhat decreased	0	1 (2.9%)
-2	A little decreased	0	2 (5.9%)
-1	Almost the same, hardly decreased at all	0	0
0	No change	17 (32.1%)	17 (50%)
1	Almost the same, hardly increased at all	1 (1.9%)	0
2	A little increased	3 (5.7%)	1 (2.9%)
3	Somewhat increased	6 (11.3%)	5 (14.8%)
4	Moderately increased	14 (26.4%)	4 (11.8%)
5	A good deal increased	7 (13.2%)	2 (5.9%)
6	A great deal increased	5 (9.4%)	0
7	A very great deal increased	0	0

GRC, global rating of change; n, number of participants.

5.5 Discussion

This RCT demonstrated that an 8-week supervised, individually tailored, ground walking training program in individuals with COPD significantly improved ESWT performance ($p < 0.001$) whereas the usual care group showed no significant change in ESWT performance ($p = 0.26$). Thus the improvement in ESWT performance between the walking training groups and the usual care group was significant ($p < 0.001$). However, the 8-week walking training program had no significant impact on PA outcomes. The usual care group also demonstrated no change in PA outcomes. There was thus no significant difference in all PA outcomes between both groups.

In this 8-week supervised walking training study, ESWT duration improved by 245 sec (95% CI, 174 to 315 sec) and 289 m (95% CI, 204 to 373 m) from baseline. These results are comparable to four studies that used ESWT performance as an outcome after a 7 or 8-week comprehensive PRP which included aerobic and strength training as well as education sessions (296-299). One of the studies demonstrated that a 4-week PRP was equally effective as a 7-week PRP in improving ESWT performance (223 sec [95% CI 152 to 294 sec] versus 217 sec [95% CI 132 to 301 sec] respectively) (296). The similarity between the findings of the above studies and those observed in the current study suggest that walking training alone is sufficient for improving walking endurance.

However, there are two studies that demonstrated a greater change in ESWT performance after a PRP. The first study by Revill et al (287) reported an improvement in ESWT time of 404 sec (95% CI 264 to 544 sec) after a 7-week PRP consisting of two supervised classes each week comprising exercise training (circuit of strength training and thoracic mobility exercises) and education in conjunction with a daily home-based walking program with individuals encouraged to increase the time spent walking throughout the 7 weeks. The greater magnitude of increase in ESWT found in Revill et al's study (287) could be due to the high dose of walking training in addition to the supervised circuit training and education sessions. The second study by Leung et al (39) demonstrated that an 8-week program of supervised walking training in 17 participants with COPD improved ESWT time by 439 ± 346 sec (39). In the current study, a participant was progressed to the next level of the

ESWT if they were able to complete more than 5 minutes (300 sec) of the ESWT, expressed that the pace was comfortable and they had the ability to continue walking. As noted previously, this was done with the aim of avoiding participants reaching the 20-minute ESWT maximum after the intervention period. In the current study, 16 (21%) participants with COPD in the walking training groups who completed the ESWT reached the 20-minute completion time of the ESWT at the end of the 8-week intervention period versus six (35%) participants with COPD in the study by Leung et al (39) who reached the 20-minute completion time of the ESWT at the end of the walking training. It is possible that increasing the speed of the ESWT in this current study might have adversely affected participants' ESWT performance following supervised walking training due to the hyperbolic relationship between endurance and speed (300). Thus, if a participant was walking at a higher work rate located at the lower end of the hyperbolic curve, despite the positive impact of exercise training on exercise capacity, the improvement in endurance capacity would be minimal. Dolmage et al (300) recommended that a target baseline performance on the ESWT equivalent to 8 minutes was likely to maximise the responsiveness to change. Thus capping the ESWT duration to approximately 5 minutes at baseline in this current study could have reduced the magnitude of change in ESWT performance after the 8-week intervention period. Therefore, in future studies, participants should only be progressed to the next level of the ESWT if they are able to complete more than 8 minutes of the ESWT. However, this may increase the number of participants reaching the 20-minute completion time of the ESWT at the end of an intervention.

The only study that attempted to determine the MDD for the performance of ESWT in response to pulmonary rehabilitation in individuals with COPD estimated that value to be 186 sec, or 203 m (48). The mean improvement in ESWT performance of the participants in current study who received supervised walking training group exceeded this threshold while the usual care group did not show any significant change over time.

The reduced PA in individuals with COPD (1) appears to be related to important healthcare outcomes such as the frequency of exacerbations, hospitalisations and mortality (118, 155). Thus, optimising PA is an important aim in the management of these individuals (9). This study found that 3 days of PA data from the SenseWear

armband was sufficient to accurately estimate daily PA as there was no significant difference in PA outcomes over any 3 random days compared to any 5 random days ($p > 0.1$). This finding concurs with that of Hart et al (149) who demonstrated that 3 days of accelerometer data were needed to provide an accurate assessment of PA levels in older adults. Despite being confident that the data collected by the SenseWear armband were accurate, as this monitor has been validated in individuals with COPD (13), there was no significant impact on PA outcomes after 8 weeks of supervised walking training. In other words, training these individuals in a solely high-intensity walking training did not appear to translate into a more active lifestyle. This was similar to the findings of a 7-week PRP which consisted of aerobic and strength training program (301).

There are several possible reasons for the lack of positive change in PA after walking training. One possible reason is that the 8-week duration of the walking training program was too short to have an impact on PA. Pitta et al (33) showed significant improvements in walking time only after 6 months of supervised exercise training. Similarly, a minimum duration of at least 12 weeks has been recommended for rehabilitation for most individuals with COPD to allow a change of a habit, in this case, increasing their activity levels (208). Physical activity is affected by a multitude of factors which include behavioural, personality characteristics, environmental circumstances, community settings, social and cultural factors and symptoms related to activity (302). Another possible reason for the failure to show a significant improvement in PA include the absence of a behavior modification program, education sessions or home exercise program in addition to supervised walking training as motivation may empower lifestyle modification to increase activity (303). Large variability in all of the measures of PA could also explain the lack of a significant change in PA. Thus, the only PA outcome that showed a trend towards improvement after walking training was steps taken per day. There was however no significant difference in the improvement in PA outcomes between the walking training groups and the usual care group after the 8-week intervention or control period.

5.5.1 Limitations

A third of participants in the walking training groups had insufficient PA data, thus the PA data obtained in this study may not be a representation of the change after walking training. As the SenseWear armband is unable to identify specific type of activity, other motion sensors such as the Dynaport Activity Monitor or the StepWatchTM Activity Monitor should be considered to be used together with the armband to provide a more accurate and comprehensive assessment of PA. The sensor in the Dynaport Activity Monitor, a tri-axial accelerometer, detects movement in multiple directions and detects change in posture (1). The SenseWear armband appears to significantly underestimate steps compared to manual counting and video observation (12-14). As the StepWatchTM Activity Monitor, a dual axis microprocessor-controlled step counter, has been shown to accurately measure steps in individuals who walk very slowly (11, 16), this monitor would complement the SenseWear armband.

5.6 Conclusion

Walking training is suitable as a mode of exercise training for individuals with COPD and has been recommended to be incorporated into the exercise training component of pulmonary rehabilitation (5). An 8-week supervised, individually tailored, ground walking training was effective at improving ESWT performance. However the ground walking training has not been shown to significantly impact on outcomes of PA.

CHAPTER 6

MIMIMAL DETECTABLE DIFFERENCE FOR ENDURANCE SHUTTLE WALK TEST PERFORMANCE

6.1 Overview

The minimal detectable difference (MDD) for endurance shuttle walk test (ESWT) performance is described in this chapter, using data from the walking and feedback training (WAFT) study described in Chapter 5. The MDD is defined as the smallest difference in the outcome of interest that individuals perceive or detect as either beneficial or harmful, and this can lead the individual or clinician to consider a change in the management (41, 212). This term is often used interchangeably with terms such as the minimal important difference (MID) and minimal clinically important difference (MCID). The main difference between these terms is that the MDD is the smallest difference noticeable (or detectable) by an individual, whereas, both the MID and MCID aim to ensure that the magnitude of this difference is important to the individual (8). Importance is related to a judgement by the individual that the magnitude of benefit is considered to be worth the effort, inconvenience or cost associated with completing the treatment (8). Alternatively, importance may be related to a reduction in the risk of some clinical event (e.g. mortality or hospitalisation). For example the MID for the Saint George's Respiratory Questionnaire was determined from the difference in scores between individuals with chronic obstructive pulmonary disease (COPD) who were admitted to hospital or died over a 1-year period, and those who did not have any major health-related events (224). The MDD does not link the magnitude of change with whether or not the individual perceives the change to be important; it is simply the magnitude of change that is noticeable or detectable by the individual (8).

The MDD is a separate construct to statistical significance. Specifically, for a change in an outcome following an intervention to be considered statistically significant, three factors are considered; the magnitude of change, variability in response and

sample size (8). If the variability is modest and / or the sample size is large, even a relatively small change may achieve statistical significance (8). A statistically significant finding implies that the difference is unlikely to be the result of chance (210). However, such a finding does not inform clinicians whether or not the individuals in the study would have noticed or detected the difference.

The MDD has been determined using two approaches, namely anchor- and distribution-based approaches (8). The anchor-based approaches relate the magnitude of change in an outcome measure following an intervention to an objective external criterion (8). For example, several studies have related the magnitude of change in field-based measures of exercise capacity, following pulmonary rehabilitation, with self-report scores on the global rating of change (GRC) scale (42-44). Specifically, a GRC scale is simple to use and administer, and asks individuals to rank their improvement or deterioration using a balanced 7-point numerical scale with written descriptors ranging from a very great deal worse (-7) to a very great deal better (+7) (45). Earlier work has suggested that in order for some anchor-based approaches for establishing the MDD that use the GRC to be reliable, the magnitude of change in the outcome measure needs to have a correlation (r) of > 0.5 with the individual's perception of change reported using the GRC score (213). This is because a $r > 0.5$ is a sufficiently high threshold to demonstrate validity between the magnitude of change and the GRC scores to determine a reliable estimate of the MDD (304). Once a moderate association has been established between the magnitude of change in an outcome measure and an individual's GRC score (i.e. $r \geq 0.5$), the MDD can be calculated as either the; (i) mean change and 95% confidence interval (CI) for a given GRC score (e.g. 'slightly better') or, (ii) slope of the line between the mean of change and the GRC scores, determined via linear regression analysis (8). In people with COPD, these anchor-based approaches using the GRC have been used to determine the MDD for the distance walked during the incremental shuttle walk test (ISWT) (44) and 6-minute walk test (6MWT) after pulmonary rehabilitation (43). These methods have also been used to determine the MDD for performance during the ESWT after bronchodilatation (48).

In the absence of a moderate association between the magnitude of change in an outcome measure and an individual's GRC score, others have used a receiver

operating characteristic (ROC) curve to estimate the MDD (43, 220, 305). Specifically, individuals are categorised, based on their GRC scores as 'slightly improved' versus 'no change', and an ROC curve is used to determine the magnitude of change in the outcome measure of interest that had the optimal capacity to separate these two groups of individuals (8, 306). The point selected is that with the best blend of sensitivity (true positive) and specificity (true negative) (8).

Distribution-based approaches establish the MDD using some measure of variability in the outcome of interest. Distribution-based approaches are not anchored to a GRC scale and therefore do not take into consideration an individual's perception of the change. In the distribution-based approach, there have been several methods used to determine the MDD for outcomes commonly used to evaluate the effects of pulmonary rehabilitation. These comprise calculating an effect size, the standardised response mean (SRM) or standard error of measurement (SEM) (8). The effect size has been defined as the standardised measure of change obtained by dividing differences in the outcome measure of interest (i.e. from baseline to post-intervention) by the SD of the baseline value (8). An effect size of 0.5 is considered to be moderate (8) and the MDD is calculated by multiplying the SD of the baseline measure by 0.5. The SRM has been defined as the changes in a group of values or scores obtained by dividing differences in the outcome measure of interest (i.e. from baseline to post-intervention) by the SD of the change in the outcome measure (46). The SRM is also known as another form of effect size (226) and some authors have used the definition of SRM synonymously with the term effect size (217, 223). The SEM is a measure of within individual variability (8), as it estimates the standard error in a set of repeated scores. It is defined as variability between an individual's observed score and the true score, and can be calculated using an intra-class correlation coefficient (ICC) or via repeated measures analysis of variance (ANOVA) (47). In contrast with other estimates of the MDD, established using anchor- or distribution-based approaches, the SEM can be used to determine the minimum detectable change (MDC) that is likely to exceed measurement error (47). In this way, it can be used to assist clinicians to determine a threshold that is likely to represent a true change following treatment that is beyond the natural variability inherent in all measures (47).

The MDD for the distance walked during field walking tests after pulmonary rehabilitation, namely the 6MWT and the ISWT, have been previously established in individuals with COPD (43, 44, 217) using both anchor- and / or distribution-based approaches. However the MDD for ESWT performance, which has been found to be more sensitive to change than distance walked during the ISWT (287) and 6MWT (285), has not been convincingly established. The ESWT is a standardised, externally paced walking test used for the assessment of endurance walking capacity (287). This test is performed at a walking speed equivalent to 85% of the participant's peak rate of oxygen consumption that has been estimated from the distance walked during the ISWT (287). The only study to date to attempt to estimate the MDD for ESWT performance reported the SRM which is a distribution-based approach (48). The planned anchor-based approach could not be used as the relationship between the ESWT performance and the GRC scores after rehabilitation was weak ($r < 0.4$) (48). The authors attributed this weak relationship to be due to either recall bias arising due to the 7-week duration of the pulmonary rehabilitation program or the high level of commitment and personal investment required to complete the pulmonary rehabilitation program; both of which were likely to affect the individual's perception of his or her exercise performance (48).

6.2 Methodology

6.2.1 Overall aim

The aim of this study was, in individuals with COPD, to determine the MDD for the change in performance during the ESWT on completion of an 8 week supervised, individually tailored, ground walking training program; expressed as both time (sec) and distance (m).

6.2.2 Research questions

- i. What is the MDD for ESWT performance using an anchor-based approach in individuals with COPD?
- ii. What is the MDD for ESWT performance using distribution-based approach in individuals with COPD?

6.2.3 Research hypotheses

The hypothesis for this study was that there would be a significant relationship ($r \geq 0.5$) between objective measurement of the change in ESWT performance and the subjective GRC ratings as perceived by the individuals with COPD after an 8-week supervised, individually tailored, ground walking training program. It was hypothesised that the estimate of the MDD derived using an anchor-based approach would be similar to the estimate of the MDD derived using the distribution-based approaches.

The data from the WAFT study (Chapter 5) were used to determine the MDD for the change in performance during the ESWT, expressed in both time (sec) and distance (m). This study has been briefly summarised below, with additional details provided in Chapter 5.

6.2.4 Study design

A prospective, single-blind, randomised controlled trial was undertaken with participants randomised into one of three groups; a walking training group (WG), a walking training with post-training feedback group (WFG) and a usual care group. Both the WG and WFG underwent the supervised ground walking training intervention over an 8-week period. All participants were recruited from the Sydney or Perth metropolitan area. All participants completed the ESWT before and after the 8-week intervention period. On completion of the 8-week period, participants were asked to complete a GRC scale in order to record their perceptions of the magnitude of change in their walking ability. Only the data from the intervention groups (WG and WFG) who completed the ESWT before and after the 8-week walking training were used in this chapter to calculate SRM and apply anchor-based approaches to determine the MDD for ESWT performance, while their baseline ESWT data were used to calculate the effect size and SEM for ESWT performance.

6.2.5 Ethical approval

Approval to conduct the study was granted by the Human Research Ethics Committees from five sites in Sydney and two sites in Perth. Written, informed

consent was obtained from all participants. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12609000472279).

6.2.6 Participants

All participants were recruited from patients who had been referred to pulmonary rehabilitation programs (PRPs) in Sydney and Perth, Australia. The inclusion criteria comprised aged > 40 years, medical diagnosis of COPD and a smoking history of \geq 10 pack years. Exclusion criteria comprised: (i) musculoskeletal, cardiovascular or neurological conditions likely to adversely affect performance during assessments or training, (ii) participation in supervised exercise training within the last 12 months, (iii) prescription of long term oxygen therapy or ambulatory oxygen during exercise training, (iv) inability to maintain percutaneous oxygen saturation > 83% during the ESWT and (v) body mass index > 35 kg/m². All participants had their medical management optimised at baseline in accordance with the COPD-X Plan which included a COPD action plan with the aim of educating participants in managing their condition and an exacerbation (275).

6.2.7 Protocol

Participants allocated to the intervention groups (WG and WFG) completed an 8-week, individually tailored, ground walking training program that comprised either three supervised sessions a week or two supervised sessions and one unsupervised exercise session each week for individuals who were unable to commit to travelling to the hospital three times a week for supervised training. Thus the maximum number of training sessions completed over the 8-week period was 24 (supervised and unsupervised sessions). The initial training intensity prescribed was equivalent to 80% of the average walking speed achieved from the better of two 6-minute walk distances (6MWDs) (169, 276). The total exercise time (excluding rests) was 30 minutes at the commencement of walking training. This was progressed by increasing the duration of exercise by 5 minutes after every sixth session to a maximum of 45 minutes by session 19. The supervised training took place along a flat corridor that ranged in length between centres from 26 to 100 m. The unsupervised sessions were recorded in a diary. In the event of a respiratory exacerbation, training was postponed until the participant was clinically stable (275)

and the training period extended to a maximum of 10 weeks to allow participants to complete a minimum of 16 sessions. At each supervised exercise session, percutaneous oxygen saturation and pulse rate were measured before and after walking training using a hand-held pulse oximeter (Respironics/Novametrix 513, Murrysville, Pennsylvania, United States [US] or RAD-5v, Masimo Corp, Irvine, California, US).

6.2.8 Outcome measures

The outcome measures relevant to the analyses presented in this chapter are the ESWT performance expressed as time (sec) and distance (m).

6.2.8.1 Endurance shuttle walk test

The ESWT is an externally paced field walking test that was performed over a 10 m course. Participants were instructed to walk around two cones, each positioned 0.5 m from each end, to a cadence dictated by an audio signal. The ESWT was performed at a walking speed equivalent to 85% of the participant's peak rate of oxygen consumption ($VO_{2\text{peak}}$) estimated from the distance walked during the best of two ISWT (287). During the test, percutaneous oxygen saturation using a hand-held pulse oximeter (Respironics/Novametrix 513, Murrysville, Pennsylvania, US or RAD-5v, Masimo Corp, Irvine, California, US) and heart rate (Polar a1 heart rate monitor; ©Polar Electro, Kempele, Finland) were continuously monitored. Dyspnea (modified Borg scale) (283) and rating of perceived exertion (284) on a scale of 0 to 10 were recorded at the end of each minute during the test. The ESWT was terminated if participants were not able to keep up with the speed after being given a warning to keep pace when they were behind the speed for the first time (e.g. due to dyspnea or leg fatigue). At the end of each walking test, dyspnea, rating of perceived exertion and leg fatigue were recorded on a scale of 0 to 10 (284).

Prior to training, two ESWTs were performed on separate days, to account for any improvements resulting from familiarisation (307). In order to optimise the responsiveness of the ESWT, speeds for the test performed prior to training were manipulated with the goal of achieving an average test duration of 8 minutes as this duration has been shown to be most likely to maximise the responsiveness to change

(300). Specifically, prior to training, the second ESWT was performed at a faster walking speed for participants who were able to complete more than 5 minutes of the ESWT, and expressed that this pace was comfortable and they had the ability to continue walking. If both tests performed prior to training were conducted at the same speed, the test which resulted in the longest time was recorded as the test result. If the tests performed prior to training were conducted at different speeds, the test performed at the faster speed was recorded as the test result.

Following training, either one or two ESWTs were performed depending on participants' willingness to come on separate days to repeat the ESWT. If both tests performed prior to training were conducted at the same speed, this same speed was selected for the test done following the intervention period. If the tests performed prior to training were conducted at different speeds, the faster speed was selected for the test done following the intervention period. Tests performed following training were terminated after reaching the 20-minute completion time of the ESWT.

6.2.8.2 Global rating of change

The GRC scores were used as an external criterion in the anchor-based approach of determining the MDD (308). On completion of the walking training, participants were asked to indicate if their walking ability had 'improved', 'worsened' or 'stayed the same'. Those participants who rated their walking ability as 'improved' or 'worsened' were then asked to rate the degree of change on the GRC scale (45). In this study, the GRC scale was a 7-point Likert scale. Improvements were scored as follows: 1 - almost the same or hardly any better at all, 2 - a little better; 3 - somewhat better, 4 - moderately better, 5 - a good deal better, 6 - a great deal better and 7 - a very great deal better. None of the participants reported a worsening of their walking ability (refer to Chapter 5, Section 5.3.2.1). The change in the ESWT performance was calculated for each rating on the GRC scale. Given the limited number of participants in some categories, the GRC scores were collapsed to three categories, where no change or a GRC score of 1 were categorised as no change, GRC scores of 2 to 3 were categorised as small change and GRC scores of 4 to 7 were categorised as substantial change.

6.3 Data management and analyses

Analyses were conducted using the Statistical Package for Social Sciences (SPSS version 18.0; Chicago, IL, USA) with a probability value ($p \leq 0.05$) used to indicate statistical significance.

6.3.1 Anchor-based approach

Changes in ESWT performance after walking training were expressed as time (sec) and distance (m). With participants grouped according to their responses on the GRC scale following training, the magnitude of change in ESWT performance between measures collected before and after training were compared using paired t-test. The anchor-based approach to determine the MDD comprised two components. First, responses to the GRC scale were collapsed from seven categories to three categories as noted in section 6.2.8.2. This was done as some of the categories were chosen by very few participants. Further, collapsing of the GRC scale to three categories had been previously used by authors to determine meaningful change in exercise capacity among older adults (43, 309). Second, the strength of the relationship between the collapsed GRC responses (x-axis) and the magnitude of change in ESWT performance following training (y-axis) was determined. If this relationship was reasonably strong (i.e. $r > 0.5$), a linear regression model would be plotted between the collapsed GRC responses and the change in ESWT performance (48). The resultant slopes would represent the change needed in ESWT performance for the participants' ratings to move one unit on the collapsed GRC scale, which were considered as estimates for MDD (48). If the relationship was weak (i.e. $r < 0.5$), a ROC curve would be constructed to determine the optimal operating point which resulted in the best blend of sensitivity and specificity to discriminate between participants who rated their walking ability following training as 'changed' versus 'unchanged'. This point was defined as the data point closest to the upper left corner of the ROC curve (43). For these analyses, participants were classified as 'changed' if they reported scores of ≥ 2 on the GRC scale versus 'unchanged' if they reported scores of < 2 on the GRC scale. The software package 'R' was used to establish the 95% CI for this optimal operating point, using bootstrapping methods (310). Specifically, for all data points plotted on the ROC curve, 2,000 samples were obtained by re-sampling the 'changed' and 'unchanged' groups. Thereafter, the

optimal operating point was obtained from each of the 2,000 samples. The limits of the 95% CI were then taken to be the 2.5th and 97.5th percentile of the 2,000 samples. The CI derived using this technique was not necessarily symmetric around the optimal operating point determined from the ROC curve.

6.3.2 Distribution-based approach

Three separate distribution-based approaches were used to estimate the MDD: half the SD of baseline measure (i.e. the effect size); half the SD of change in measures collected before and after training (i.e. the SRM) and; the MDC, derived from the SEM (311).

Specifically, the MDD determined using effect size was calculated as follows:

$0.5 \times \text{SD of measures of the ESWT performance performed prior to exercise training.}$

The MDD determined using SRM was calculated as follows:

$0.5 \times \text{SD of change in measures of the ESWT performance (i.e. post-training measure – pre-training measure).}$

Calculation of the MDC comprised three components. First, participants who performed both ESWTs, prior to exercise training, at the same speed were selected as this allowed comparison between the two measures of the baseline ESWT performance. Second, the SEM was calculated as the square root of the mean square error derived from ANOVA (47). The ANOVA was selected to determine SEM as the ESWT was repeated on separate days and thus may have been influenced by systematic and random errors (i.e. a learning effect) (47). Third, the determined SEM was placed into a formula derived using the methods described by Beckerman et al (312) to calculate the coefficient of repeatability. The formula for MDC was calculated as follows:

$1.96 \times \sqrt{2} \times \text{SEM.}$

As the MDC derived using this method was based on measures collected during only two ESWTs at baseline, this estimate was equivalent to the smallest measurement change where 1.96 was derived from the 95% CI of no change while $\sqrt{2}$ is included in the formula as two repeated ESWTs were conducted at baseline (312). This value for the MDC is the value beyond which a clinician or researcher can be confident 95% that the difference for any individual was beyond measurement error inherent within the test, and therefore represents a true 'training' effect (210).

6.3.3 Sample size

A minimum of 55 participants was required for an anticipated area under the ROC curve (AUC) of 0.70 with a standard error of 0.05. The AUC represents the probability that the data correctly discriminate between participants who have and who have not improved, where an AUC of 0.7 to 0.8 is considered acceptable (8).

6.4 Results

A total of 143 participants were recruited and 95 of these were randomised to walking training. Thirteen (14%) participants who were randomised to walking training withdrew from the study (Chapter 5, Figure 5-3). A total of 78 (82%) participants who were randomised to walking training completed the ESWT before and after the 8-week walking training. Seventeen (18%) participants declined to complete the ESWT at the end of the 8-week walking training period. Of the 78 participants, 69 (73%) rated their walking ability on the GRC scale. Of these 69 participants, only data from 55 (58%) participants were used to determine the MDD using the anchor-based approach as 14 of these 69 participants had an exacerbation during their walking training and therefore their data were excluded from the analysis. This was because of recall bias from the long time span of the rehabilitation as participants would have difficulty remembering how they were prior to the 8-week rehabilitation period and thus their perception of their walking ability were more likely to be influenced by a recent event such as an exacerbation (48).

The data from all 78 participants were used in the analysis for the distribution-based approach to determine the effect size. Of the 78 participants randomised to walking training who completed the ESWT before and after the 8-week walking training, 20

of them had an exacerbation during the intervention period and were excluded from analysis for SRM. Data from 13 (14%) participants were not used in the calculation of the SEM. This was because these participants were progressed at baseline to the next level of the ESWT on the second day of testing as according to methodology, they were able to complete more than 5 minutes of the ESWT and had the ability to continue walking. In summary, 58 and 65 participants contributed data to the distribution-based determination of the MDD and MDC, respectively.

The characteristics of the participants who contributed data for the analyses undertaken in this chapter are presented in Table 6-1.

6.4.1 Effect of walking training on endurance shuttle walk test performance

The 78 participants allocated to the walking training group completed 19 ± 4 exercise sessions. As presented in Chapter 5 (Section 5.3.2.1), the duration and distance achieved in the ESWT by the 78 participants increased significantly by 245 ± 313 sec and 289 ± 376 m respectively after the 8-week period; an improvement of 92 ± 148 % (Table 6-2). Sixteen (21%) participants reached the 20 minute limit of the ESWT at the 8-week assessment. Figure 6-1 illustrates the change in ESWT performance plotted against responses to the GRC scale. Compared with measures taken prior to training, the improvement in ESWT following training was statistically significant for those who rated themselves 3 (somewhat better), 4 (moderately better) or 5 (a good deal better) (Figure 6-1).

Table 6-3 summarises the magnitude of change in performance during the ESWT with participants grouped according to their responses on the collapsed GRC scale. The seven participants whose GRC scores were classified as no change, did not change their ESWT performance (1 ± 52 sec [$p = 0.9$] or 5 ± 58 m [$p = 0.8$]). The 13 participants whose GRC scores were classified as small change, improved their ESWT performance by 186 ± 275 sec or 212 ± 313 m ($p = 0.03$). The 35 participants, whose GRC scores were classified as substantial change, improved their ESWT performance by 326 ± 338 sec or 397 ± 419 m ($p < 0.001$).

6.4.2 Estimates of minimal detectable difference determined using the anchor-based approach

A significant relationship was observed between the collapsed GRC scores and the ESWT performance expressed as time ($r = 0.36$; $p = 0.008$) and distance ($r = 0.35$; $p = 0.008$) (Figure 6-2). As the strength of these relationships were modest ($0.3 < r < 0.5$) (217), an ROC curve was used to determine the optimal operating point to discriminate between participants who rated themselves as changed versus unchanged at the end of the exercise training program (8).

The AUC for ESWT performance expressed as time was 0.703 (95% CI; 0.561 to 0.845) (Figure 6-3). The AUC for ESWT performance expressed as distance was 0.716 (95% CI; 0.576 to 0.856) (Figure 6-3). The sensitivity and specificity for the optimal operating point of the ROC curve ESWT performance expressed as time were 0.629 and 0.250, respectively. The sensitivity and specificity for the optimal operating point of the ROC curve for ESWT performance expressed as distance were 0.629 and 0.200 respectively. The optimal operating point for the ESWT performance expressed as time and distance was 113 sec (95% CI; 23 to 139 sec) and 192 m (95% CI; 60 to 200 m), respectively.

Table 6-1: Characteristics of participants who were randomised to walking training and completed the 8-week intervention period (n = 82).

Characteristics	
Gender	48 M (59%) / 34 F (41%)
Age (yr)	70±8
BMI (kg/m ²)	25.3±4.5
MMRC dyspnea grade (n [%])	
Grade 0	6 [7%]
Grade 1	39 [48%]
Grade 2	21 [25%]
Grade 3	16 [20%]
BODE index (median [IQR])	3 [2 to 4]
FEV ₁ (L)	1.14±0.42
FEV ₁ (% predicted)*	44±15
FVC (L)	2.68±0.86
FVC (% predicted)*	75±17
FEV ₁ /FVC (%)	44±14
ISWT distance (m)	322±112
ESWT distance (m)	417±318
ESWT time (sec)	326±205
6MWD (m)	466±84

Data are mean±standard deviation unless otherwise stated. *predicted values based on Hankinson et al (246). BMI, body mass index; BODE, body mass index, obstostruction, dyspnea and exercise capacity index; ESWT, endurance shuttle walk test; F, female; FEV₁, volume exhaled during first second of a forced expiration; FVC, forced vital capacity; IQR, interquartile range; ISWT, incremental shuttle walk test; kg, kilograms; L, litres; M, male; m, metres; MMRC, Modified Medical Research Council (grade 0 to 4); n, number of participants; sec, seconds; yr, years; %, percent; 6MWD, 6-minute walk distance.

Table 6-2: Endurance shuttle walk test performance for the walking training groups.

	n	Baseline	Week 8	Change	95% CI	p value
ESWT (sec)	78	330±208	574±389	245±313	174 to 315	<0.001
ESWT (m)	78	422±324	710±504	289±376	204 to 373	<0.001
End test HR (bpm)	77 [#]	115±17	114±16	-1±13	-4 to 2	0.60
End test SpO ₂ (%)	77 [#]	89±5	88±5	-1.1±4.5	-2.2 to -0.1	0.03
End test dyspnea	77 [#]	5.1±2.1	5.3±2.0	0.2±1.9	-0.3 to 0.6	0.44
End test leg fatigue	77 [#]	2.7±2.5	3.4±2.6	0.8±2.1	0.3 to 1.2	0.002
End test RPE	77 [#]	5.3±2.3	5.4±2.1	0.1±2.1	-0.3 to 0.6	0.59

Data are mean±standard deviation. #Some of the participants at baseline were not able to have their heart rate or percutaneous oxygen saturation detected by the heart rate monitor or pulse oximeter at the end of the ESWT or were not able to provide a rating for dyspnea or leg fatigue at the end of the ESWT. bpm, beats per minute; CI, confidence interval; ESWT, endurance shuttle walk test; HR, heart rate; m, metres; n, number of participants; p, probability; RPE, rating of perceived exertion; sec, seconds; SpO₂, percutaneous oxygen saturation; %, percent.

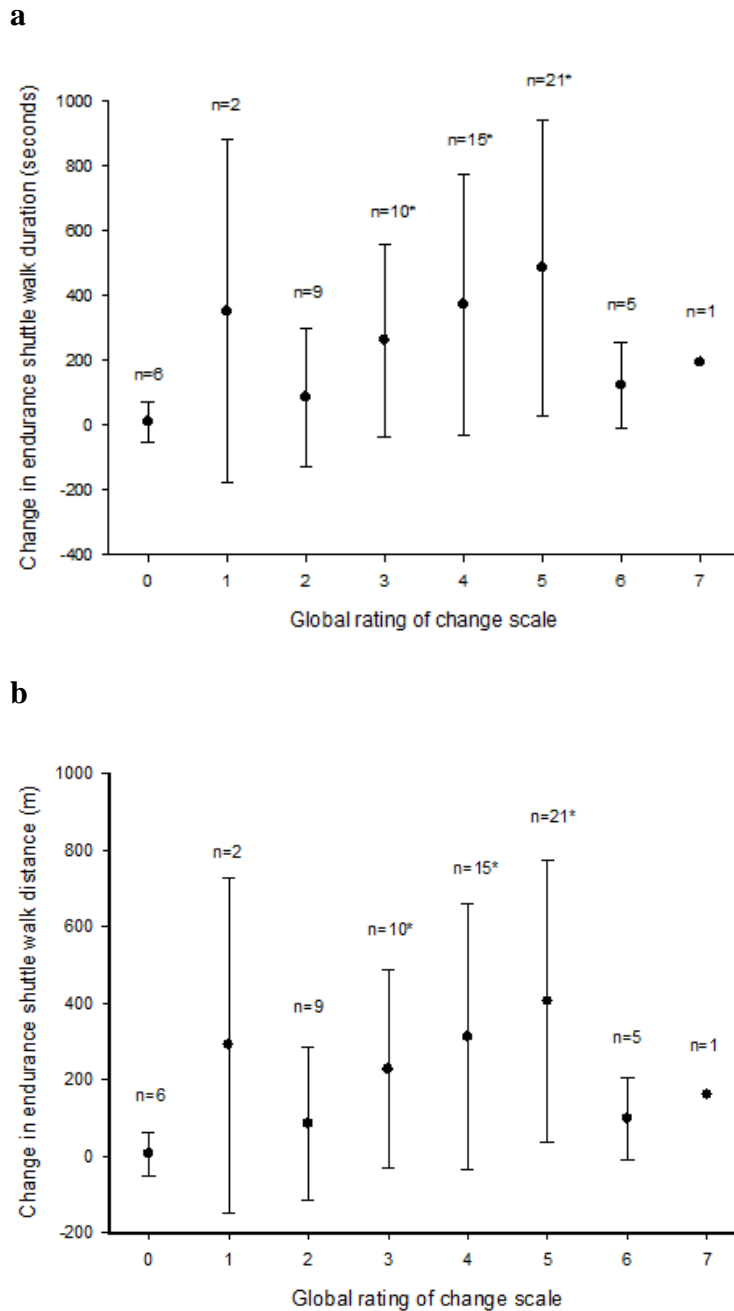


Figure 6-1: The change in ESWT (a) duration and (b) distance (y-axis) for participants in the walking training groups, with participants grouped according to their global rating of change scores (x-axis) in walking ability after training.

There was no significant change in ESWT performance for ratings 6 and 7 due to small n values. Data are mean±standard deviation. * indicates a significant change from baseline ($p < 0.05$) in ESWT performance. ESWT, endurance shuttle walk test; n, number of participants.

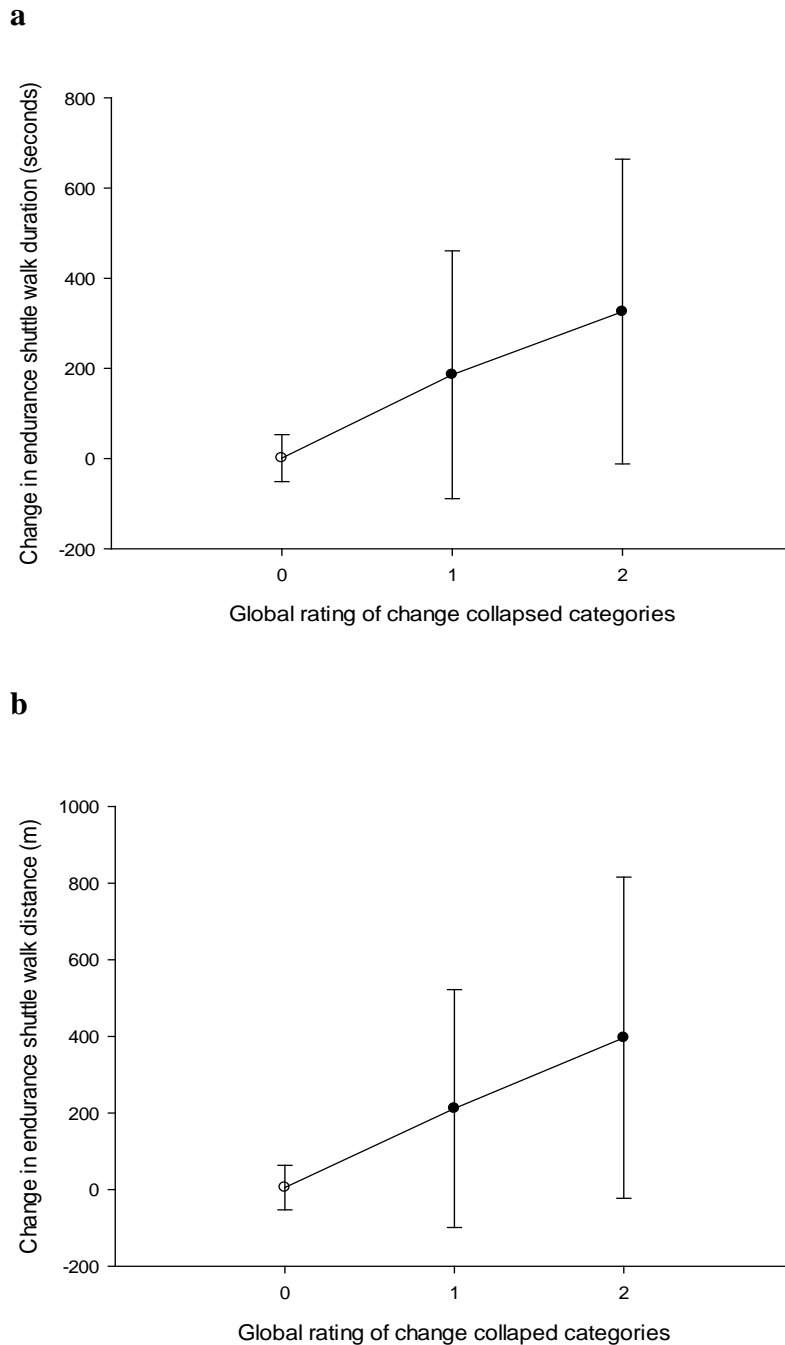


Figure 6-2: Relationship between the change in ESWT performance expressed as (a) time and (b) distance (y-axis) and global rating of change scores collapsed as previously described (309) (x-axis).

A score on x-axis of '0' corresponded to GRC categories of 'not changed' and 'almost the same, hardly better at all'. A score on x-axis of '1' corresponded to GRC categories of 'a little better' and 'somewhat better' (or small change). A score on x-axis of '2' corresponded to GRC categories of 'moderately better', 'a good deal better', 'a great deal better' and 'a very great deal better' (or substantial change). Data are mean \pm standard deviation.

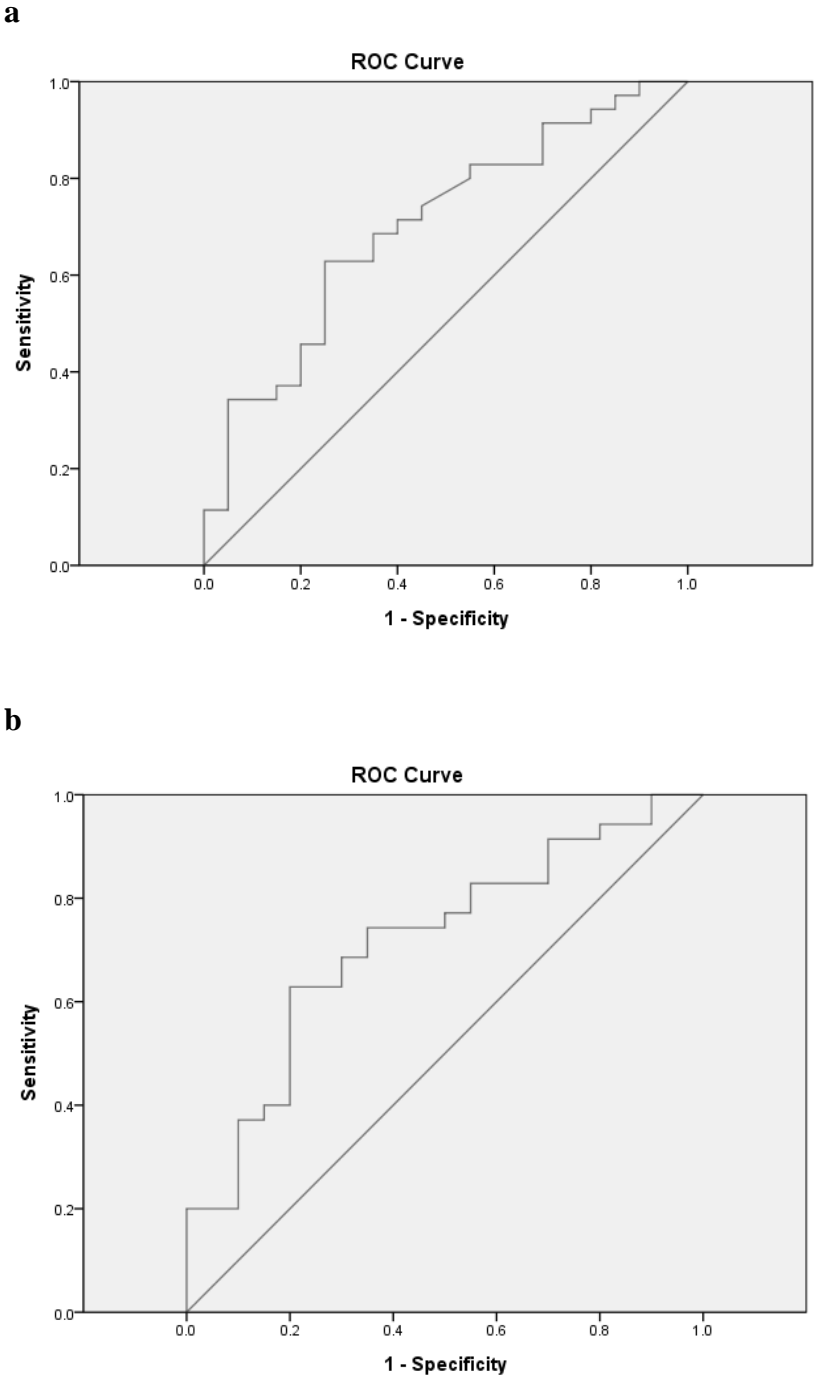


Figure 6-3: Receiver operating characteristic (ROC) curve for ESWT performance expressed as (a) time and (b) distance.

Table 6-3: Endurance shuttle walk test performance based on collapsed GRC categories.

Variable	GRC collapsed categories	n	MDD
Time (sec)	No change	7	1±52
	Small change	13	186±275
	Substantial change	35	326±338
Distance (m)	No change	7	5±58
	Small change	13	212±311
	Substantial change	35	397±419

Data are mean±standard deviation. GRC, global rating of change; m, metres; MDD, minimal detectable difference; n, number of participants; sec, seconds. The GRC ratings of 0 to 1, GRC ratings 2 to 3 and GRC ratings 4 to 7 were grouped as no change, small change and substantial change respectively.

6.4.3 Estimates of the minimal detectable difference determined using distribution-based approach

6.4.3.1 Effect size

According to this approach, the MDD, expressed as time and distance were estimated to be 104 sec and 162 m, respectively.

6.4.3.2 Standardised response mean

Using this approach, the MDD, expressed as time and distance were estimated to be 156 sec and 188 m, respectively.

6.4.3.3 Minimal difference derived from standard error of measurement

The SEM, expressed in terms of time and distance, was 86 sec and 120 m respectively. The MDC, expressed in terms of time and distance, was 238 sec and 333 m, respectively.

6.5 Discussion

The MDD for ESWT performance expressed in time and distance as determined using an anchor-based approach (i.e. the ROC curve) were 113 sec (95% CI, 23 to 139 sec) and 192 m (95% CI, 60 to 200 m) respectively. The MDD for ESWT performance expressed in time and distance as determined by the distribution-based approaches ranged between 104 to 156 sec and 162 to 188 m. The MDC was considerably larger, being 238 sec and 333 m.

The MDD is the threshold value for a change in an outcome of interest that is considered noticeable to the individual (8). The estimates obtained by the anchor-based approach do not consistently correspond to the estimate obtained by the distribution-based approach (49). Anchor-based approaches to determine the MDD are often considered to be superior to distribution-based approaches as the latter are solely based on statistical criteria and may be more influenced by the characteristics of the study sample (212). Distribution-based approaches essentially represents an effect estimate based on measures of variability (217). In contrast, anchor-based approaches involve comparing the magnitude of change in an outcome measure

following an intervention to an external criterion for which the GRC scores are widely used (49). Thus anchor-based approaches determine if the clinical outcome is perceived by the participant. However, anchor-based approaches using the GRC scores may be influenced by recall bias (222) as participants often scored on the GRC scales based on their current status rather than the measuring transition as intended (45). The concurrent use of both approaches is recommended to increase the confidence in the final estimate of the MDD (215).

To date, the only study which attempted to determine the MDD for ESWT performance for patients undergoing pulmonary rehabilitation used a distribution-based approach and derived the estimate as one half a SD of the change in ESWT (pre to post rehabilitation), expressed as time and distance (48). The distribution-based approach of using SEM was not possible in the study by Pepin et al (48) as the ESWT was not repeated at least twice before or after rehabilitation. There was also a weak correlation between the GRC ratings and the change in ESWT performance ($0.35 \leq r \leq 0.37$) in the study by Pepin et al (48), thus anchor-based approaches such as using a linear regression model to determine the relationships between the GRC and the change in ESWT performance were not undertaken.

The MDD derived as half a SD of the changes in ESWT, expressed as time and distance in the study by Pepin et al (48) was somewhat different from that derived in the present study (186 versus 156 sec or 203 versus 188 m). This could be due to variability in the exercise regimens between the two studies. Specifically, the addition of resistance training to aerobic training as in the study by Pepin et al (48) might be more effective in improving outcomes in ESWT performance as resistance training has the potential of increasing muscle mass and strength (313).

Another possible reason for the discrepancy is the methodology used to determine the speed for undertaking the ESWT. The true effect of the walking training may be underestimated as earlier works suggests between 14% to 35% of participants are able to complete the full 20 minutes of the ESWT after rehabilitation (39, 287), with a resultant 'ceiling effect'. In an attempt to avoid a 'ceiling effect' (i.e. participants reaching the 20-minute maximum post walking training) in the current study, the ESWT was performed at a faster walking speed for participants who were able to

walk more than 5 minutes during the ESWT at baseline. This may have reduced the responsiveness of the ESWT. Previous research has shown that the critical power, which represents the maximum sustainable rate of aerobic capacity, occurs at a lower work rate in individuals with COPD than age-matched healthy adults (314). This reduced critical power might be due to a ventilatory limitation, namely progressive hyperinflation with exercise (160), and inefficient gas exchange quantified by the amount of dead space to tidal volume ratio (315). Further, Dolmage et al (300) demonstrated that exercise training in individuals with COPD only shifted the maximum walking speed that could be endured indefinitely, without changing the hyperbolic curve constant. The implication of this was if a participant was walking at a speed located at the lower end of the hyperbolic curve, despite the positive impact of exercise training on exercise capacity, this improvement would be minimal. Thus, in order to optimise the responsiveness of the ESWT, speeds for the test performed prior to training should be manipulated with the goal of achieving an average test duration of 8 minutes as this duration has been shown to be most likely to maximise the responsiveness to change (300). The baseline ESWT time for the rehabilitation group and bronchodilatation group in the study by Pepin et al (48) was approximately 3.8 minutes (230 sec) and 8 minutes (484 sec) and the SRM calculated was 186 sec and 70 sec, respectively. The baseline ESWT time in the current study was 5.5 minute (330 sec) and the SRM calculated was 156 sec. This suggests that the MDD is influenced by the baseline ESWT duration due to the relationship between power and endurance capacity (314).

In the current study after supervised walking training program, the participants' GRC ratings correlated significantly with the change in ESWT time expressed in seconds ($r = 0.36$) and ESWT distance expressed in metres ($r = 0.35$). These were likely to be insufficient to produce robust estimates of the MDD using many of the established anchor-based methods (232). The modest correlation ($r < 0.5$) between the GRC ratings and change in ESWT performance after walking training program may be due to possible recall bias as the walking training program was 8 weeks in duration and a considerable amount of effort and time was invested in the rehabilitation which would affect the participant's perception of health (48). As such, the ROC curve was used to discriminate between individuals who rated themselves as changed versus unchanged at the end of an intervention (8). In addition to not being dependent on a

moderate to strong relationship between GRC ratings and improvement in ESWT, using the ROC method has the advantage of accommodating all available data and not being influenced by a small number of values within a category of the GRC scale (49).

The MDC values (238 sec and 333 m) provide an estimate of the random variation of the ESWT and suggests that an individual would need to change by 238 sec or 333m to be 95% confident that this change was beyond natural variability in the ESWT performance (8, 226). These values are larger than the estimates of MDD calculated using both anchor- and distribution-based approaches, thus highlighting the limitations of using the MDD to interpret changes in individuals (234).

The strength of the estimate of the MDD for ESWT performance in the present study is that the difference in values obtained with the approaches did not appear to be important as estimates obtained via distribution-based approaches (effect size and SRM) were within 95% CI of the anchor-based approach (218). Further, the estimate of MDD with the 95% CI using the ROC curve did not include zero, thus increasing the confidence in the anchor-based estimate for ESWT performance in the present study.

6.5.1 Implications

Determining the MDD is useful as it can identify improvements which can lead clinicians to consider a change in the clinical management (212). The benefits of the MDD include linking the magnitude of change to treatment decisions in clinical practice and helping with the choice of sample size (212, 233). However, the estimates obtained from the ROC, effect size and SRM are useful for interpreting changes in groups of individuals (233), while the MDC derived from SEM is useful for determining whether the change in an individual exceeds the measurement error and is therefore likely to represent a training effect (312).

6.5.2 Limitations

The limitation was having a baseline ESWT time that was not at the most responsive point of the power-endurance curve, thus possibly providing a larger estimate of the

MDD than that would have been expected if the ESWT time at baseline was closer to 8 minutes.

6.6 Conclusions

Although the ESWT has been found to be more sensitive to change than measures made during other field walking tests, the MDD for ESWT performance using an anchor-based approach has not been established. Using an anchor-based approach, the estimated MDD for ESWT performance on completion of an 8 week supervised, individually tailored, ground walking training program was approximately 113 sec (95% CI, 23 to 139 sec) or 192 m (95% CI, 60 to 200 m).

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

The aim of this program of research was to investigate the measurement properties, namely accuracy and responsiveness of two motion sensors to measure physical activity (PA) in individuals with chronic obstructive pulmonary disease (COPD), identify strategies to optimise their PA, determine the effects of a supervised ground walking training on the performance of the endurance shuttle walk test (ESWT) and PA, and determine the minimal detectable difference (MDD) for the ESWT.

This chapter summarises the novel findings presented in this thesis as well as the implications these findings have in the clinical setting.

7.1 The measurement properties of StepWatch™ Activity Monitor and ActivPAL™

The stationary tasks and transitions between sit to stand were not detected as motion by either device. This is consistent with the properties of the StepWatch™ Activity Monitor (SAM) which only recorded steps. In contrast, the ActivPAL™ is able to record time spent being inactive versus active, outcomes related to posture changes, but it was not able to detect the task of sit to stand. Therefore, the data of this study suggests that the ActivPAL™ was not sensitive to measure transitions between sitting and standing if the new posture was not sustained for 2 minutes.

Accuracy of the StepWatch™ Activity Monitor and ActivPAL™

Regarding data collected using the SAM, there was no interaction (wheeled walker [WW] x walking speed), effect of WW or walking speed on the difference between step rates derived using the SAM and via direct observation during all four walking tasks. Regarding data collected using the ActivPAL™, there was no interaction (WW x walking speed) or effect of WW, but there was a significant effect of walking speed ($p = 0.03$) on the difference between step rate derived using the ActivPAL™ and direct observation. Thus, the novel finding of this study is that the use of a WW did not affect the capacity of the SAM or the ActivPAL™ to detect step rate.

Although the data indicates that the ActivPAL™ underestimated step rate at slow walk speeds, this difference is very small compared to other popular, more expensive, commercially-available motion sensors.

Responsiveness of the StepWatch™ Activity Monitor and ActivPAL™

For data collected using the SAM, there was no interaction (WW x walking speed) but a significant effect of WW and walking speed on step rate. Likewise, for data collected using the ActivPAL™, there was no interaction (WW x walking speed) but a significant effect of WW and walking speed on step rate. This suggests that the SAM and ActivPAL™ could detect the difference in step rate associated with changing from the slow to normal walk speed, regardless of whether the participant was using a WW.

Thus, both of these motion sensors can be used to assess PA in individuals with COPD, including those who use a walking aid such as a WW.

7.2 The impact of a wheeled walker on physical activity, health-related quality of life (HRQoL) and fear of falling

The most important finding of this study was that, in this population, having a WW available for use at home and in the community conferred an increase in the number of steps taken per day ($732 \pm 1,027$ steps/day; $p < 0.02$) as well as the time spent walking at a moderate intensity (9 ± 13 min/day; $p < 0.02$). To date, this is the only study to show that a WW provided as an intervention to selected individuals with COPD, who had recently completed training with a WW during supervised exercise classes, was able to increase PA. The use of the WW had no impact on HRQoL, a finding which may be attributed to only a short period (5 weeks) of using a WW. The main barrier towards the use of a WW is its weight which makes it difficult to lift the WW into and out of the car.

The main barrier towards the use of the WW is related to its weight, thus it would be beneficial to develop a WW that is significantly lighter than those currently available or add upper limb resistance exercises to the PRP to increase upper limb strength.

7.3 Summary of the walking and feedback training (WAFT) study

This randomised controlled trial demonstrated that an 8-week supervised, individually tailored, ground walking training program in individuals with COPD improved ESWT performance by 245 sec (95% CI, 174 to 315 sec) and 289 m (95% CI, 204 to 373 m) from baseline ($p < 0.001$) whereas the usual care group showed no significant change in ESWT performance ($p = 0.26$). Thus the improvement in ESWT performance between the walking training groups and the usual care group was significant ($p < 0.001$).

However, the 8-week walking training program only showed a trend towards improvement in steps taken per day that was not significant. The possible reason for the lack of significant improvement in PA after walking training could be that the 8-week duration of the walking training program was too short to change habits and have an impact on PA. This is because PA is affected by a multitude of factors which include behavioural, personality characteristics, environmental circumstances, community settings, social and cultural factors and symptoms related to activity (302). Further, a third of participants in the walking training groups had < 3 days of valid PA data to be included in the analyses, thus the PA data obtained in this study may not be a representation of the change after walking training. Future study is required to address the impact of exercise training on PA in individuals with COPD.

7.4 The minimal detectable difference of the endurance shuttle walk test performance

The MDD has been defined as the smallest difference in the outcome of interest that is noticeable to an individual after treatment (41). As ESWT has superior responsiveness to other field-based walking tests (287), determining its MDD will allow clinicians to evaluate the impact an exercise program may have from a patient's perspective. The MDD for ESWT performance was determined, using ESWT outcomes obtained from the 8-week supervised, individually tailored, ground walking training program of the walking and feedback training (WAFT) study.

The MDD for ESWT performance on completion of an 8-week supervised, individually tailored, ground walking training program as determined by the anchor-

based approach using the ROC curve was approximately 113 sec (95% CI, 23 to 139 sec) and 192 m (95% CI, 60 to 200 m). Determining the MDD is useful as it can identify improvements which can lead clinicians to consider a change in the clinical management (212), linking the magnitude of change to treatment decisions in clinical practice and helping with the calculation of sample size (212, 233).

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APPENDICES

Appendix A : Table of Audio signals speeds for setting consistent walking pace

6MWD(m)	Speed(m/min)	Speed (m/s)	Seconds per beep
150	25.0	0.417	12.00
165	27.5	0.458	10.91
180	30.0	0.500	10.00
195	32.5	0.542	9.23
210	35.0	0.583	8.57
225	37.5	0.625	8.00
240	40.0	0.667	7.50
255	42.5	0.708	7.06
270	45.0	0.750	6.67
285	47.5	0.792	6.32
300	50.0	0.833	6.00
315	52.5	0.875	5.71
330	55.0	0.917	5.45
345	57.5	0.958	5.22
360	60.0	1.000	5.00
375	62.5	1.042	4.80
390	65.0	1.083	4.62
405	67.5	1.125	4.44
420	70.0	1.167	4.29
435	72.5	1.208	4.14
450	75.0	1.250	4.00
465	77.5	1.292	3.87
480	80.0	1.333	3.75
495	82.5	1.375	3.64
510	85.0	1.417	3.53
525	87.5	1.458	3.43
540	90.0	1.500	3.33
555	92.5	1.542	3.24
570	95.0	1.583	3.16
585	97.5	1.625	3.08
600	100.0	1.667	3.00
615	102.5	1.708	2.93
630	105.0	1.750	2.86
645	107.5	1.792	2.79

6MWD, 6-minute walk distance; m, metres; min, minutes; s, seconds.

Appendix B : Activity diary for wheeled walker study

When? Try to do your walking exercise daily

If you are provided with the wheeled walker, please use it.

Odometer Reading: Record the number displayed on the screen.

Outdoor Walking: Refers to walking outside the house/home.

Indoor Walking: Refers to normal walking in and around the house.

Week Commencing ____ / /20 to ____ / /20

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Odometer Number							
Outdoor Walking Time (minutes)							
Indoor Walking Time (minutes)							
Reason (s) for not using the wheeled walker							

Comments:

Appendix C : Walking Training Study Training Sheet

This is an example of the walking training study training sheet of the first 6 sessions

Name _____ Age _____ Telephone _____
 Doctor _____ Doctor's Telephone _____
 Class days _____ Commencement _____
 Relevant past medical history _____

Relevant Medications _____

Initial prescription (metres) _____

Target Intensity Breathlessness level 3-4 and/or Effort level 3-4

Class No.	1	2	3	4	5	6
Date						
Time (minutes)						
Distance / laps						
SpO ₂						
Pulse rate						
Breathlessness						
Time walked						
Distance / laps						
Rests						
SpO ₂						
Pulse Rate						
Breathlessness						
Effort						
Leg fatigue						
Comments						

Rests: Participants are permitted to take short rests in the event of intolerable symptoms, with the total exercise time being exclusive of rests

Progression: increase duration by 5 minutes **after every 6th session** (i.e. session 7, 13 and 19) to a maximum of 45 minutes by session 19. Once the required duration is reached, if symptoms permit, the intensity will be increased by increasing walking speed or, if walking speed becomes limited by stride length, further increases will be achieved by adding weights in 2 kilograms increments in a weight belt.

SpO₂, percutaneous oxygen saturation.

Appendix D : Global rating of change for walking ability

Since you started this research program, has there been any change in your walking ability?

My walking ability has:

- Improved
- Worsened
- Not changed

If your walking ability has improved, give a rating stating how much improvement has been achieved.

- Almost the same, hardly better at all
- A little better
- Somewhat better
- Moderately better
- A good deal better
- A great deal better
- A very great deal better

If your walking ability has worsened, select the statement which best matches how much it has worsened.

- Almost the same, hardly any worse at all
- A little worse
- Somewhat worse
- Moderately worse
- A good deal worse
- A great deal worse
- A very great deal worse

Appendix E : Global rating of change for physical activity

Since you started this research program, has there been any change in how active you are in your daily life?

My activity has:

- Increased
- Stayed the same
- Decreased

If your activity has increased, select the statement which best matches by how much it has increased.

- Hardly increased at all, almost the same,
- A little increased
- Somewhat increased
- Moderately increased
- A good deal increased
- A great deal increased
- A very great deal increased

If your activity has decreased, select the statement which best matches by how much it has decreased.

- Hardly decreased at all, almost the same,
- A little decreased
- Somewhat decreased
- Moderately decreased
- A good deal decreased
- A great deal decreased
- A very great deal decreased