

# Optimising the Model of Pulmonary Rehabilitation Following Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)

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## Dedication

*This thesis is lovingly dedicated to my husband Guilherme, for always having faith in me even when I haven't and for being on my side – not physically, but in all ways as it was possible – in every step of the way; to my wonderful and thoughtful parents Eduardo and Marcia for giving me the opportunity to come overseas for this adventure and the emotional support since the start of this journey.*

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*"If I have seen further, it is by standing on the shoulders of giants."*

Isaac Newton

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# List of abbreviations

%predicted – percentage of predicted normal

6MWD – 6-minute walk distance

6MWT – Six Minute Walk Test

ECOPD – Exacerbation of COPD

ATS - American Thoracic Society

COPD – Chronic Obstructive Pulmonary Disease

CRQ – Chronic Respiratory Questionnaire

ERS – European Respiratory Society

FEV<sub>1</sub> – forced expiratory volume in one second

FVC – Forced vital capacity

GOLD - Global Initiative for Chronic Obstructive Lung Disease

HRQOL – Health related quality of life

MMRC – Modified Medical Research Council

MVPA – moderate-to-vigorous physical activity

PR – Pulmonary rehabilitation

SD – Standard Deviation

WHO - World Health Organisation

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# Thesis Abstract

Exacerbations are common events in the natural history of COPD with negative impacts on morbidity and mortality. Although early pulmonary rehabilitation is recommended following an exacerbation of COPD, many eligible patients do not receive it and there is no consensus on the optimal model. The aim of this thesis was to optimise the model of pulmonary rehabilitation following exacerbations of COPD.

A narrative review showed that recovery of lung function, airway inflammation and symptoms generally occurred in the first 14 days following a COPD exacerbation. People with older age, worse chronic dyspnoea and more severe COPD are at risk of experiencing prolonged recovery. A secondary analysis of a randomised controlled trial (n=166) demonstrated that 34% of participants had a severe exacerbation in the year following pulmonary rehabilitation. Severe exacerbations were more likely in those with worse lung function and poorer quality of life at program commencement. The systematic review (n=28 included papers) showed that pulmonary rehabilitation programs with a duration longer than three weeks, including exercise training as well as education, and starting after hospital discharge were most effective in reducing hospital readmissions. Finally, action research methods (Phase I feasibility n=10/ Phase II qualitative interviews n=12 clinicians and 14 hospitalised patients)/ Phase III re-pilot n=5) found that although an early home-based pulmonary rehabilitation program is feasible after a severe exacerbation, many hospitalised patients with COPD did not meet eligibility criteria, including 24% with a comorbid condition that impacted safety of home-based exercise. This research reinforces the negative impact of exacerbations in people with COPD and identifies individuals in whom recovery may be prolonged. Early pulmonary



rehabilitation programs have potential to enhance recovery and reduce rehospitalisation. Models of early pulmonary rehabilitation that facilitate uptake and completion in a broader range of people with COPD, including those with comorbid conditions, are required.

# Statement of Authorship

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgment in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

Ethics approval was required for the work presented by La Trobe University Human Ethics Committee, externally approved on 13 April 2016 from The Alfred HREC approved project - 475/15 (Appendix A).

This work was supported by a La Trobe University Postgraduate Research Scholarship and a La Trobe University Full Fee Research Scholarship

Signed :



Date: 22 May 2020

Bruna Borges Wageck

# Candidate's Declaration

Chapters Two, Three, Four and Five are manuscripts published or submitted to publication and involved other authors, in the case of these chapters contributions of the candidate was as follows:

Chapter	Publication Title	Publication Status	Contribution
Two	Recovery Following Exacerbations of Chronic Obstructive Pulmonary Disease - A Review	Published	70%
Three	The impact of COPD exacerbations in the year following pulmonary rehabilitation: a secondary analysis of a randomised controlled trial	Submitted to publication	60%
Four	Characteristics of pulmonary rehabilitation programs following exacerbation of COPD: a systematic review	Submitted to publication	66%
Five	Early home-based pulmonary rehabilitation following exacerbation of COPD: A feasibility study using an action research approach	Submitted to publication	60%

Signed:   
Bruna Borges Wageck

Date: 22 May 2020

## Supervisor's Declaration

I hereby certify that the declaration above is a correct reflection of the extent of the contributions made by the student candidate towards each chapter in this thesis.

A handwritten signature in black ink, appearing to read 'Anne E Holland', written in a cursive style.

Date: 22 May 2020

Supervisor: Professor Anne E Holland

# Publications and Presentations

All manuscripts presented in Chapters Two, Three, Four and Five of this thesis were designed, conducted and written during the period of the candidature for the specific purpose of obtaining the degree of Doctor of Philosophy. Each manuscript was prepared in accordance with specific requirements of the relevant journal. The contribution of the student candidate, and each co-author, for each study is included in the preface of the relevant chapter.

## **Published Manuscripts:**

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# CHAPTER ONE

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*Introduction and background*



## 1.1 Chronic Obstructive Pulmonary Disease

### 1.1.1 Pathophysiology

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease that causes respiratory airflow and alveolar abnormalities (1, 2). COPD is an irreversible condition characterized by abnormal inflammatory responses commonly caused by exposure to noxious particles or gases (1, 2). Estimates from The Australian Institute of Health and Welfare (AIHW) suggest that one in every 20 Australians over the age of 45 has COPD (3). Moreover, the prevalence of COPD increases with advancing age, with as many as 7% of Australians aged greater than 65 years having COPD (3). In 2017, COPD was the fifth leading cause of death in Australia (3).

Chronic obstructive pulmonary disease results from a complex interaction between genetic factors and the environment (4). Exposure to cigarette smoke is a well-known risk factor for COPD, however, less than 50% of smokers develop COPD during their life, while there are people who never smoked that develop the condition (4). Other factors can contribute to developing COPD, such as: indoor air pollution (burning wood, biomass fuels), outdoor air pollution, abnormal lung growth and development, airway hyper-reactivity and chronic bronchitis (4). Occupational exposures such as chemical agents and fumes are also important risk factors for developing COPD (4).

The chronic inflammation process in the lungs associated with COPD causes irreversible airway narrowing and airflow limitation (5). Airway remodelling usually affects smaller airways and results in increased resistance to airflow, poorer compliance of the lungs and

progressive airflow obstruction (6). Abnormal inflammatory responses in the lung may also result in chronic bronchitis (mucous hypersecretion), emphysema (tissue destruction), and bronchiolitis (disruption of repair and defence mechanisms which causes airway inflammation) (6). Moreover, the lung loses its elastic recoil characteristics due to alveolar wall destruction from airway remodelling (6). Thus, hyperinflation is a common finding in COPD, due to gas trapping within the lungs (6). Another important change in lungs affected by COPD is ciliary dysfunction, which is worsened when associated with mucus hypersecretion (6).

Physiologic changes in COPD are not exclusive to the lungs. Systemic complications in COPD may include skeletal muscle dysfunction (change in fibre-type composition and atrophy) as a consequence of hypoxia, hypercapnia or acidosis; systemic inflammation (increased proinflammatory cytokines in the systemic circulation) and muscle disuse as a result of sedentarism (7). Cardiovascular and neurologic changes may also be associated with systemic changes from COPD (7).

People presenting with chronic cough, sputum production, shortness of breath and a history of exposure to risk factors such as smoking, or living or working with high air pollution, can be suspected of having COPD. Diagnosis of COPD is based on the patient's history of environmental exposure, presence of cough, sputum production, or dyspnoea and confirmed by a lung function test (1, 2). The GOLD strategy suggests that any patient aged greater than 40 years old presenting with these symptoms should undertake spirometry to confirm the diagnosis (2). A diagnosis of COPD requires post-bronchodilator forced expiratory ratio (FER - the forced expiratory volume in one second (FEV<sub>1</sub>) divided for the forced vital

capacity (FVC)), of less than 0.7 (2). Disease severity is also defined on the basis of spirometry - see Table 1 (2, 8).

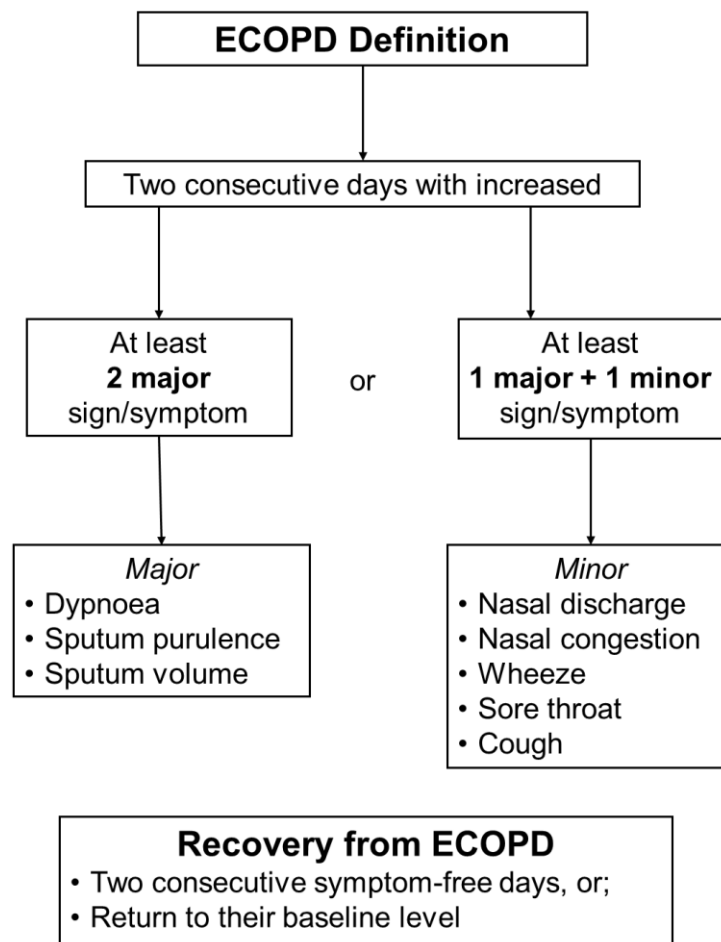
**Table 1.** Classification of COPD severity based on post-bronchodilator FEV<sub>1</sub>

<b>Classification</b> <b>(patients with FEV<sub>1</sub>/FVC &lt;0.7)</b>	<b>Severity</b>	<b>Post-bronchodilator FEV<sub>1</sub></b>
<b>GOLD 1</b>	Mild	FEV <sub>1</sub> ≥ 80% predicted
<b>GOLD 2</b>	Moderate	50% ≤ FEV <sub>1</sub> < 80% predicted
<b>GOLD 3</b>	Severe	30% ≤ FEV <sub>1</sub> < 50% predicted
<b>GOLD 4</b>	Very severe	FEV <sub>1</sub> < 30% predicted

Table legend: GOLD: Global Initiative for Chronic Obstructive Lung Disease strategy (2); FEV<sub>1</sub>: forced expiratory volume in one second; FVC: Forced vital capacity.

### 1.1.2 Exacerbation of COPD

One of the key factors that contributes to the progression of the disease is an acute change in the stable condition, referred to as an exacerbation of COPD (ECOPD) (9). During the natural course of COPD exacerbations are commonly experienced, and are characterized by worsening of both symptoms and the chronic inflammation in the airways, as compared to baseline condition (10). Etiologic factors such as viral or bacterial infection increase inflammatory responses in the airways leading to airway wall oedema and increased mucus production both of which contribute to narrowing of the tracheobronchial tree and worsening airway obstruction (10). The definition of ECOPD is frequently based on worsening symptoms. For research purposes ECOPD has been defined as two consecutive days of worsening on two major symptoms (Figure 1) (11).



**Figure 1.** Definition of exacerbation of COPD (ECOPD)

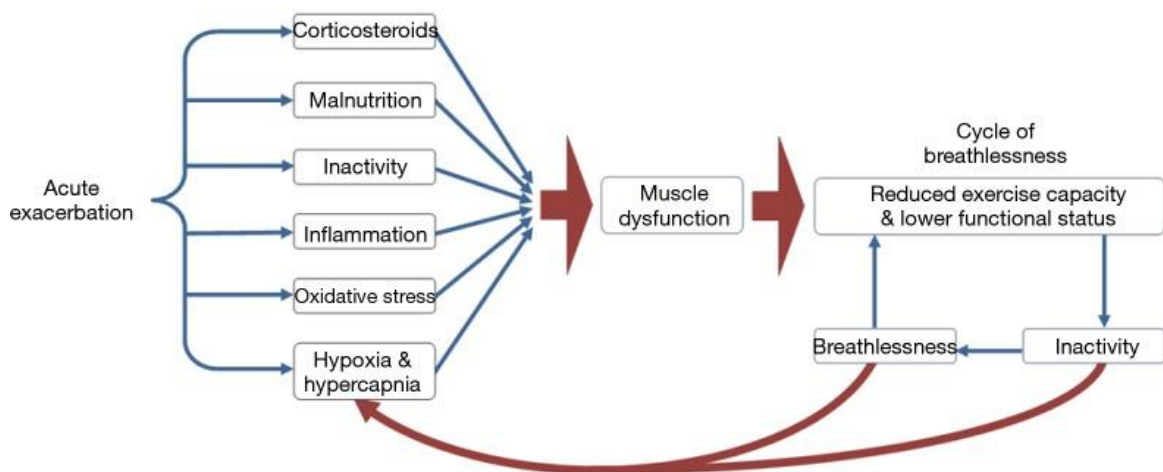
Definition for ECOPD from Seemungal et al. (11) and the definition of recovery for ECOPD from Donaldson et al. (9).

Exacerbations of COPD are one of the leading causes of hospital admission and death in people with COPD (12, 13), and can be considered both in terms of severity (e.g. the level of dyspnoea) and frequency (recurrence of exacerbation, regardless of severity) (14). During an ECOPD, symptoms may become overwhelming, resulting in a need for changes in medication (signifying a moderate exacerbation) and/or hospitalisation for supportive therapy (a severe exacerbation) (11). Worsening symptoms are associated with a reduction in health

status, poorer health-related quality of life and reduced exercise capacity (15, 16). In addition to the reduced exercise capacity evident during an ECOPD, muscle strength and muscle mass have also been shown to decrease in those people requiring hospitalisation for an exacerbation (17). Furthermore, the literature suggests that hospital admissions and readmission are significantly related to anxiety and depression factors (18). Individuals with COPD who are frequent exacerbators are more than twice as likely to have severe ECOPD (requiring hospitalisation) than infrequent exacerbators (15% vs 7%) (19). In addition, people who have frequent exacerbations over the course of a year often fail to return to their stable condition within the first month after exacerbation onset (20).

The definition of recovery of ECOPD is having two consecutive days when symptoms have returned to the stable condition (Figure 1) (9). Longer time to recovery is related to inferior health status and a higher risk of having another ECOPD (9), however the time course of the natural recovery process is not well established. Whilst most people with COPD will recover within 14 days, it is clear that some people may have delayed recovery, or may not regain their previous status (21). The timelines for recovery, and the factors that affect recovery, have not been well described. The bulk of the literature regarding ECOPD focuses on designing interventions that would increase speed of recovery or result in better outcomes after exacerbation (22); however, strategies designed specifically to enhance recovery from ECOPD are difficult to implement without a comprehensive understanding of the recovery process. Chapter Two of this thesis is a narrative review that synthesises literature describing the natural course of recovery from an ECOPD. Understanding the recovery process might enable recognition of the best period to implement specific interventions for ECOPD.

Exacerbations of COPD have different symptoms and severity for each person, and in more severe occurrences require hospitalisation. Symptoms of exacerbations usually consist of increased dyspnoea, cough and sputum volume compared to the individual's stable condition (23). Frequent exacerbations impact on functional capacity and quality of life of people with COPD reducing independence for daily life activities and even locomotion (24). The physical inactivity resulting from increased symptoms such as dyspnoea, together with hospitalisations during ECOPD, can have an important impact on muscle disuse; generating a cycle of disuse – inactivity – dyspnoea in this population (Figure 2). This disuse and inactivity provides a rationale for the use of pulmonary rehabilitation post ECOPD, to increase activity levels and improve skeletal muscle function (22). The potential role for pulmonary rehabilitation post ECOPD is described in the following section.



**Figure 2.** Inactivity circle and the impact of ECOPD on muscle dysfunction

Reference: Jones et al. (25)

## 1.2 Pulmonary rehabilitation

### 1.2.1 Definition and benefits

Pulmonary rehabilitation is a comprehensive intervention including exercise training and education designed to promote health and reduce symptoms associated with COPD (26). It is a nonpharmacologic therapy that is delivered alongside pharmacological treatments for people with COPD (27). The GOLD strategy endorses pulmonary rehabilitation as a recommended treatment for all patient groups (27). In addition, clinical guidelines from the American Thoracic Society and European Respiratory Society (ATS/ERS) state that pulmonary rehabilitation and pharmacotherapy are complementary treatments for patients with COPD (1). The Australian and New Zealand pulmonary rehabilitation guidelines recommend pulmonary rehabilitation for people with COPD either in a stable condition or after ECOPD (28).

Pulmonary rehabilitation programmes for people with stable COPD effectively improve exercise capacity, quality of life and reduce symptoms and health care utilisation (29). The programme reduces the perceived intensity of dyspnoea, number of hospitalizations and hospital length of stay, as well as reduces anxiety and depression associated with COPD (29). Importantly, the clinical outcome improvements achieved during pulmonary rehabilitation are usually extended for the months to follow (30); however, the results are often not maintained long term (31). Studies of people with COPD in a stable condition demonstrate return to pre-pulmonary rehabilitation levels of exercise capacity and quality of life one year after attending a pulmonary rehabilitation programme (31, 32). The reasons for this regression are unclear. One possible factor that could contribute to this deterioration of

function is the occurrence of ECOPD during the follow up period. An ECOPD affects exercise capacity and quality of life, both of which have been demonstrated to fail to completely recover after an ECOPD (21). However, the impact of exacerbations in the year following pulmonary rehabilitation on long term clinical outcomes has not been investigated. Chapter Three of this thesis presents a study examining the impact of ECOPD on exercise capacity and quality of life in the year following pulmonary rehabilitation; additionally, it investigates possible predictors of exacerbations in the year following pulmonary rehabilitation and their relationship with clinical outcomes. Understanding which groups of patients are at risk of ECOPD, and consequently poor outcomes, following pulmonary rehabilitation may allow closer clinical monitoring and could potentially influence new research focusing on specific interventions for individuals with COPD at most risk.

Pulmonary Rehabilitation starting early after ECOPD improves quality of life and exercise capacity, and it could decrease the negative effects of inactivity during the episode (22). As a result, the Australian and New Zealand Pulmonary Rehabilitation guidelines recommend that people with COPD undertake pulmonary rehabilitation as soon as two weeks after hospital discharge for an ECOPD (28). Such recommendations are based on evidence, including a study of 60 individuals hospitalized for ECOPD which found that 33% of participants in the usual care group were re-admitted to hospital within 3 months, while only 7% of the participants who undertook pulmonary rehabilitation early after hospital discharge for ECOPD were readmitted (33). A Cochrane systematic review updated in 2016 including 20 studies demonstrated high-quality evidence for pulmonary rehabilitation in enhancing quality of life and functional capacity, and moderate-quality evidence for reduction in hospital admissions in those who undertook pulmonary rehabilitation post ECOPD (pooled OR 0.44,



95% CI, 0.21 to 0.91,  $P=0.03$ ) (22). The updated review included six studies (670 participants) in a meta-analysis which demonstrated a non-significant effect of rehabilitation on mortality (low-quality evidence; pooled OR 0.68, 95% CI 0.28 to 1.67) (22). Although the results of the systematic review are encouraging, one study included in the review update has raised important concerns related to safety of starting pulmonary rehabilitation early after ECOPD (34). Despite initial encouraging outcomes of early pulmonary rehabilitation studies (22) recent data have been far less encouraging and suggest that a re-evaluation of this intervention may be required.

A randomised controlled trial conducted in the United Kingdom ( $n=389$ ) randomised participants with ECOPD to either very early rehabilitation (started within 48 hours of hospital admission) or usual care (34). Very early pulmonary rehabilitation (aerobic and resistance exercise) was commenced in hospital and was followed by an unsupervised exercise programme until 6 weeks after discharge, supported by telephone (34). Greening et al. (34) reported no differences between groups relating to hospital readmissions, physical function and health status at 6 weeks after discharge. However, the study found a higher mortality risk in the very early pulmonary rehabilitation group after 12 months (OR 1.74, 95% CI, 1.05 to 2.88,  $P=0.03$ ) (34). Whilst the reason for this increased mortality is not known, it is possible that the programme structure was a contributor. The intervention started very early in the recovery period (during hospitalisation); the home-based programme was largely unsupervised; and fewer intervention participants undertook a traditional centre-based rehabilitation in the following 12 months compared to the control group (14% vs 22% respectively,  $p=0.04$ ) (34). It has been suggested that participants in the intervention group may have seen their rehabilitation needs as having been met, and this failure for very early

rehabilitation to articulate with the traditional model of pulmonary rehabilitation, delivered in the stable clinical state with known efficacy and long term benefit, may be responsible for the adverse findings (34). The complex nature of early pulmonary rehabilitation interventions often makes it difficult to establish what characteristics of the intervention are critical to the findings (35). Pulmonary rehabilitation programs vary in structure and content, which will be explored in the following section.

### 1.2.2 Structure of pulmonary rehabilitation programmes

Pulmonary rehabilitation programmes are most commonly located in the hospital as an outpatient service (1). In people with stable COPD a home-based pulmonary rehabilitation programme can also achieve equivalent clinical benefits as centre-based pulmonary rehabilitation (31). For improvements to be achieved with pulmonary rehabilitation, exercise training must be individually tailored and progressive to exceed daily life activity loads and increase muscle strength and aerobic capacity (26). Exercise training is an essential component of pulmonary rehabilitation, in addition to which self-management education has also been recognized as a key component for management of COPD (26, 27). Common key elements included within a pulmonary rehabilitation programme are:

Endurance training: designed to increase aerobic capacity, should be performed at a symptom-limited level of intensity. Dyspnoea score between 3 to 4 on the modified Borg scale (28). The modalities commonly used for endurance training in pulmonary rehabilitation programmes include walking (ground walking or treadmill) and stationary cycling (26).

Resistance training: is designed to increase muscle strength, however there is no consensus as to what are the best exercises or muscle groups to be trained in people with COPD. Given people with COPD commonly report difficulties with daily activities that include the upper limbs and reaching over the head movements (i.e. dressing, bathing, shopping) inclusion of exercises for these muscle groups should be considered (36).

Education and self-management: including topics such as pathophysiology of COPD, interpretation of medical testing, breathing strategies, benefits of such as exercises, irritant avoidance (smoking cessation), and healthy food intake, are considered a key element of pulmonary rehabilitation (26, 37). The aim of self-management training is to promote self-efficacy increasing knowledge and skills for people about their lung condition, the best way of using health care professionals, and achieving their health goals (37). Self-management strategies are important in order to promote behaviour change aiming to reduce anxiety and depression factors associated to COPD and ECOPD (18); and increase patient's skill on how to manage their disease (26).

The Australia and New Zealand pulmonary rehabilitation guidelines recommend patients with moderate-severe COPD undertake pulmonary rehabilitation to reduce inactivity and exacerbations (28). While pulmonary rehabilitation has been broadly studied and applied for people with stable COPD (29), pulmonary rehabilitation programmes are also recommended for people after ECOPD (22). Although the Cochrane Review of pulmonary rehabilitation after ECOPD reported important results (22), the structure of the included pulmonary rehabilitation programmes was heterogeneous regarding programme characteristics (22). Studies delivered exercise programmes alone (38) or associated with education (39); starting

during hospital admission (38) or after discharge (39), with and without supervision (34, 38, 40). There is no consensus in the literature regarding optimal structure of a pulmonary rehabilitation programme after ECOPD concerning duration, frequency, location, or supervision. To address the lack of evidence regarding structure of pulmonary rehabilitation after exacerbations, Chapter Four presents a systematic review describing the impact of pulmonary rehabilitation programme characteristics on clinical outcomes following an ECOPD.

### 1.2.3 Barriers to uptake and new approaches

Although pulmonary rehabilitation is an important and recommended treatment for people with COPD (1, 2, 22, 29), a large number of individuals with COPD who would benefit have limited access to programmes (41, 42). In Australia, fewer than 10% of people eligible for pulmonary rehabilitation have ever accessed a programme (3). This reflects issues associated with programme uptake (being referred to a service, but failing to attend the initial appointment) (43), participation (attendance at sessions during the programme) and completion (attending a pre-determined number of rehabilitation sessions, commensurate with achieving a sufficient dose of rehabilitation) (41). In a UK wide pulmonary rehabilitation service audit, for every 100 people referred to pulmonary rehabilitation (from 68000 referrals during the audit period) more than 30% fail to attend the initial appointment (lack of uptake) (44). Of the people who do start pulmonary rehabilitation, less than 2 in every 3 (or around 40% of the initial 100 referrals) attend sufficient rehabilitation sessions to be classified as a rehabilitation ‘completer’ (44). There are multiple, well-documented, factors that limit access to and uptake and completion of pulmonary rehabilitation

programmes including poor referral rates, finite availability of services, and patient related factors (45, 46).

A systematic review including 48 studies of both individuals with COPD and healthcare practitioners working in COPD identified key barriers to pulmonary rehabilitation referral, uptake and completion were commonly related to the environment, limited understanding of both referral processes and what pulmonary rehabilitation is, as well as unclear understanding and expectations of the benefits of pulmonary rehabilitation (41). Knowledge (or lack of) of the referral process to pulmonary rehabilitation by clinicians, understanding by the patient of why and what they have been referred to, and previous (positive or negative) experience of pulmonary rehabilitation for clinicians associated with other referrals they have made can all influence the uptake of pulmonary rehabilitation (41).

Patient related barriers to attending a pulmonary rehabilitation programme are also widely reported and include disruption to usual routine, travel to the location, inconvenient time and location of programmes, lack of knowledge about the benefits of pulmonary rehabilitation and the influence of the patient's doctors about pulmonary rehabilitation (43). People who commence a pulmonary rehabilitation programme but fail to complete it frequently have comorbidities, including depression, associated with COPD (43). Current smokers are also less likely to complete a pulmonary rehabilitation programme than non-smokers (43).

Limited knowledge about the benefits associated with completing a programme of pulmonary rehabilitation, and a lack of support, are also important factors associated with non-completion (43).

While reported barriers to outpatient pulmonary rehabilitation access, uptake and completion have largely been documented in people with stable COPD, it would seem likely that people with COPD following an ECOPD would face similar or even greater issues in accessing pulmonary rehabilitation programmes. Referrals to pulmonary rehabilitation after hospital discharge are low with only 24-40% of eligible patients referred to pulmonary rehabilitation on discharge for ECOPD (39, 42). Irrespective of referral, recent reports suggest that less than 2% of all patients hospitalized due ECOPD undertake pulmonary rehabilitation within 6 months of hospital discharge, with fewer than 3% starting pulmonary rehabilitation in the year after discharge (47).

To overcome barriers to accessing pulmonary rehabilitation researchers are developing new approaches and alternative models of delivering pulmonary rehabilitation, such that a larger number of people may be able to access services (31, 40). Home-based programmes could be a good solution to increase the reach of pulmonary rehabilitation and its associated benefits (31). An important multicentre study published in 2017 showed that a home-based programme, using minimal resources, delivered equivalent benefits to centre-based pulmonary rehabilitation in people with stable COPD (31). A sub-group analysis within the study indicated that patients in the home-based group felt supported and that they could continue their exercise routine after the end of pulmonary rehabilitation (48). The home-based programme was designed to overcome barriers associated with attendance at outpatient pulmonary rehabilitation. It is possible that this model of programme delivery may be beneficial to assist people following hospitalisation for ECOPD to access pulmonary

rehabilitation services. Chapter Five reports an action research project designed to assess the feasibility of a home-based pulmonary rehabilitation programme starting early after ECOPD. The research was designed in three phases: assessing feasibility of a home-based pulmonary rehabilitation programme; qualitative interviews with patients and clinicians to improve the model; and, re-testing the programme delivery.

## 1.3 Summary

Exacerbations are important events in the natural history of COPD that influence long-term outcomes. Recovery following ECOPD is poorly understood, both in terms of time course and influencing factors. Furthermore, there is not much information on the impact of exacerbations in the year following pulmonary rehabilitation. Although pulmonary rehabilitation is recommended for people following ECOPD the structure of tested programs is heterogeneous and there is not a consensus about what characteristics are important to achieve its benefits. Finally, the current model of centre-based pulmonary rehabilitation does not reach the majority of people with COPD early after exacerbations.



## 1.4 Thesis overview

The objective of this thesis was to optimise the model of pulmonary rehabilitation following exacerbations of COPD. The specific aims of each chapter were to:

- 1- Describe the natural recovery process following ECOPD for lung function, inflammatory markers, symptoms, physical activity and quality of life;
- 2- Examine the impact of ECOPD on clinical outcomes at 12 months after pulmonary rehabilitation and identify predictors of ECOPD in the year after pulmonary rehabilitation;
- 3- Determine the impact of the pulmonary rehabilitation program characteristics on clinical outcomes following an ECOPD;
- 4- Design and test a pulmonary rehabilitation protocol addressing barriers to uptake and completion of pulmonary rehabilitation following ECOPD.

To achieve these aims, the following four studies were undertaken:

*Chapter Two* is a narrative review that describes the natural recovery process following an ECOPD (Aim 1).

*Chapter Three* is a secondary analysis from a randomised controlled trial exploring the impact of exacerbations on clinical outcomes one year after exacerbation (Aim 2).

*Chapter Four* is a systematic review to understand what are the characteristics of pulmonary rehabilitation programs following ECOPD that are important in order to achieve benefits (Aim 3).

*Chapter Five* is an action research project to test the feasibility of a home-based model of pulmonary rehabilitation early after ECOPD (Aim 4).

*Chapter Six* presents an overview of overall findings of the thesis, clinical implications of the findings and future research directions.

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# CHAPTER TWO


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*Recovery Following Exacerbations of Chronic  
Obstructive Pulmonary Disease - A Review*

## 2.1 Declaration of Authorship – Chapter Two


### Student's Declaration

The nature and extent of contributions to Chapter Two of this thesis are as follows:

Name	Nature of contribution	Contribution	Signature
Bruna Wageck	Protocol development, data search and extraction, writing and review of manuscript	70%	
Narelle S Cox	Protocol development and review of manuscript	10%	
Anne E Holland	Study concept and design, data analysis and review of manuscript	20%	

### Supervisor's Declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter Two of this thesis by the student and all listed

Supervisor name	Signature
Professor Anne E Holland	

## 2.2 Preface

Exacerbations of chronic obstructive pulmonary disease (ECOPD) are one of the leading causes of hospital admission and death in people with chronic obstructive pulmonary disease (COPD). Exacerbations have detrimental effects on health status and quality of life of people with COPD, and longer recovery following an exacerbation is related to poorer health status and a higher risk of having another exacerbation. To reduce the impact of ECOPD, much current research is focussed on developing new strategies for improving recovery post exacerbation. However, in order to best restore health and function post ECOPD, an understanding of the natural recovery process following exacerbation is required. Understanding the natural pattern of recovery from an exacerbation in COPD is important in order to develop interventions that are necessary, effective and timely to restore health or reduce the negative consequences of ECOPD.

The aim of the narrative review presented here was to describe the natural recovery course following ECOPD as relates to lung function, inflammatory markers, symptoms, physical activity and quality of life. Findings from this review identify the importance of recognising prolonged recovery and highlight the need to develop and assess interventions that could enhance recovery post exacerbation.

One publication has arisen from this chapter, a narrative review published in *COPD Journal of Chronic Obstructive Pulmonary Disease* that has an impact factor 2.503.

## 2.3 Manuscript



COPD: Journal of Chronic Obstructive Pulmonary Disease



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## Recovery Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease – A Review

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### ABSTRACT

Acute exacerbations are associated with disease progression, hospital admission and death in people with chronic obstructive pulmonary disease (COPD). The detrimental outcomes associated with acute exacerbations highlights a need to understand the time course of recovery following acute exacerbation of COPD (AECOPD) so that effective and timely interventions can be provided. The aim of this narrative review was to describe the natural recovery in physiology, symptoms and function following AECOPD. Substantial recovery of lung function and airway inflammation occurs in the first week after onset of an AECOPD, whilst systemic inflammatory markers may take up to two weeks to recover. Symptoms generally improve over the first 14 days, however marked variation is evident between studies and individuals. There are limited data regarding the time course of recovery for functional capacity, quality of life and strength. In a small number of patients (<10%) recovery of lung function and symptoms has not occurred by three months. Features of patients at risk of a prolonged recovery following AECOPD include older age, more severe lung disease, presence of chronic bronchitis, lower body mass index and more chronic dyspnoea. Exacerbation features associated with prolonged recovery are symptoms of the common cold at exacerbation onset, evidence of viral infection, more severe dyspnoea during the exacerbation and persistent systemic inflammation. In clinical practice efforts should be made to recognise prolonged recovery, which puts patients at risk of poor outcomes, and to address the consequences of AECOPD including physical inactivity and skeletal muscle weakness. Whether delivery of specific interventions at distinct time points in the recovery process can enhance recovery remains to be determined.

### ARTICLE HISTORY

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### KEYWORDS



Exercise capacity; lung function; inflammatory markers; quality of life; chronic obstructive respiratory disease; exacerbation

### Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by significant functional limitation and high mortality (1). One of the key factors associated with disease progression is an acute change in the condition, referred to as an acute exacerbation of COPD (AECOPD) (2). There is no universally accepted definition for an AECOPD, however the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy for COPD management describes exacerbations as a worsening of symptoms compared with the patient's baseline (1). For research purposes (Figure 1), an AECOPD has previously been defined as two consecutive days with an increase in at least two major signs and/or symptoms; or the presence of one major together with a minor sign and/or symptom (3,4). Recovery from an AECOPD has been defined as two consecutive days without symptoms; or, a return of symptoms to their baseline level (2). The time course to achieve recovery of physiology, symptoms and function following AECOPD has not been comprehensively described.

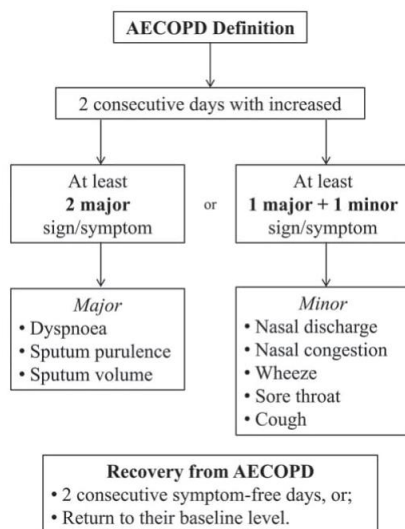
Exacerbations of COPD reduce both quality of life and physical function, which may not spontaneously recover

(5,6). Exacerbations can be considered both in terms of severity (e.g. the level of breathlessness) and frequency (recurrence of exacerbation, regardless of severity) (7). During an AECOPD levels of breathlessness may become overwhelming, resulting in a need for changes in medication (signifying a moderate exacerbation) and/or hospitalisation for supportive therapy (a severe exacerbation) (3). Exacerbation severity is meaningful to patients and measures of severity can be used to identify when recovery has occurred. However, frequency of AECOPD is also an important marker. Exacerbations are one of the leading causes of hospital admission and death in people with COPD (5,8). People with COPD who have frequent exacerbations over the course of a year often fail to return to their stable condition within the first month after exacerbation onset (9). Frequent exacerbators are usually older, ex-smokers, with more severe disease and experience more chronic dyspnoea (1,10). Frequent exacerbators are more than twice as likely to have severe AECOPD (requiring hospitalisation) than infrequent exacerbators (15% vs 7%) (11). Understanding the natural course of recovery from an AECOPD is important in order to recognise when recovery

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**Figure 1.** Definition of acute exacerbation of COPD (AECOPD). Definition for AECOPD from Seemungal et al. (3) and the definition of recovery for AECOPD from Donaldson et al. (2).

has not occurred, to identify when additional interventions could be needed that may shorten the time of recovery following AECOPD, and thus reduce the negative consequences of exacerbations.

The aim of this review was to describe the natural recovery following AECOPD for lung function, inflammatory markers, symptoms, physical activity and quality of life.

### Respiratory function

A number of studies have quantified the reduction in lung function at exacerbation onset and the time course of recovery. Data from a cohort study with 73 participants who had moderate to severe COPD indicated the median (interquartile range (IQR)) percentage decline in forced expiratory volume in one second (FEV<sub>1</sub> in L) from baseline to exacerbation onset was 5.1% (IQR -15.0 to 6.2%) (12). On average, 88% of the total recovery in lung function occurs in the first week after onset of an AECOPD (Figure 2), with continued improvement over the following month (9,13). A study of hospitalised patients with an AECOPD found that both FEV<sub>1</sub> and forced vital capacity (FVC) improved significantly to day 10 compared to at the onset of exacerbation (9). Both FEV<sub>1</sub> and FVC continued improving to day 40 (9). However, the study did not have baseline data for when participants were in a stable condition, and as a result it was not possible to be certain that recovery of FEV<sub>1</sub> was complete at this time point. The median time for recovery of PEFR to baseline has been reported as five days (IQR 0–14 days) (2) or six days (1–14 days) (3). The rate at which respiratory function recovers will be influenced by the treatment received. Corticosteroid treatment results in more rapid recovery of FEV<sub>1</sub> over the first 72 hours (mean 140 ml greater compared to no corticosteroids, 95% confidence

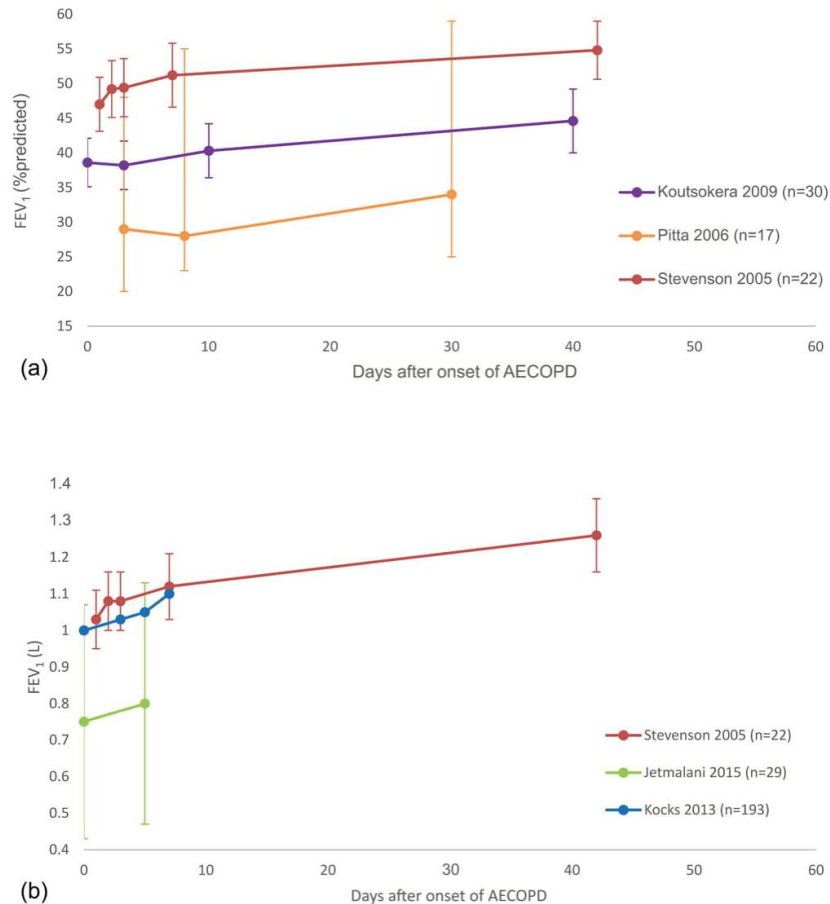
interval (CI) 90–200 ml), however no difference was evident at later time points (14).

Although improvement in lung function appears to occur most rapidly during the first week after an exacerbation, other authors have reported a longer recovery period, or incomplete recovery. A study of over 100 participants with moderate to severe COPD over 2.5 years found that recovery of PEFR to baseline values was complete in 75% of exacerbations at 35 days, whereas in 7% of exacerbations PEFR recovery had not occurred by 91 days (3). In a cohort of 384 people with moderate to severe COPD followed for 1,039 days, PEFR did not return to baseline by day 99 in 257 out of 3087 exacerbations (8%) (2). Parker et al. (15) assessing patients with a moderate AECOPD found significant changes in FEV<sub>1</sub> from baseline did not occur until day 14 after onset of the exacerbation (15). In this study, participants were divided into two groups at 60 days following AECOPD: 'Symptomatically Recovered' (dyspnoea returned to baseline levels) and 'Symptomatically Non-recovered' (15). Individuals classified as 'Symptomatically Recovered' had significant improvement in FEV<sub>1</sub> from baseline to the recovery visit at day 60 ( $0.98 \pm 0.08$  L to  $1.20 \pm 0.08$  L respectively,  $p < 0.05$ ). Individuals classified as 'Symptomatically Non-recovered' had a small increase in FEV<sub>1</sub> after 60 days that was not statistically significant (data not reported) (15). The reasons for incomplete recovery are not clear, but may relate to repeated exacerbations. In one study, repeat exacerbation had occurred in 22% of participants by day 50 (12). This is clinically important, as re-exacerbation is associated with a greater decline in lung function over time (16).

Recently other respiratory function measures have been investigated for their ability to predict onset of an AECOPD and describe the recovery process (17,18). Remote home monitoring of breathing rate showed a decrease in average resting respiratory rate over the first week following an AECOPD, however there was marked inter-individual variation, with some patients showing no changes in respiratory rate, suggesting this measure may not be sufficiently sensitive to physiological change in this period (17). A large randomised controlled trial ( $n = 312$ ) in people with COPD and GOLD stage II–IV used remote monitoring of airway mechanics with the forced oscillation technique (FOT) to detect the onset of exacerbations, initiate treatment and monitor recovery (19). There was no effect on the primary outcomes of time to first hospitalisation or health-related quality of life, however re-hospitalisation may have been reduced in those undergoing remote monitoring with FOT. Respiratory alerts, triggered by a trend in worsening of at least one FOT parameter, were accompanied by worsening respiratory symptoms on 50% of occasions and prompted a change in treatment on 34% of occasions. These data suggest that FOT may be sensitive for detecting onset of AECOPD, unlike spirometry and PEFR which may not significantly worsen before an exacerbation (3). The clinical utility and cost effectiveness of using FOT in routine care remain to be established.

Overall, the body of literature shows a consistent decline in lung function at the onset of AECOPD, with most





**Figure 2.** Recovery of lung function after AECOPD. Day 0 is onset of exacerbation. Data are mean  $\pm$  SD unless otherwise stated. (a) Recovery of FEV<sub>1</sub> %predicted over time. (b) Recovery of FEV<sub>1</sub> (L) over time. FEV<sub>1</sub> = forced expiratory volume in one second; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; *n* = number of participants; L = litres; %predicted = percentage of predicted normal.

Note: Data from Jetmalani et al. (74) are a combination of the means and SD from two groups presented in the study (75). Data from Kocks et al. (46) were derived from the graph, there is no SD.

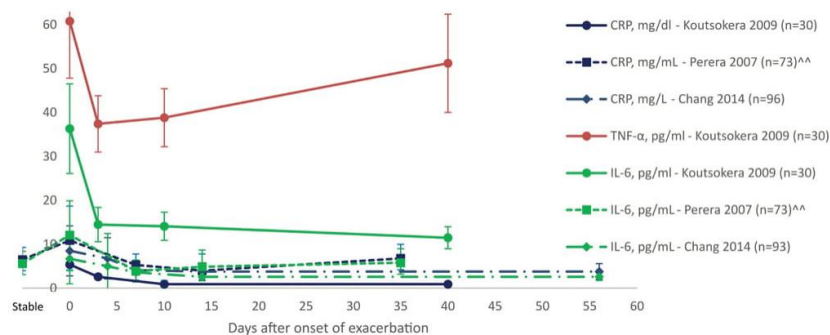
recovery occurring within the first week. However, in a small number of individuals (less than 10%) full recovery of lung function may not occur by three months. Many studies documenting the recovery of lung function have been of small sample size which could limit the extent to which these results represent the COPD population at large. However, it seems likely that some patients do not experience complete recovery of lung function parameters even many months following an AECOPD, underscoring the importance of these events in the natural history of the disease.

### Inflammatory markers

Inflammatory markers increase during an AECOPD. Such markers include interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and C-reactive protein (CRP). The systemic inflammatory response during an AECOPD can be measured by blood analysis, while airway

inflammation is assessed by the presence of inflammatory markers in sputum or exhaled breath condensate (20). An increase in IL-6 has been associated with a decrease in exercise tolerance in stable patients (21), and high TNF- $\alpha$  has been related to muscle weakness in experimental tests in animal models (22), suggesting that inflammation may be associated with worse functional performance.

Resolution of airway inflammatory markers after an exacerbation generally occurs before recovery of systemic inflammation (12,23). Chang et al. (23) measured systemic and airway inflammatory markers of hospitalised patients with an AECOPD at days zero (admission), four, seven and fourteen and found that airway inflammatory markers decreased significantly ( $p < 0.01$ ) on day four and then remain at the same levels over the following ten days (23); while systemic inflammation decreased significantly at day seven and again on day 14 ( $p < 0.001$  for IL-6 and CRP) (23). The decrease in inflammatory markers over this time period is likely to be influenced by treatment for AECOPD, particularly corticosteroids. The more quickly that airway



**Figure 3.** Recovery of systemic inflammatory markers over time. Day 0 is onset of exacerbation. Data are mean  $\pm$  SD, unless otherwise stated. CRP = C-reactive protein; IL-6 = interleukin-6; TNF- $\alpha$  = tumour necrosis factor-alpha; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; pg = picograms; ml = millilitre; mg = milligram; dl = decilitre;  $n$  = number of participants.  $\circ\circ$  data presented as median.

inflammatory markers were reduced was associated with a shorter time to symptom recovery (sputum IL-6:  $r_s = 0.57$ ,  $p = 0.004$ ; sputum IL-8:  $r_s = 0.48$ ,  $p = 0.01$ ) and shorter time to lung function improvement (PEFR versus systemic inflammation Mantel  $R$  value: 0.770) (12,23). Other authors have reported a longer time for resolution of systemic inflammation in people experiencing an AECOPD (Figure 3) (9, 12). Persistently high levels of systemic inflammation may indicate a risk of re-exacerbation. A higher CRP at day 14 is a significant predictor of recurrent exacerbation by day 50 ( $p = 0.004$ ), independent of disease severity, exacerbation frequency or oral steroid treatment (12). The GOLD strategy reports that in patients with a history of exacerbations, anti-inflammatory treatments with Level A evidence for reduction in future exacerbations are inhaled corticosteroids (in addition to a long acting bronchodilator), phosphodiesterase-4 (PDE-4) inhibitors and long-term antibiotics (azithromycin and erythromycin) (24). The European Respiratory Society/American Thoracic Society guidelines recommend treatment with the PDE-4 inhibitor roflumilast to prevent future exacerbations in patients with severe disease, chronic bronchitis and recurrent exacerbations despite optimal therapy (25). Oral mucolytics and macrolide antibiotics are also recommended for the same purpose in those with moderate to severe disease and recurrent exacerbations despite optimal therapy (25).

## Symptoms

Exacerbations of COPD are characterised by an increase in symptom severity compared to baseline. Increased symptoms are associated with worse health status, poorer health-related quality of life and reduced exercise capacity (26,27). Symptom assessment may comprise questionnaires, scales, or total symptom count – which is a sum of the number of increased symptoms (e.g. dyspnoea, cough, sputum production, wheezing and night-time awakenings) usually presented as a total score per day (3,12). Table 1 presents the time course of symptom resolution after onset of AECOPD across eight studies. Although a number of studies show the resolution of symptoms before two weeks (2,3,9,12,15,23,28,29), there are also patients for whom it takes much longer. Perera et al. (12) found that 23% of their 73 participants did

not have full symptom recovery by day 35 after the onset of an AECOPD (12). Parker et al. (15) also found that participants who reported full symptom recovery ( $n = 12$ ) took a mean of 41 days for dyspnoea intensity to return to pre-exacerbation level (15). However, the small number of participants in these studies makes it uncertain if this is representative of the wider COPD population. Data from a cohort study with a larger population (334 participants) found that symptoms were fully recovered in a mean of 14.5 days (SD 8.5 days) after the onset of AECOPD (2). Another study in 101 patients with moderate to severe COPD reported symptomatic recovery in 86% of patients by day 35 (3). Symptom recovery may lag behind the recovery of lung function, with PEFR recovery preceding symptom recovery by an average of 3.6 days (2). A longer symptom duration has been associated with poorer health status (measured by St. Georges Respiratory Questionnaire) and a significantly shorter time to the onset of the next exacerbation (2). Patients with more symptoms during an AECOPD also spend more time confined to the home (26). A combination of sore throat with either dyspnoea or cough increase the number of days per week patients stay at home (26). The prolonged effect of AECOPD on symptom severity, as well as the impact of symptoms on quality of life and function, highlights the need for actions to improve symptoms as quickly as possible following an AECOPD.

## Health status and quality of life

Poor health-related quality of life (HRQOL) is associated with increased mortality in COPD, particularly in the first year following a severe acute exacerbation (30,31). Thus, measurement of HRQOL and health status are important to understand the impact of the disease on daily life (32,33). There are many reliable and valid questionnaires to assess long-term changes in health status and HRQOL in COPD, however whether these are sensitive to change in the small window of an AECOPD is less clear (34). One of the tools used to measure health status is the COPD Assessment Tool (CAT) (35). Studies show that the CAT is responsive to change during recovery from an AECOPD (36–38). Mackay et al. (39) found that health status measured on the CAT



**Table 1.** Symptoms recovery in days and tools used for assessment.

Author	Sample size	Baseline FEV <sub>1</sub> (%predicted)	Assessment tool	Assessment timeline	Symptom resolution (days)
Seemungal et al. (4)	101	41.9 ± 19.7	Total symptom score	Daily over 2.5 years	7 (4–14)
Seemungal et al. (24)	83	42.4 ± 19.8	Total symptom score	Daily over 2.5 years	8 (3–15)
Parker et al. (13)	12 (fully recovered group)	44.2 ± 2.0 (n = 20)	Participants were asked if their dyspnoea had returned to their pre-exacerbation level	Days 0 (within 72h admis- sion), 14, 30 and 60	41 ± 6
Perera et al. (11)	73	45 ± 18.0	Total symptom score: was binary coded as one (present or increased over baseline) or zero (absent or not increased) and then summed.	Daily until 50 days after onset of exacerbation	9 (4–18)
Koutsokera et al. (8)	35	38.5 ± 3.5	Total symptom score: derived from the sum of five symp- toms (dyspnoea, cough, spu- tum production, wheezing and night-time awakenings), each of which was assessed with a modified Borg scale	Days 0 (admission), 3, 10 and 40	10 <sup>a</sup>
Chang et al. (21)	93	47 ± 43.6	Dyspnoea using: mMRC.	Days 0, 4, 7 14 and 8 weeks	4 <sup>a</sup>
Alahmari et al. (25)	73	52.9 ± 16.5	Total symptom score: obtained by summing each increased respiratory symptom recorded on diary cards per day	Daily for at least 35 days	11 (8–17)
Donaldson et al. (2)	334	45.7 ± 16.6	Total symptom score	Daily for at least 365 days	10 (6–18)

Data are mean ± SD or median (25th to 75th percentile) except where indicated.

<sup>a</sup>Day of assessment that symptoms were recovered.

FEV<sub>1</sub>: forced expiratory volume in one second; %pred: % predicted; mMRC: modified Medical Research Council questionnaire; h: hours; Total symptom score is the sum of presence (yes = 1) and absence (no = 0) of seven respiratory symptoms.

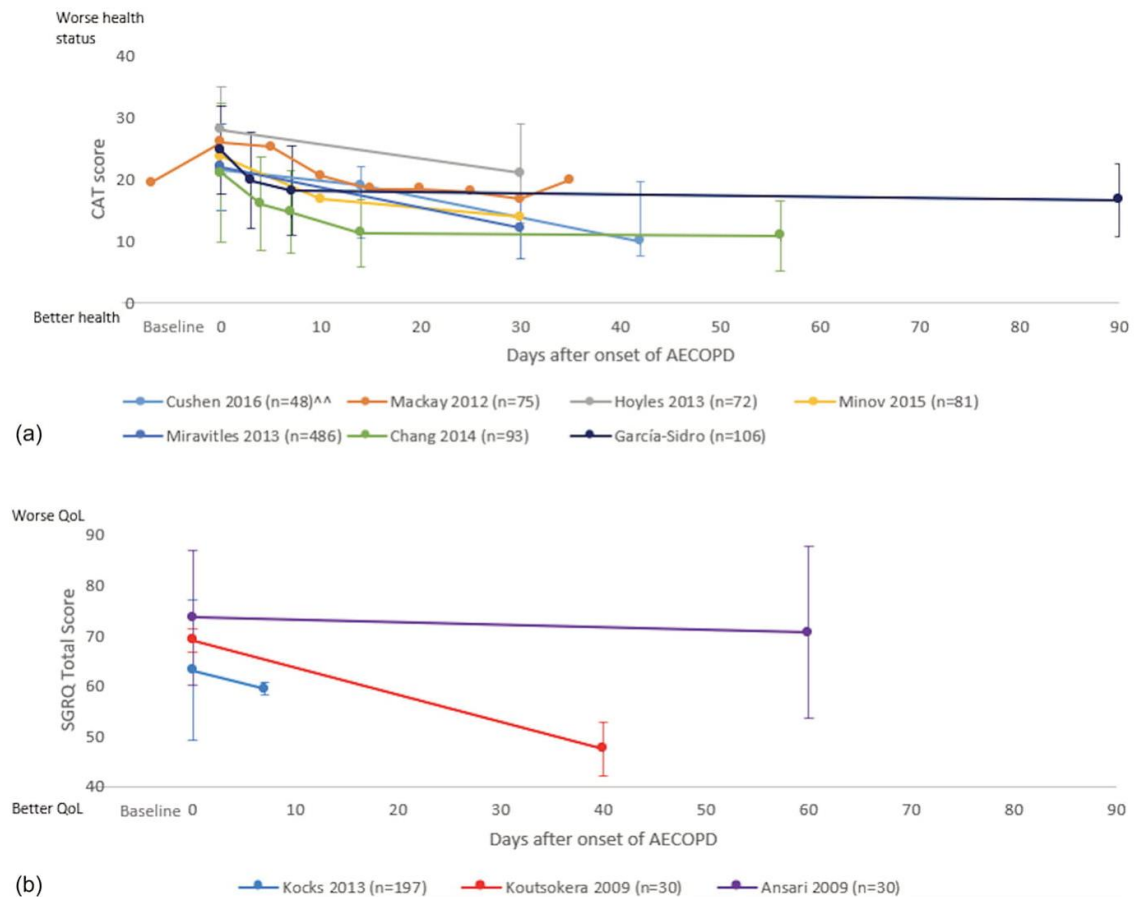
recovered to baseline in a median of 11 days (IQR 5 to 17 days) (39). Figure 4a illustrates the changes in health status measured by the CAT after an exacerbation and demonstrates that health status improves during the first month after an AECOPD with the most rapid improvement detected in the first two weeks (23,38–43). In patients hospitalised with a severe exacerbation, the CAT items that recovered most rapidly related to breathlessness, sputum and energy levels, whilst the item related to confidence was slowest to recover (44). The degree of recovery in CAT score may also important prognostic information. In 106 patients admitted with a severe exacerbation of COPD, an improvement in CAT score of less than four points between admission and discharge was an independent predictor of treatment failure at three months (new exacerbation, hospital readmission or death) (41).

Health-related quality of life can be assessed using disease specific health related questionnaires such as St George's Respiratory Questionnaire (36) and the Chronic Respiratory Questionnaire (CRQ) (45). Studies using disease specific questionnaires to assess quality of life generally show improvement during the first month after exacerbation (Figure 4b) (9,46). One study showed only a slight improvement in quality of life (St George Respiratory Questionnaire) at two months after onset of AECOPD, and the improvement did not exceed the minimum important difference (MID) of four points (47). The difference in findings of this study compared to other studies (9,46) may be the long time to reassessment (two to three months) in a population with a progressive disease and susceptible to recurrent exacerbations. Also, the study did not assess quality of life during the early stages of recovery to give a clear picture of the recovery process (47). Parker et al. (15)

assessed changes from baseline in HRQOL using the CRQ in 20 patients hospitalised for AECOPD (15). The study reported statistically significant improvement in the CRQ-dyspnoea domain on days 14, 30 and 60 when compared to the onset of exacerbation (change from day 0: 1.5 ± 0.3; 1.4 ± 0.4 and 1.8 ± 0.5 respectively  $p < 0.01$ ) (15); an improvement that exceeded the MID (difference of 0.5) (48). Unfortunately, most studies do not present data from the early stages of the recovery process (Figure 4), possibly because assessments of HRQOL are difficult to administer during hospitalisation when the relevance of the questions to daily activities is less clear. While the overall trajectory of recovery in HRQOL is not clear, studies consistently showing an improvement over the first two weeks after onset of an AECOPD.

### Physical activity and exercise capacity

Regular physical activity participation is important for reducing morbidity and mortality in people with COPD (49,50). However, during and immediately following an AECOPD physical activity participation declines (50,51). A longitudinal study of 18 patients with COPD (mean FEV<sub>1</sub> 52 ± 20% predicted) found a 17% reduction ( $p < 0.0001$ ) in the time spent in 'higher level physical activity' (vector magnitude units – VMU of ≥3,000) during an exacerbation compared to baseline (52). During the recovery period following an exacerbation, the number of daily steps also decreased, with a median of 3.5 days (IQR 1–8 days) from exacerbation onset to return to baseline step count (28). Physical inactivity during an AECOPD is greater when patients are hospitalised (51). Borges et al. (51) monitored 20 patients during hospitalisation and found they spent 83%



**Figure 4.** Recovery of health-related quality of life during following AECOPD. Baseline indicates pre-exacerbation data. Day 0 is onset of exacerbation. Data expressed as mean  $\pm$  SD unless otherwise stated. (a) Demonstrates the recovery curve measured by CAT score. (b) Demonstrates the recovery curve measured by SGRQ score. SGRQ score = Saint George's Respiratory Questionnaire; CAT score = chronic obstructive pulmonary disease assessment test score; AECOPD = acute exacerbation of chronic obstructive pulmonary disease;  $n$  = number of participants; QoL: Quality of life.

Note: Ansari et al. (47) presented only results from the hospitalised participants group. Data from Kocks et al. (46), Mackay et al. (39) and Chang et al. (23) were extracted from the graph.

of their time inactive, either lying down or sitting (51). The same study compared time spent walking during a hospital stay compared to one month after discharge, and found a significant increase in the minutes of walking per day one month after discharge (mean 7 minutes/day to 42 minutes/day respectively,  $p < 0.001$ ) (51). It was not possible to determine whether the time spent walking per day one-month post AECOPD was comparable to the stable baseline condition as participants were only recruited at the hospital after onset of AECOPD. A similar study with a larger population (76 participants) also found that patients hospitalised for an AECOPD spent little time in weight-bearing activities (walking and standing) (50). At one month following discharge participants in this study increased their time spent in standing or walking (137 minutes/day) compared to walking time measured on the second (50 minutes/day) and seventh (65 minutes/day) day after admission to hospital (50). Despite the improved walking time one month after discharge, the amount of walking completed remained low when compared to people with COPD in a stable condition (50,53).

During an AECOPD, reduced time spent in weight-bearing activities has been associated with lower quadriceps force ( $r = 0.47$ ;  $p = 0.048$ ) and participants with weaker quadriceps during hospitalisation had less improvement in walking time in the first month after discharge ( $r = 0.58$ ;  $p = 0.03$ ) (50). Pitta et al. (50) noted that lower physical activity levels in the first month after hospital discharge increased the risk of hospital readmission in the following year ( $p = 0.03$ ) (50). Physical activity is also a predictor of mortality in people with COPD, with people with very low or worsening physical activity two months after AECOPD having a higher mortality risk (54). Given these relationships between physical inactivity and longer term critical outcomes, restoration of physical activity levels following AECOPD may be an important target for interventions.

People with COPD experience progressive deterioration in exercise capacity during the disease course (55). However only a few studies have investigated the impact of AECOPD on functional exercise capacity and the time course of recovery, possibly because it is difficult to perform exercise tests



**Table 2.** Factors associated with prolonged recovery from an AECOPD.

Characteristic associated with delayed recovery	Study	Relationship
<b>Demographic features</b>		
Older age	Liang et al. (9)	Older age predicted non-recovery OR 1.029 (95% CI 1.016–1.042)
More severe lung disease	Donaldson et al. (2)	Annual rate of nonrecovered exacerbations increased in more severe patients by 0.0018 events/year per 1% lower FEV <sub>1</sub> %predicted
	Koutsoukera et al. (8)	Late-recoverers had lower baseline FEV <sub>1</sub> %predicted compared to the early-recoverers; mean 32 (SD 3) vs 47 (6) % respectively, $p = 0.028$
	Liang et al. (9)	Worse GOLD stage predicted non-recovery OR 1.491 (95% CI 1.256–1.770)
Lower body mass index	Liang et al. (9)	Lower BMI predicted non-recovery OR 0.951 (95% CI 0.918–0.985)
Higher levels of chronic dyspnoea	Liang et al. (9)	Worse MMRC predicted non-recovery OR 1.352 (95% CI 1.189–1.539)
Chronic bronchitis	Liang et al. (9)	Recovery was longer in patients with chronic bronchitis (mean 19 (SD 16) vs 15(14) days, $p = 0.003$ )
<b>Exacerbation features</b>		
Symptoms of common cold on day of exacerbation onset	Donaldson et al. (2)	38% of those with prolonged recovery vs 30% without
Sore throat on day of exacerbation onset	Seemungal et al. (4)	Increased recovery time by 2.5 days (95% CI 1.8–3.3)
Persistent systemic inflammation	Donaldson et al. (2)	18% of those with prolonged recovery vs 12% without
	Perera et al. (11)	Patients without symptom recovery at day 35 had a persistently higher serum CRP compared with those patients who had recovered ( $p = 0.03$ ).
Severity of exacerbation symptoms	Seemungal et al. (4)	Higher levels of dyspnoea at exacerbation onset increased recovery time mean 3.31 days (95% CI 2.65–3.98).
Viral infection	Seemungal et al. (24)	Recovery of symptoms in those with viral infection was median 13 days (IQR 5–20 days) vs 6 days (3–13 days) in those without

BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; FEV<sub>1</sub>: forced expiratory volume in one second; GOLD: Global initiative for Obstructive Lung Disease; IQR: interquartile range; MMRC: modified Medical Research Council scale; OR: odds ratio.

during this time period. In patients experiencing an AECOPD, the distance walked in six minutes decreased by an average of 49 metres (m) (13.1%) on day three after onset of exacerbation when compared to when they were stable ( $p = 0.001$ ), but increased significantly at day seven compared to day three ( $p < 0.001$ ) (56). Six-minute walk distance (6MWD) was lower at day eight in patients who were admitted to hospital in the previous year compared to those without previous hospitalisation (median 200 m (IQR 155–298 m) vs 351 m (IQR 164–520 m);  $p = 0.12$ ) (50). One month after discharge 6MWD increased by a median of 73m (IQR, 27 to 149 m;  $p = 0.01$ ) compared with the hospitalisation period (day eight after exacerbation) however it is not known if functional capacity had returned to baseline level at this point (50).

The influence of functional impairment on readmissions and mortality following AECOPD demonstrates the importance of measuring recovery in function in these patients. Recently a number of new measures of exercise capacity have emerged that may be useful in the setting of AECOPD. Sit to stand tests, step tests and 4-metre gait speed tests are easier to perform than a 6-minute walk test in highly symptomatic patients and more suitable for the inpatient setting (57–59). However these measures are not yet widely used and as yet there are no data pertaining to the sensitivity of these tests for monitoring recovery from an AECOPD.

### Outcomes following AECOPD

Risks of hospital readmission and death are increased following an AECOPD. In the year following an AECOPD the risk of readmission has been reported as 63% (60) and the

risk of death 23% (61). Long-term use of oral corticosteroids, hypercapnia, older age (61), and exacerbation frequency (8) have been identified as risk factors associated with higher mortality after AECOPD (8,61). A recent study provides insight into how this risk is modified over the time course of recovery (62). Amongst more than 2 million Medicare beneficiaries in the United States who were discharged from hospital following AECOPD, the one-year readmission rate was 64% and mortality was 26% (62). The risk of death was highest at 3–4 days following hospital discharge. The average time for the risk of death to decline by 50% was 17 days in those who did not receive ventilatory support, compared to 4 and 3 days in those who required non-invasive and invasive ventilation respectively (62). The time required for the risk of hospital readmission to fall by 50% was much longer, at 43 days, 39 days and 28 days, and remained elevated at one year when compared to Medicare beneficiaries without COPD (62). This illustrates that the risk of adverse outcomes remains high for some time after AECOPD, and although 'recovery' of a more favourable risk profile occurs, it is prolonged and may be incomplete. This is consistent with data showing incomplete recovery of respiratory function and symptoms in a significant minority of patients (3,12). Treatment of the initial exacerbation with systemic corticosteroids reduces the risks of both treatment failure and re-exacerbation at 30 days, with relative risks (RR) 0.48 (95% CI 0.35–0.67) and 0.78 (0.63–0.97) respectively (14). Similarly, treatment with antibiotics reduces the risk of treatment failure in ambulatory patients (RR 0.67, 0.51–0.87) (63), with a similar trend in admitted patients (RR 0.65, 0.38–1.12) (64). However not all patients require treatment with antibiotics and efforts to accurately identify those who will benefit are ongoing (63).

### Which patients with AECOPD are at risk of prolonged recovery?

Recovery after an AECOPD may be prolonged in some subgroups. This is important as delayed or incomplete recovery is associated with extended hospitalisation and poor long-term outcomes (2). Hospitalisation costs form the largest component of the total costs of COPD exacerbations and thus a prolonged inpatient stay has critical health economic implications (65). It may be useful to identify the characteristics of those at risk of prolonged recovery in whom additional interventions could be required, to minimise hospital days and improve longer term outcomes. The factors related to prolonged recovery are presented in Table 2. Demographic features of those with prolonged recovery following AECOPD include older age, more severe lung disease, presence of chronic bronchitis, lower body mass index and more chronic dyspnoea. Exacerbation features associated with prolonged recovery are symptoms of the common cold at exacerbation onset, evidence of viral infection, more severe dyspnoea during the exacerbation and persistent systemic inflammation.

### Implications for research and clinical practice

Data presented in this review indicate that most people with COPD have a substantial improvement in physiological parameters (lung function, inflammatory markers) within the first week after onset of an exacerbation. Improvement in symptoms, quality of life and physical activity may take longer, with average recovery periods of at least two weeks. It is unclear whether improvement in physiological variables following AECOPD documented in the literature represents a complete recovery after AECOPD, due to the lack of baseline measurements in most studies, however it seems likely that in a small number of patients (<10%) recovery of respiratory function has not occurred by three months (2,3). Recovery following an AECOPD is not commonly tracked during clinical research (2,3,26,66), making it challenging to understand the process of recovery and the best timing of interventions by clinicians.

The data presented here indicate that clinicians should assume that most patients take at least two weeks for a 'complete' symptomatic recovery. However, it must be acknowledged that in some people with COPD, symptoms will persist for longer periods. Prolonged recovery is observed in frequent exacerbators who take longer to recover symptoms and health status (2). Prolonged recovery is also more likely in those who are older, have more severe disease and more severe symptoms (Table 2). Patients who take longer to recover have more frequent hospitalisations (67) which may further exacerbate the decline in functional status and physical inactivity that is evident during an AECOPD. Inactivity increases the future risk for hospitalisation, which in turn may impact upon functional capacity and quality of life, further increasing the risk of readmission to hospital. Therefore, patients may end up in a cycle of prolonged recovery, inactivity and re-admissions. The cycle needs to be discontinued and interventions in the early stages after AECOPD may be an option to break the inactivity cycle.

To break the cycle of prolonged recovery-inactivity-hospitalisation, interventions that commence during or immediately after hospital admission may be warranted. It is not clear whether treatments aimed at identified risk factors (e.g. persistent systemic inflammation) are of value. It is possible that treatments aimed at the consequences of an AECOPD, such as physical inactivity, may be more practical. Although some studies have shown that exercise training during hospitalisation is of benefit after AECOPD the evidence is inconsistent (6). Some randomised controlled trials show that patients who undergo early exercise-based rehabilitation have reduced hospital admissions in the following year (68,69), whilst others do not (70,71). Uptake of exercise programmes early following an AECOPD is very low, suggesting it may not be acceptable to patients who are still highly symptomatic (72). Day four of an AECOPD is when a reduction in airway inflammation is seen to occur and is related to a gradual decrease in symptoms, suggesting exercise may be more feasible after this time (23). Comprehensive pulmonary rehabilitation programmes may be more feasible when started at least 14 days from onset of AECOPD, when systemic inflammation is reduced, symptoms have largely recovered, and patients may have greater tolerance of exercise interventions. This is well aligned with data showing greater benefits of pulmonary rehabilitation delivered at this time than when commenced in the inpatient period (73).

Understanding the natural course of recovery following an AECOPD is important to be able to recognise when recovery is prolonged and when patients are at risk of poor outcomes. Current data provide good evidence for the time course of recovery for lung function and inflammation. However, there is limited literature describing the natural recovery process for functional capacity, symptoms, quality of life and strength. Another limitation of the literature is that most studies have not presented baseline data from prior to the onset of AECOPD, which prevents the understanding of the complete recovery process. Research that systematically documents the recovery process over the first month following an AECOPD is needed. A better understanding of the recovery process after an AECOPD may, in the future, enable delivery of therapeutic interventions at the most appropriate point in the recovery process. Most of the studies presented in this review considered exacerbation severity, which allowed us to assess whether 'recovery' following AECOPD had occurred across domains of respiratory function, inflammation, symptoms, health status and function. However, it is also important to consider the frequency of exacerbations, as those with frequent AECOPD may be slower to recover<sup>9</sup> and have worse long-term outcomes (16). The conclusions of this review regarding recovery from AECOPD are therefore limited to exacerbation severity rather than frequency.

### Conclusions

Acute exacerbations are common events in the natural history of COPD. Physiological measures such as lung function



and inflammation improve during the first week after onset of an AECOPD, however other aspects of recovery such as symptoms, health status, quality of life and functional capacity take longer to improve. Limited information regarding the recovery of functional capacity, strength and health status make it challenging to provide interventions at the most effective time point following an AECOPD. Characteristics of patients who experience delayed recovery after AECOPD have been identified. In clinical practice efforts should be made to recognise when recovery is prolonged, putting patients at risk of poor outcomes, and to address the consequences of AECOPD including physical inactivity and skeletal muscle weakness. Further research is required to understand whether additional interventions could enhance recovery and improve long term outcomes in these individuals.

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The authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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# CHAPTER THREE


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*The impact of COPD exacerbations in the year  
following pulmonary rehabilitation: secondary  
analysis of a randomised controlled trial*

### 3.1 Declaration of Authorship – Chapter Three

#### Student's Declaration


The nature and extent of contributions to Chapter Three of this thesis are as follows:

Name	Nature of contribution	Contribution	Signature
Bruna Wageck	Study concept, protocol development, data collection, data analysis, writing and review of manuscript	60%	
Anne E Holland	Study concept and design, data analysis and review of manuscript	16%	
Narelle S Cox	Protocol development, data collection and review of manuscript	10%	
Angela T Burge	Data collection and review of manuscript	5%	
Ajay Mahal	Study concept and review of manuscript	1%	
Catherine J Hill	Study concept and review of manuscript	1%	
Annemarie L Lee	Delivery of intervention and review of manuscript	1%	
Rosemary Moore	Delivery of intervention and review of manuscript	1%	
Caroline Nicholson	Data collection and review of manuscript	1%	
Paul O'Halloran	Study concept and review of manuscript	1%	
Aroub Lahham	Data collection and review of manuscript	1%	

Rebecca Gillies	Data collection and review of manuscript	1%
Christine F McDonald	Study concept and review of manuscript	1%

#### Supervisor's Declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter Three of this thesis by the student and all listed

Supervisor name	Signature
Professor Anne E Holland	

## 3.2 Preface

The narrative review presented in Chapter Two found that lung function and airway inflammatory markers take about one week to recover following exacerbation of COPD; while recovery of symptoms, systemic inflammation and quality of life takes longer - approximately 14 days to recover. However not all participants will fully recover after three months and in some cases the baseline status will not be restored. The review confirmed that lower physical activity in the months following exacerbation increases risk of hospital readmission in the following year. Pulmonary rehabilitation, a program of exercise training and self-management education, has been demonstrated to reduce the need for future hospitalisation in people with stable COPD, however the mechanism by which this occurs is unclear. Pulmonary rehabilitation achieves positive effects on exercise capacity and quality of life and reduces symptoms. It can be delivered at either an outpatient centre or directly into the patients' home with the same benefits. Although pulmonary rehabilitation improves functional capacity and quality of life, the results are not maintained long term. It is not clear why this deterioration in outcomes occurs, or whether having an exacerbation could be associated with poorer outcomes long term.

The aim of this study was to examine the impact of exacerbations on clinical outcomes at 12 months after pulmonary rehabilitation. This study also aimed to document the frequency and severity of COPD exacerbations in the year following pulmonary rehabilitation; and identify predictors of exacerbations in the year after pulmonary rehabilitation. Findings of this study will help to understand the impact of exacerbations in the year following pulmonary

rehabilitation. It suggests that future research on strategies to maintain the benefits of pulmonary should address exacerbation prevention and management.

The manuscript arising from this study was submitted for publication to *Respirology* on 13<sup>th</sup> May 2020 and is currently under review. The journal has an impact factor 4.756.

# Submission Confirmation

 **Print**

Thank you for your submission

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### 3.3 Manuscript

**The impact of COPD exacerbations in the year following pulmonary rehabilitation:  
secondary analysis of a randomised controlled trial**

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**Word count Abstract:** 250 words

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**Summary at a glance:**

Pulmonary rehabilitation is an effective treatment for people with chronic obstructive pulmonary disease (COPD), but its benefits are poorly maintained. Severe exacerbations occur frequently following pulmonary rehabilitation and predict worse 12-month outcomes. Strategies to maintain the benefits of pulmonary rehabilitation should address exacerbation prevention and management.

Funding: B Wageck is the recipient of a full fee research scholarship (LTUFFRs) and postgraduate research scholarships (LTUPRS) from La Trobe University, Melbourne, Australia

## Abstract

**Background:** Pulmonary rehabilitation is an effective treatment for people with chronic obstructive pulmonary disease (COPD), but its benefits are poorly maintained. The aim of this study was to evaluate the impact of COPD exacerbations in the year following pulmonary rehabilitation on outcomes at 12 months.

**Methods:** This was a secondary analysis from a trial of home versus hospital-based rehabilitation in COPD, with 12 months of follow-up. Moderate and severe exacerbations were identified using administrative data (prescriptions) and hospital records (admissions) respectively. The impact of exacerbations at 12 months following pulmonary rehabilitation was evaluated for quality of life (Chronic Respiratory Questionnaire, CRQ), dyspnoea (modified Medical Research Council, mMRC), exercise capacity (6-minute walk distance, 6MWD) and objectively measured physical activity (moderate-to-vigorous physical activity, MVPA).

**Results:** 166 participants were included, with mean age(SD) 69(9) years and forced expiratory volume in one second (FEV<sub>1</sub>) 49(19)%predicted. Moderate exacerbations occurred in 68% and severe exacerbations in 34% of participants. Experiencing a severe exacerbation was an independent predictor of worse 12-month outcomes for CRQ (total, fatigue and emotional function domains), mMRC, 6MWD and MVPA (all  $p < 0.05$ ). Participants who completed pulmonary rehabilitation were less likely to have a severe exacerbation (29% vs 48%,  $p = 0.02$ ). Severe exacerbations were more likely in those with worse baseline CRQ total (odds ratio 0.97, 95% CI 0.95 to 0.99) and FEV<sub>1</sub> %predicted (0.98, 95% CI 0.96 to 0.99).

**Conclusion:** Severe exacerbations occur frequently following pulmonary rehabilitation and predict worse 12-month outcomes. Strategies to maintain the benefits of pulmonary rehabilitation should address exacerbation prevention and management.

**Key words:** COPD, exacerbations, pulmonary rehabilitation, long term maintenance, predictors

**Short Title:** COPD exacerbations in the year following PR.

**List of abbreviations:**

6MWD: Six minute walk distance

ECOPD: Exacerbation of COPD

COPD: Chronic obstructive pulmonary disease

CRQ: Chronic Respiratory Questionnaire

FEV<sub>1</sub>: Forced expiratory volume in one second

FVC: Forced vital capacity

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HRQoL: Health-related quality of life

IQR: Interquartile range

mMRC: Modified Medical Research Council

MVPA: Moderate-to-vigorous physical activity

OCS: Oral corticosteroids

RR: Risk relative

SD: Standard deviation

## **Introduction**

Chronic obstructive pulmonary disease (COPD) is characterised by significant functional limitation and high mortality (1). Exacerbations of COPD are associated with disease progression and are one of the leading causes of hospital admission (2) and death (3), highlighting the importance of interventions to prevent exacerbations or minimise their impact. Optimal treatment of COPD focuses on medication management, patient education, action plans for exacerbations, and pulmonary rehabilitation (4). Pulmonary rehabilitation, a program of exercise training and self-management education, is considered essential in the care of people with COPD(4, 5). Pulmonary rehabilitation improves exercise capacity and quality of life and reduces symptoms and health care utilisation in people with stable COPD (6). However, these improvements are not maintained long term. At 12 months following pulmonary rehabilitation, measures of exercise capacity, symptoms and health-related quality of life (HRQoL) have returned towards their pre-rehabilitation values(7, 8). Maintenance exercise programs have not been effective in preventing this deterioration (9). It is possible that exacerbations in the post-pulmonary rehabilitation period contribute to the lack of sustained benefit at 12 months, but this has not been systematically evaluated. Understanding the impact of exacerbations on long-term outcomes, and in whom exacerbations are likely to occur, may assist in designing more effective maintenance strategies following pulmonary rehabilitation.

The aims of this study were to: (i) document the frequency and severity of COPD exacerbations in the year following pulmonary rehabilitation; (ii) examine the impact of exacerbations on clinical outcomes at 12 months after pulmonary rehabilitation; and (iii) identify predictors of exacerbations in the year after pulmonary rehabilitation.

## Methods

### Study Participants

This is a secondary analysis of data collected from the HomeBase trial (8), a randomized controlled trial that recruited 166 people with COPD from two Australian tertiary hospitals between October 2011 and April 2014. The HomeBase trial compared a low cost, home-based model of pulmonary rehabilitation to a traditional centre-based program. The trial protocol and outcomes have been reported previously (8, 10) and the study protocol was registered (NCT01423227, clinicaltrials.gov). Eligibility criteria were a diagnosis of COPD ( $FEV_1/FVC$  ratio  $< 0.7$ ), with a smoking history of at least 10 years and age 40 years or older. Exclusion criteria were a diagnosis of asthma, attendance at a pulmonary rehabilitation program in the last two years, a COPD exacerbation within four weeks prior to study enrolment, or presence of any comorbidities which prevented participation in an exercise training program.

Participants randomized to centre-based pulmonary rehabilitation received usual supervised pulmonary rehabilitation in a hospital outpatient setting twice a week, with encouragement to exercise at least another three times per week at home. Participants randomised to home-based pulmonary rehabilitation (HomeBase) received an initial home visit from a physiotherapist followed by seven, once-weekly telephone calls from a physiotherapist for progression of the exercise prescription and self-management training. Participants in the HomeBase group were encouraged to exercise five days of the week for at least 30 minutes comprising aerobic and resistance training. Both pulmonary rehabilitation programs had a duration of eight weeks and participants recorded their home exercise participation in a diary.

### *Exacerbations of COPD*

The number of moderate and severe exacerbations for each participant in the 12 months following pulmonary rehabilitation was obtained using data collected from the hospital medical records and Australian government Medicare Benefits Schedule and Pharmaceutical Benefits Scheme records. An exacerbation was classified as severe if it resulted in a hospital or emergency department admission (4, 11-13), or moderate if it resulted filling of a prescription for oral corticosteroids (OCS) and/or antibiotics (11-14), in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy classification for exacerbation severity (4) (Table S1, online supplement). It was not possible to identify mild exacerbation of COPD (change in symptoms with small change in management such as increased bronchodilators), as data for daily symptom changes were not collected during the trial. To be classified as a new exacerbation the event must have occurred more than 14 days following the previous event (11, 15).

#### *Outcomes of pulmonary rehabilitation*

Measures of exercise capacity, health-related quality of life and symptoms were obtained at baseline, after eight-week intervention period, and 12 months follow-up. Functional exercise capacity was measured using the six minute walk test (6MWT), a valid measure of exercise capacity in people with COPD that is responsive to pulmonary rehabilitation (16). Health-related quality of life was measured with the self-reported Chronic Respiratory Disease Questionnaire (CRQ)(17), a disease specific measure which assesses the domains of dyspnoea, fatigue, emotional function and mastery. Higher scores indicate better quality of life. The modified Medical Research Council Scale (mMRC) is a validated measure of the functional impact of dyspnoea in people with COPD (18). Physical activity was measured in a subgroup of participants (home-based group n = 29; centre-based group n = 38) using the Senswear armband (19) and reported as total time spent in moderate to vigorous physical

activity (MVPA, min/day) time spent in bouts of MVPA lasting more than 10 minutes, and sedentary awake time (min/day). Completion of pulmonary rehabilitation was defined as attending at least 70% of planned sessions (8).

### **Statistical analysis**

Data analysis was conducted using SPSS V.25.0 (IBM, New York). Descriptive statistics (mean and standard deviation (SD) or median and interquartile range [IQR] or number (n (%))) were used to describe frequency and severity of exacerbations in each group. Relative risk of having an exacerbation was calculated for dichotomous measures. Kaplan-Meier survival analyses were used to describe the time to first exacerbation after pulmonary rehabilitation. Clinical outcomes of interest were change from baseline (pre-pulmonary rehabilitation) to 12 months following pulmonary rehabilitation, in order to evaluate long-term benefits. Univariate analyses comparing outcomes in individuals who did and did not experience an exacerbation during the 12 months follow-up were conducted using t-tests or a non-parametric equivalent. Multiple linear regression analysis was used to evaluate the independent impact of experiencing an exacerbation (any exacerbation or severe exacerbation) on clinical outcomes at 12 months, controlling for group allocation (home or centre-based pulmonary rehabilitation), baseline values (functional capacity, quality of life), age, gender, FEV<sub>1</sub> and smoking status. Logistic regression was performed to assess predictors of exacerbations in the year following pulmonary rehabilitation. Independent variables of interest were predictors of exacerbations previously identified in a large cohort of patients with COPD (20), including FEV<sub>1</sub> % predicted, history of gastro-oesophageal reflux and baseline health-related quality of life. Other known predictors of exacerbations



(exacerbation history, white cell count) were not available in our dataset. Completion of pulmonary rehabilitation (yes/no) was included as a potential predictor, as this was associated with future hospitalisation in our trial(8). Separate models were constructed for severe exacerbations, or any exacerbation (moderate or severe).

## **Results**

Data from 166 participants in the HomeBase trial who completed centre-based (n=86) or home-based (n=80) rehabilitation were included. Data were missing for n=13 participants who declined to perform one or more tests at the follow-up assessments (8). Demographic characteristics of participants are presented at Table 1.

During the year following pulmonary rehabilitation 123 (74%) participants had at least one exacerbation and 56 (34%) participants had at least one severe exacerbation (Table 1). There was no difference between groups in the risk of having any exacerbation (RR 1.06 [95%CI 0.89 to 1.26], p=0.51) or a severe exacerbation (RR 0.75 [95%CI 0.48 to 1.16], p=0.20). Following pulmonary rehabilitation, median [IQR] time to first exacerbation was 48 [15 to 125] days in the HomeBase group compared to 26 [12 to 112] days for the centre-based group (p = 0.93), with similar findings for time to first severe exacerbation (median 117 days [30 to 283] vs 128 [31 to 221], p=0.18). As there were no significant differences in exacerbation risk between groups, data were combined for subsequent analyses.

Univariate analysis showed no statistically significant difference between those who experienced any exacerbation compared to those who did not for change in functional capacity, health-related quality of life, dyspnoea or physical activity from baseline to 12 months after pulmonary rehabilitation (Table 2). Individuals who experienced a severe

ECOPD tended to have worse outcomes than those with moderate or no exacerbations; this reached statistical significance only for CRQ fatigue domain (Table 2). However, in multiple linear regression analysis controlling for baseline features, having a severe exacerbation was an independent predictor of worse outcomes at 12 months following pulmonary rehabilitation for health-related quality of life (CRQ total, fatigue, mastery and emotional function), dyspnoea (mMRC), functional capacity (6MWD) and daily physical activity (total MVPA) (Table 3). Age, FEV<sub>1</sub>, smoking status and group allocation were not independent predictors of 12-month outcomes. Experiencing any exacerbation (moderate or severe) was not an independent predictor of clinical outcomes at 12 months following pulmonary rehabilitation (Table S2).

Participants who completed pulmonary rehabilitation (attending at least 70% of sessions) were significantly less likely to have a severe exacerbation in the following 12 months (29% vs 48%,  $p=0.02$ ). Aside from program completion, the initial response to pulmonary rehabilitation at 8 weeks did not differ between patients with and without a subsequent exacerbation, regardless of exacerbation severity (Table S3). A logistic regression model showed that for every 10-point increase in CRQ total score at baseline, the odds of a severe exacerbation were reduced by 24% ( $p=0.01$ ). For every 10% increase in FEV<sub>1</sub>% predicted at baseline, the odds of a severe exacerbation were reduced by 32% ( $p=0.002$ , Table 4). Pulmonary rehabilitation completion reduced the odds of a severe exacerbation by 46%, but this did not reach statistical significance ( $p=0.10$ ).

## **Discussion**

This secondary analysis of a clinical trial data shows that exacerbations are common in people with COPD in the year following pulmonary rehabilitation, with severe exacerbations occurring in one third of our sample. Those who experienced severe exacerbations had worse 12-month outcomes for health-related quality of life, symptoms, exercise capacity and daily physical activity. Severe exacerbations were more likely in those who had entered pulmonary rehabilitation with lower respiratory function and poorer health-related quality of life. Those who are unable to complete 70% of their pulmonary rehabilitation sessions may also be at higher risk of severe exacerbation in the year following the program.

The number of patients experiencing at least one COPD exacerbation requiring hospitalisation (34%) was high in our study. Recent clinical trials and cohort studies have reported that over 12 months less than 15% of participants experience a severe exacerbation requiring hospitalisation (21, 22). Consistent with the features of patients who are typically referred to pulmonary rehabilitation, our participants had high symptom burden and low functional capacity. They may therefore represent a different subset of the COPD population to those commonly enrolled in trials of pharmaceutical treatments or cohorts. Although there is some evidence that pulmonary rehabilitation may reduce subsequent hospitalisation, particularly when delivered after an exacerbation (23), the results of the current study suggest that pulmonary rehabilitation participants remain at high risk of hospitalisation in the year following the program.

Maintaining the benefits of pulmonary rehabilitation over time has been called the ‘holy grail’ of pulmonary rehabilitation research (24). Our results highlight the important impact of severe exacerbations on the long-term outcomes of pulmonary rehabilitation. A previous study has examined the exacerbations in the six months following pulmonary rehabilitation, demonstrating a reduction in exercise capacity and reduced health-related quality of life at

two weeks following exacerbation onset (25). Our study extends this work, showing that patients experiencing a severe exacerbation at any time in the year following pulmonary rehabilitation do have limited recovery, with worse outcomes at 12 months than their peers who do not experience an exacerbation. These data suggest that strategies to maintain the benefits of pulmonary rehabilitation are unlikely to be successful unless exacerbation risk is addressed. Existing maintenance strategies, generally consisting of supervised exercise programs offered at a lower frequency than the initial pulmonary rehabilitation program, do not appear effective(9). A more targeted approach for those experiencing exacerbations may be required.

Predicting which individuals will experience an exacerbation in the year after pulmonary rehabilitation is challenging but important, in terms of both for targeting preventative efforts and for intervening to improve outcomes. Not surprisingly our data indicate that pulmonary rehabilitation participants with more severe lung disease and worse health-related quality of life are at higher risk of exacerbation. Failure to complete pulmonary rehabilitation may also be important, reinforcing the need to support patients with COPD to attend regularly (or participate regularly if they are doing the home-based program) and to finish the program. During pulmonary rehabilitation, strategies to enhance self-management skills may be valuable to optimise identification and treatment of exacerbations. A recent study highlighted the potential of exacerbation action plans to reduce respiratory-related hospitalisation in people with COPD and comorbidities (including at least one of ischaemic heart disease, heart failure, diabetes, anxiety or depression)(26). Participants in our study had a median of four comorbid conditions(8), so this strategy warrants further examination. In patients who have experienced a severe exacerbation it may be useful to re-enrol in pulmonary rehabilitation. There is some evidence that repeat programs are effective in reversing decline in exercise

capacity and may ameliorate worsening symptoms(27). Nonetheless, given the well documented challenges in enrolling patients with COPD in pulmonary rehabilitation immediately following an exacerbation (28), it may be more fruitful to repeat pulmonary rehabilitation once clinical stability is regained.

Strengths of this study include the relatively large sample of participants with COPD who are typical of those referred to outpatient pulmonary rehabilitation in many centres; 12 months of follow-up; and detailed data on health care utilisation over 12 months, allowing exacerbations to be ascertained. Limitations include the absence of data on exacerbation history prior to pulmonary rehabilitation, which is a powerful predictor of future exacerbations (20); the small number of participants with physical activity data; and the post-hoc nature of the analysis.

In conclusion, exacerbations of COPD occur commonly in the year following pulmonary rehabilitation. Experiencing a severe exacerbation requiring hospitalisation is an independent predictor of worse outcomes at 12 months following pulmonary rehabilitation for health-related quality of life, symptoms, exercise capacity and daily physical activity. These findings can be used to inform future research aimed at maintaining the benefits of pulmonary rehabilitation following program completion.

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## Tables

**Table 1** Demographic characteristics of participants

	Home-based group (n=80)	Centre-based group (n=86)	Both groups (n= 166)
Age, years	69.6 (9.2)	68.4(9.5)	69.0 (9.4)
Male/female, n	48/32	51/35	99/67
FEV <sub>1</sub> , litres	1.3 (0.48)	1.25 (0.60)	1.28 (0.54)
FEV <sub>1</sub> % predicted	49.7 (13.4)	40.7 (15.6)	49.9 (19.2)
FEV <sub>1</sub> /FVC	0.47 (0.16)	0.45 (0.14)	46.3 (15.1)
Pack-year, n	47 (36)	50 29)	49 (32)
Baseline 6MWD, m	379.5(121)	411 (107)	403 (114)
mMRC, n (%)			
0	2 (3%)	0 (0%)	2 (1%)
1	33 (41%)	36 (42%)	69 (42%)
2	22 (28%)	28 (33%)	50 (30%)
3	21 (26%)	19 (22%)	40 (24%)
4	2 (3%)	3 (4%)	5 (3%)
Any exacerbation, n (%)	61 (76%)	62 (72%)	123 (74%)
Moderate exacerbation, n (%)	57 (71%)	55 (64%)	112 (68%)
Severe exacerbation, n (%)	23 (29%)	33 (38%)	56 (34%)

Figure legend: Data presented are mean (SD) unless otherwise stated. <sup>a</sup> data presented as median [IQR].

FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; 6MWD, 6 min walk distance; CRQ, Chronic Respiratory Questionnaire; mMRC, modified Medical Research Council scale

**Table 2.** Clinical outcomes at 12 months after pulmonary rehabilitation (change from baseline) for participants with and without exacerbations during follow-up.

	ANY EXACERBATION			SEVERE EXACERBATION		
	Exacerbation	No exacerbation	p value	Severe exacerbation	No exacerbation or moderate exacerbation	p value
6MWD, m	11 [-33 to 49]	17.5 [-34 to 43]	0.89	0 [-76 to 42]	17 [-22 to 50]	0.25
CRQ Dyspnoea	1 [-3 to 7]	2 [-1.5 to 6]	0.87	0.5 [-4 to 7]	2 [-2 to 6]	0.49
CRQ Fatigue	1 [-3 to 4]	2 [0 to 5]	0.21	0 [-4 to 3]	2 [-0 to 5]	0.03
CRQ Emotional Function	2 [-3 to 8]	2 [-2 to 9]	0.82	1 [-4.3 to 7]	4 [-2 to 8]	0.10
CRQ Mastery	1 [-1 to 5]	2 [-1 to 4.5]	0.89	1 [-2 to 5]	1.5 [-1 to 5]	0.35
CRQ Total	6 [-4 to 18]	8 [-2 to 21]	0.54	2 [-8 to 18]	9.5 [-2 to 20]	0.07
mMRC	0 [-1 to 1]	0 [0 to 1]	0.76	-1 [-1 to 1]	0 [0 to 1]	0.18
Total MVPA, min/day	-131 [-373 to 30]	61 [-169 to 211]	0.15	-282 [-460 to -26]	-1 [-198 to 112]	0.13
Duration MVPA in bouts, min/day	-14 [-90 to 5]	39 [-59 to 138]	0.14	-27 [-118 to 5]	0 [-74 to 56]	0.64
Sedentary awake time, min/day	-826 [-1605 to 147]	-102 [-720 to 398]	0.28	-806 [-71209 to -23]	-393 [-1225 to 399]	0.22

Table legend: Data are change from baseline (pre-rehabilitation) to 12 months, median [interquartile range]. p values represent difference between groups who did or did not have an exacerbation.

6MWD, 6-min walk distance; CRQ, Chronic Respiratory Questionnaire; MMRC, modified Medical Research Council scale; MVPA, moderate to vigorous physical activity; Duration MVPA bouts: duration of MVPA when in bouts of at least 10 min.

**Table 3.** Multiple linear regression analysis for impact of severe exacerbations during follow-up on clinical outcomes at 12 months.

	Variable	B	95%CI	Standardised Beta	P value	R <sup>2</sup> for model
CRQ Total						0.22
	Constant	46.91	7.45 to 86.37		0.02	
	Severe exacerbation	-10.89	-18.73 to -3.05	-0.243	0.007	
	Group allocation	0.57	-6.25 to 7.38	0.014	0.87	
	Age	-0.08	-0.51 to 0.35	-0.034	0.71	
	Gender	1.04	-5.93 to 8.01	0.025	0.77	
	FEV <sub>1</sub>	3.69	-2.66 to 10.03	0.100	0.25	
	Smoking status	-0.77	-10.00 to 8.47	-0.014	0.87	
	Baseline CRQ Total	-0.46	-0.65 to -0.26	-0.422	<0.001	
CRQ Dyspnoea						0.19
	Constant	9.21	-3.21 to 21.63		0.14	
	Severe exacerbation	-1.22	-3.67 to 1.22	-0.088	0.32	
	Group allocation	0.06	-2.11 to 2.24	0.005	0.96	
	Age	-0.08	-0.21 to 0.05	-0.106	0.24	
	Gender	2.47	0.28 to 4.66	0.192	0.03	
	FEV <sub>1</sub>	1.18	-0.83 to 3.20	0.103	0.25	
	Smoking status	-0.90	-3.86 to 2.06	-0.055	0.55	
	Baseline CRQ Dyspnoea	-0.40	-0.60 to -0.19	-0.337	<0.001	
CRQ Fatigue						0.31
	Constant	10.50	0.15 to 20.75		0.05	
	Severe exacerbation	-3.46	-5.45 to -1.46	-0.283	0.001	
	Group allocation	0.51	-1.25 to 2.27	0.045	0.57	
	Age	-0.02	-0.12 to 0.09	-0.023	0.78	
	Gender	-0.24	-2.05 to 1.57	-0.021	0.79	
	FEV <sub>1</sub>	0.32	-1.34 to 1.98	0.031	0.71	
	Smoking status	0.54	-1.83 to 2.90	0.037	0.45	
	Baseline CRQ Fatigue	-0.59	-0.78 to -0.40	-0.507	<0.001	
CRQ Emotional						0.30
	Constant	17.950	3.688 – 32.211		0.01	
	Severe exacerbation	-4.61	-7.45 to -1.77	-0.270	0.002	
	Group allocation	0.06	-2.41 to 2.53	0.004	0.96	
	Age	0.02	-0.14 to 0.17	0.019	0.83	
	Gender	-1.33	-3.87 to 1.20	-0.084	0.30	
	FEV <sub>1</sub>	1.15	-1.16 to 3.47	0.082	0.33	
	Smoking status	0.57	-2.77 to 3.90	0.028	0.74	
	Baseline CRQ Emotional	-0.48	-0.63 to -0.32	-0.533	<0.001	

CRQ Mastery					0.28
	Constant	10.80	0.87 to 20.74		0.03
	Severe exacerbation	-1.93	-3.89 to 0.04	-0.163	0.05
	Group allocation	-0.13	-1.88 to 1.61	-0.012	0.88
	Age	0.03	-0.08 to 0.14	0.045	0.62
	Gender	-0.20	-1.88 to 1.64	-0.011	0.89
	FEV <sub>1</sub>	0.95	-0.70 to 2.59	0.097	0.26
	Smoking status	-1.01	-3.35 to 1.33	-0.072	0.40
	Baseline CRQ Mastery	-0.53	-0.70 to -0.36	-0.535	<0.001
6MWD					0.08
	Constant	94.56	-93.25 to 282.37		0.32
	Severe exacerbation	-36.49	-71.69 to -1.27	-0.205	0.04
	Group allocation	14.13	-15.99 to 22.24	0.089	0.35
	Age	-1.14	-2.97 to 0.69	-0.128	0.22
	Gender	7.44	-23.43 to 38.32	0.047	0.63
	FEV <sub>1</sub>	18.29	-12.86 to 49.440	0.128	0.25
	Smoking status	-2.76	-43.06 to 37.54	-0.014	0.89
	Baseline 6MWD	-0.14	-0.30 to 0.01	-0.197	0.07
MMRC					0.23
	Constant	2.41	0.01 to 4.81		0.05
	Severe exacerbation	0.58	0.12 to 1.03	0.219	0.01
	Group allocation	0.20	-0.20 to 0.61	0.084	0.317
	Age	-0.00	-0.03 to 0.02	-0.018	0.83
	Gender	-0.55	-0.96 to -0.15	-0.227	0.008
	FEV <sub>1</sub>	-0.26	-0.65 to 0.13	-0.117	0.20
	Smoking status	-0.14	-0.67 – to 0.40	-0.044	0.615
	Baseline MMRC	-0.64	-0.89 to -0.39	-0.445	<0.001
Total MVPA					0.32
	Constant	-34.28	-1296.02 to 1227.46		0.96
	Severe exacerbation	-371.26	-724.99 to - 17.54	-0.462	0.04
	Group allocation	77.10	-201.54 to 355.75	0.109	0.58
	Age	-3.30	-18.09 to 11.50	-0.087	0.65
	Gender	-52.25	-295.85 to 191.36	-0.073	0.66
	FEV <sub>1</sub>	-86.83	-371.14 to 197.48	-0.116	0.54
	Smoking status	382.39	76.04 to 688.73	0.457	0.16
	Baseline MVPA Total	-0.27	-0.49 to -0.05	-0.468	0.18

Duration MVPA Bouts					0.18
Constant	360.16	-335.5 to 1055.77		0.30	
Severe exacerbation	-147.15	-354.67 to 60.37	-0.347	0.16	
Group allocation	14.60	-146.13 to 175.31	0.039	0.85	
Age	-5.05	-13.40 to 3.30	-0.252	0.23	
Gender	-33.21	-172.84 to 106.43	-0.088	0.63	
FEV <sub>1</sub>	-90.17	-254.02 to 73.67	-0.228	0.27	
Smoking status	137.96	-50.02 to 325.93	0.313	0.14	
Baseline MVPA bouts	-0.15	-0.396 to 0.11	-0.252	0.25	
Total Sedentary time					0.26
Constant	3261.2 9	-2033.07 to 8555.65		0.22	
Severe exacerbation	-144.41	-1665.39 to 1376.57	-0.043	0.85	
Group allocation	-204.73	-1519.82 to 1110.37	-0.069	0.75	
Age	15.86	-64.34 to 96.05	0.099	0.69	
Gender	-431.30	-1583.61 to 721.01	-0.143	0.45	
FEV <sub>1</sub>	50.01	-1134.80 to 1234.82	0.016	0.93	
Smoking status	-264.27	-1586.18 to 1057.64	-0.075	0.69	
Baseline sedentary time	-0.76	-1.39 to -0.14	0.306	0.02	

Table legend: Dependent variables are change from baseline to 12 months following pulmonary rehabilitation. 6MWD, 6-minute walk distance; CI, confidence interval for B; CRQ, Chronic Respiratory Questionnaire; FEV<sub>1</sub>, forced expiratory volume in one second; MVPA, moderate to vigorous intensity physical activity.

Severe exacerbation during follow-up is coded as 0 = no, 1 = yes; Pulmonary rehabilitation group is coded as 1 = home-based, 2 = centre-based; Age is measured in years; FEV<sub>1</sub> is measured in litres; Smoking status is coded as 0= never smoked or quit, 1 = current smoking.

**Table 4.** Logistic regression predicting likelihood of having severe exacerbation 12 months after pulmonary rehabilitation.

	<b>B</b>	<b>SE</b>	<b>p</b>	<b>Odds ratio</b>	<b>95% CI</b>
Pulmonary rehabilitation completion	-0.624	0.384	0.10	0.536	0.252 – 1.138
History of GOR	0.419	0.369	0.26	1.520	0.738 – 3.131
FEV <sub>1</sub> % predicted	-0.033	0.011	0.002	0.968	0.948 – 0.988
CRQ Total at baseline	-0.024	0.010	0.01	0.976	0.957 – 0.994
Constant					

Table legend: CI, confidence interval for odds ratio; CRQ, Chronic Respiratory

Questionnaire; FEV<sub>1</sub>, forced expiratory volume in one second; GOR, gastroesophageal reflux.

Severe exacerbation during follow-up is coded as 0 = no, 1 = yes; Pulmonary completion is coded as 0 = no, 1 = yes.

## 3.4 Supplemental Material

<b>SUPPLEMENTARY INFORMATION</b>
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**TITLE: The impact of COPD exacerbations in the year following pulmonary rehabilitation: secondary analysis of a randomised controlled trial**

**Authors' full names:**

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## **Appendix S1- Methods**

### **Exacerbation definition**

Coding of exacerbations was performed by one researcher (BW) and checked by a second researcher (AH). Data from hospital and pharmacy usage for each participant were first display in chronological order starting from the first day of the 12-month follow-up period. A single exacerbations was counted for 15 days from the start of exacerbation, after this period it was considered as another exacerbation. Exacerbations were considered when:

**Moderate exacerbations:** collection of prescription medication (oral corticosteroids and/or antibiotics) was considered as moderate exacerbation (Table 1). Collection of inhalers commonly used to treat COPD (ipratropium or inhaled corticosteroids) was not considered as an exacerbation. Medication prescribed repeatedly over the following months was not considered as a new exacerbation (eg long-term antibiotics). If antibiotics were collected on the same day as any topical antibiotics it was not registered as exacerbation once it was assumed that the medication was prescribed for reasons other than respiratory.

**Severe exacerbations:** Hospital admission or emergency department visit for a respiratory condition was considered to be a severe exacerbation (Table 1). Antibiotics and/or oral corticosteroids collected during admission were not registered as new exacerbation. If the participant had collected ipratropium or inhaled corticosteroids within 15 days before admission, this was considered to denote a single exacerbation and the exacerbation was counted as severe.

**Table S1-** Exacerbation definition based on health care usage

Severity	Exacerbation definition based on health care usage
Moderate	Collected a new prescription for oral corticosteroids and/or antibiotics based on the Pharmaceutical Benefits Scheme (Australia) data.
Severe	Respiratory-related admission to hospital or emergency department visit with a primary discharge diagnosis of COPD.

Table legend: Exacerbation definitions are based on the GOLD strategy(1). COPD: chronic obstructive pulmonary disease

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary <https://goldcopd.org/>: GOLD; 2020

**Table S2-** Multiple regression analysis - impact of any exacerbation during follow-up on clinical outcomes at 12 months.

	Variable	B	95%CI	Standardised Beta	p	R <sup>2</sup> for model
CRQ Total						0.18
	Constant	42.197	0.324 to 84.070		0.05	
	Exacerbation during follow-up	-4.680	-13.639 to 4.279	-0.091	0.30	
	Group allocation	-0.165	-7.224 to 6.893	-0.004	0.96	
	Age	-0.55	-0.500 to 0.390	-0.023	0.81	
	Gender	1.919	-5.214 to 9.052	0.046	0.60	
	FEV <sub>1</sub>	4.771	-1.784 to 11.327	0.129	0.15	
	Smoking status	-2.830	-12.179 to 6.520	-0.053	0.55	
	Baseline CRQ Total	-0.406	-0.603 to -0.208	-0.375	<0.001	
CRQ Dyspnoea						0.18
	Constant	8.529	-4.365 to 21.423			
	Exacerbation during follow-up	-0.364	-3.128 to 2.400	-0.023	0.80	
	Group allocation	-0.10	-2.207 to 2.186	-0.001	0.99	
	Age	-0.070	-0.200 to 0.060	-0.097	0.29	
	Gender	2.559	0.364 to 4.754	0.199	0.02	
	FEV <sub>1</sub>	1.330	-0.702 to 3.361	0.116	0.20	
	Smoking status	-1.141	-4.074 to 1.791	-0.069	0.44	
	Baseline CRQ Dyspnoea	-0.382	-0.583 to -0.182	-0.327	<0.001	
CRQ Fatigue						0.25
	Constant	9.301	-1.738 to 20.340		0.10	
	Exacerbation during follow-up	-1.776	-4.100 to 0.548	-0.127	0.13	
	Group allocation	0.283	-1.562 to 2.128	0.025	0.76	
	Age	0.000	-0.111 to 0.111	0.000	0.99	
	Gender	0.028	-1.849 to 1.905	0.003	0.98	
	FEV <sub>1</sub>	0.658	-1.071 to 2.387	0.065	0.45	
	Smoking status	-0.042	-2.469 to 2.385	-0.003	0.97	
	Baseline CRQ Fatigue	-0.544	-0.742 to -0.346	-0.469	<0.001	
CRQ Emotional						0.25
	Constant	15.528	0.210 to 30.847		0.05	
	Exacerbation during follow-up	-1.654	-4.939 to 1.631	-0.084	0.32	
	Group allocation	-0.182	-2.761 to 2.417	-0.011	0.89	
	Age	0.029	-0.134 to 0.192	0.032	0.73	
	Gender	-0.914	-3.540 to 1.711	-0.058	0.49	
	FEV <sub>1</sub>	1.718	0.697 to 4.133	0.122	0.16	
	Smoking status	0.285	-3.702 to 3.312	-0.014	0.87	

	Baseline CRQ Emotional	-0.427	-0.585 to -0.268	-0.479	<0.001
CRQ Mastery					0.26
	Constant	10.682	0.287 to 21.078		0.04
	Exacerbation during follow-up	-1.164	-3.400 to 1.073	-0.086	0.31
	Group allocation	-0.305	-2.083 to 1.473	-0.028	0.74
	Age	0.035	-0.076 to 0.145	0.056	0.53
	Gender	-0.026	-1.802 to 1.750	-0.002	0.98
	FEV <sub>1</sub>	1.040	-0.633 to 2.713	0.107	0.22
	Smoking status	-1.333	-3.673 to 1.006	-0.095	0.26
	Baseline CRQ Mastery	-0.516	-0.687 to -0.344	-0.516	<0.001
6MWD					0.05
	Constant	79.674	-120.165 to 279.514		
	Exacerbation during follow-up	-12.007	-51.164 to 27.150	-0.608	0.54
	Group allocation	10.908	-19.821 to 41.636	0.069	0.48
	Age	-0.932	-2.788 to 0.924	-0.105	0.32
	Gender	9.972	-21.385 to 41.328	0.063	0.53
	FEV <sub>1</sub>	22.070	-9.473 to 53.613	0.154	0.17
	Smoking status	-9.103	-49.727 to 31.521	-0.045	0.67
	Baseline 6MWD	-0.131	-0.289 to 0.028	-0.182	0.11
MMRC					0.19
	Constant	2.537	0.024 to 5.051		0.05
	Exacerbation during follow-up	0.213	-0.321 to 0.747	0.070	0.43
	Group allocation	0.232	-0.184 to 0.648	0.096	0.27
	Age	-0.006	-0.030 to 0.019	-0.043	0.63
	Gender	-0.582	-0.998 to -0.166	-0.239	0.01
	FEV <sub>1</sub>	-0.305	-0.708 to 0.097	-0.138	0.14
	Smoking status	-0.038	-0.583 to 0.507	-0.012	0.89
	Baseline MMRC	-0.604	-0.862 to -0.346	-0.422	<0.001
Total MVPA					0.24
	Constant	-249.339	-1571.824 to 1073.146		0.70
	Exacerbation during follow-up	-172.798	-476.660 to 131.064	-0.222	0.25
	Group allocation	-65.390	-317.204 to 186.425	-0.093	0.60
	Age	1.983	-12.732 to 16.699	0.052	0.78
	Gender	-49.281	-314.425 to 215.863	-0.069	0.71
	FEV <sub>1</sub>	16.127	-257.611 to 289.864	0.021	0.91
	Smoking status	332.715	13.351 to 652.079	0.398	0.04

	Baseline MVPA total	-0.224	-0.454 to 0.005	-0.389	0.06
Duration MVPA Bouts					0.19
	Constant	358.779	-332.380 to 1049.938		0.30
	Exacerbation during follow-up	-125.083	-294.759 to 44.593	-0.305	0.14
	Group allocation	-38.517	-175.508 to 98.475	-0.104	0.57
	Age	-2.958	-10.924 to 5.007	-0.148	0.45
	Gender	-47.282	-190.759 to 96.196	-0.125	0.51
	FEV <sub>1</sub>	-60.199	-208.920 to 88.523	-0.152	0.41
	Smoking status	119.502	-63.504 to 302.508	0.271	0.19
	Baseline MVPA bouts	-0.145	-0.393 to 0.104	-0.252	0.24
					0.27
Total Sedentary time	Constant	3520.561	-1737.077 to 8778.199		0.18
	Exacerbation during follow-up	-396.690	-1596.337 to 802.957	-0.121	0.50
	Group allocation	-232.550	-1329.880 to 864.780	-0.078	0.67
	Age	16.996	-55.733 to 89.726	0.106	0.64
	Gender	-490.499	-1647.082 to 666.084	-0.162	0.39
	FEV <sub>1</sub>	49.520	-1044.784 to 1143.823	0.016	0.93
	Smoking status	-313.326	-1633.277 to 1006.625	-0.089	0.63
	Baseline sedentary time	-0.737	-1.336 to -0.139	-0.540	0.02

Table legend: Dependent variables are change from baseline to 12 months following pulmonary rehabilitation. 6MWD, 6-minute walk distance; CI, confidence interval for B; CRQ, Chronic Respiratory Questionnaire; FEV<sub>1</sub>, forced expiratory volume in one second; MVPA, moderate to vigorous intensity physical activity.

Severe exacerbation during follow-up is coded as 0 = no, 1 = yes; Pulmonary rehabilitation group is coded as 1 = home-based, 2 = centre-based; Age is measured in

years; FEV<sub>1</sub> is measured in litres; Smoking status is coded as 0 = never smoked or quit, 1 = current smoking. Significant results in bold.

**Table S3-** Response to pulmonary rehabilitation (change from baseline to eight weeks) for participants with and without exacerbations during follow-up.

	ANY EXACERBATION			SEVERE EXACERBATION		
	Exacerbation	No exacerbation	p value	Severe exacerbation	No exacerbation or moderate exacerbation	p value
6MWD, m	17 [-5 to 46]	31 [-3 to 52]	0.45	10 [-18 to 42]	23 [-1 to 53]	0.12
CRQ Dyspnoea	4 [-0.5 to 8]	2.5 [-2 to 7]	0.28	4 [1 to 10]	3 [-1 to 8]	0.23
CRQ Fatigue	2 [-1 to 4]	2.5 [0 to 4]	0.18	1 [-2 to 4]	2 [-1 to 4]	0.16
CRQ Emotional Function	2 [-3 to 7]	2 [0 to 6]	0.55	0 [-5 to 5]	3 [-1 to 7]	0.05
CRQ Mastery	2 [-1 to 5.5]	2 [0 to 5]	0.49	2 [-2 to 6]	2 [-1 to 5]	0.55
CRQ Total	7 [-5 to 19]	9 [-10 to 18]	0.99	4 [-8 to 17]	9 [-3 to 20]	0.16
mMRC	0 [-1 to 0]	0 [-1 to 0]	0.72	0 [-1 to 1]	0 [-1 to 0]	0.11
Total MVPA, min/day	4 [-149 to 231]	29 [-303 to 196]	0.69	-83 [-199 to 145]	64 [-70 to 219]	0.17
Duration MVPA in bouts, min/day	27 [-12 to 90]	17 [-114 to 107]	0.56	0 [-72 to 70]	29 [-6 to 111]	0.12
Sedentary awake time, min/day	-569 [-1358 to 157]	-285 [-566 to 137]	0.42	-259 [-1225 to 223]	-492 [-1400 to 82]	0.47

Table legend: Data are median and interquartile range for change from baseline to end rehabilitation (8 weeks); p value represents comparison between those with and without exacerbations.

6MWD, 6 min walk distance; CRQ, Chronic Respiratory Questionnaire; MMRC, modified Medical Research Council scale; MVPA, moderate and vigorous physical activity; Duration MVPA bouts: duration of physical activity when in bouts of at least 10 min.

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# CHAPTER FOUR

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*Characteristics of pulmonary rehabilitation  
programs following exacerbation of COPD: A  
systematic review*



## 4.1 Declaration of Authorship – Chapter Four

### Student's Declaration

The nature and extent of contributions to Chapter Four of this thesis are as follows:

Name	Nature of contribution	Contribution	Signature
Bruna Wageck	Study concept, protocol development, data search and extraction, data analysis, writing and review of manuscript	66%	
Anne E Holland	Study concept, protocol development, data analysis, writing and review of manuscript	20%	
Narelle S Cox	Study concept, protocol development, data analysis, writing and review of manuscript	10%	
Joanna Lee	Data extraction and check, and review of manuscript	3%	
Lorena Romero	Search strategy and review of manuscript	1%	

### Supervisor's Declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter Four of this thesis by the student and all listed

Supervisor name	Signature
Professor Anne E Holland	

## 4.2 Preface

The secondary analysis of a randomised controlled trial presented in Chapter Three found that exacerbations are a common event in the year following pulmonary rehabilitation and people with COPD that have severe exacerbations have poorer outcomes in the year after pulmonary rehabilitation. The study also found that severe exacerbations are more likely to occur in people with lower respiratory function and poorer quality of life. Failing to complete the program of pulmonary rehabilitation is also a risk factor for exacerbation. Therefore, people with COPD remain at risk of having exacerbations and may not fully recover to their baseline status.

Pulmonary rehabilitation improves functional capacity and symptoms. Pulmonary rehabilitation commenced early after an exacerbation of COPD appears to improve health status and may reduce negative outcomes such as need for hospitalisation. However, results vary, which may be related to the timing of rehabilitation commencement. Confounding this, to date, there has been no consensus on what constitutes ‘early’ pulmonary rehabilitation, with studies commencing the rehabilitation program as early as ‘medically appropriate’ in hospital (3 to 5 days after admission) and as late as three to four weeks after discharge. Also, previous studies are heterogeneous in program characteristics such as the content of rehabilitation, frequency, supervision, and location of delivery.

Chapter Four is a systematic review aiming to determine the impact of pulmonary rehabilitation program characteristics on patient outcomes following an exacerbation of

COPD. Findings of this review suggests that pulmonary rehabilitation programs with a duration longer than three weeks, including exercise training as well as education, and starting after hospital discharge were most effective in reducing hospital readmissions. Also, the review shows that functional capacity and quality of life improve in all pulmonary rehabilitation programs, regardless of the program setting.

The manuscript arising from this study was submitted for publication to Journal of Cardiopulmonary Rehabilitation and Prevention on 19 May 2020 and is currently under review. The journal has an impact factor 1.568.

**Journal of Cardiopulmonary Rehabilitation and Prevention**  
**Characteristics of Pulmonary Rehabilitation Programs Following an Exacerbation of**  
**Chronic Obstructive Pulmonary Disease: a Systematic Review**  
 --Manuscript Draft--

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## 4.3 Manuscript

### **Characteristics of Pulmonary Rehabilitation Programs Following an Exacerbation of Chronic Obstructive Pulmonary Disease: a systematic review**

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## **Structured Abstract**

**Purpose:** Early pulmonary rehabilitation has beneficial impacts on people with COPD when delivered after an exacerbation, however program characteristics are diverse. This systematic review aimed to determine the impact of pulmonary rehabilitation program characteristics (mode, length, commencement, frequency, location and supervision) on clinical outcomes following an exacerbation of COPD. **Methods:** Studies were screened from Medline, Medline in progress, Embase, CINAHL, SCOPUS, CENTRAL, and PEDro. Included studies were randomized controlled trials of early pulmonary rehabilitation after an exacerbation of COPD (commenced within 4 weeks of hospital discharge). The primary outcomes were hospital readmissions and mortality. **Results:** Thirty studies were included. Exercise training alone was delivered in 40% of studies. Program duration varied from length of inpatient stay to 12 weeks. The interventions commenced as early as within 24 hours of hospitalisation for acute exacerbation, up to two weeks after discharge. Early pulmonary rehabilitation was compared to usual care, and no studies made a direct comparison of the program characteristics of interest. Program characteristics associated with reduced risk of hospital admission were commencement after discharge, duration longer than three weeks, a supervised exercise program, and delivery of exercise and education (relative risks of readmission 0.6 to 0.79), however it was not possible to determine which of these characteristics made the most important contribution. Mortality risk did not vary according to program characteristics. **Conclusion:** Programs longer than 3 weeks, started after hospital discharge or including an educational component in addition to exercise were most effective at reducing hospital readmissions.

## **Condensed Abstract**

This review aimed to determine the impact of early pulmonary rehabilitation program characteristics on clinical outcomes after exacerbation of COPD. Programs longer than three weeks, started after hospital discharge or including an educational component in addition to exercise were most effective at reducing hospital readmissions.

## INTRODUCTION

People with chronic obstructive pulmonary disease (COPD) often have significant functional limitation and high risk of mortality <sup>1</sup>. One of the key factors that contributes to progression of the disease is an acute change in the condition, referred to as an exacerbation of COPD <sup>2</sup>. An exacerbation event is described as a worsening of symptoms compared with the patient's baseline <sup>1</sup>. An exacerbation of COPD is defined as two consecutive days with an increase in at least two major symptoms/signals (dyspnoea, sputum purulence or volume); or the presence of one major symptom/signal associated with a minor symptom/signal (nasal discharge or congestion, wheeze, sore throat, or increased cough) <sup>3,4</sup>. Exacerbations are one of the leading causes of hospital admission and death in people with COPD, underscoring the importance of identifying and providing interventions that reduce the negative consequences of exacerbations <sup>5,6</sup>.

Pulmonary rehabilitation has been recommended after an exacerbation of COPD <sup>7</sup> with increasing interest in investigating the effects of pulmonary rehabilitation delivered at this time<sup>8</sup>. The most recent update of the Cochrane Review on early pulmonary rehabilitation after exacerbations of COPD shows moderate evidence that pulmonary rehabilitation decreases hospital admissions and low quality evidence that it decreases mortality in people with COPD post exacerbation <sup>8</sup>. However, the review by Puhan et. al. <sup>8</sup> does not analyse the different characteristics of each pulmonary rehabilitation program and how these could affect outcomes.

Previous trials of pulmonary rehabilitation in people with an exacerbation of COPD have had a wide variety of program characteristics, including start time (inpatient vs outpatient), exercise combinations (strength and/or endurance), and length and frequency of program.



Although the majority of the literature has suggested improvements following pulmonary rehabilitation, the variability of pulmonary rehabilitation parameters could influence the patient outcomes and it is unclear which components of the rehabilitation are the most important <sup>8,9</sup>. Effective and essential components of pulmonary rehabilitation following an exacerbation COPD have not been determined. The aim of this review was to determine the impact of the pulmonary rehabilitation program characteristics on clinical outcomes following an exacerbation of COPD.

## **METHODS**

### ***MATERIALS AND METHODS***

This systematic review was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations <sup>10</sup>. The review was prospectively registered at PROSPERO CRD42016038029.

### ***ELIGIBILITY CRITERIA***

For this systematic review, we included both randomized and quasi-randomized controlled trials comparing early pulmonary rehabilitation (within 4 weeks after discharge) to usual care or a control condition in patients with COPD who had recently been hospitalised for an exacerbation of COPD. To fulfill the review purpose we included all studies that delivered exercise after exacerbation of COPD, not only studies that followed pulmonary rehabilitation guidelines, to ensure we covered all components from pulmonary rehabilitation programs and were able to make comparisons (including education). Studies were not limited by type of

report, language or date. The authors decided not to include studies that compared two types of intervention without a control group due to the limited likelihood of obtaining consistent comparisons. To be eligible for inclusion studies need to be of exercise training, with or without education or self-management training, delivered in any location with or without professional supervision; and commencing either during hospitalisation or within four weeks of discharge.

### ***SEARCH METHODS FOR IDENTIFICATION OF STUDIES***

The search strategy was performed electronically in June 2016 and updated in April 2020. The search strategy was applied in the following databases: Medline, Medline in progress, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and PEDro (Physiotherapy Evidence Database). Search filters were developed by the authors and adapted to each database characteristics (example of search strategy can be seen in the Supplemental Digital Content A).

### ***DATA COLLECTION***

After running the electronic search strategy, two authors screened the titles and abstracts to eliminate those that clearly did not meet the inclusion criteria. Those studies that appeared eligible for inclusion based on their title and abstract, as well as those studies whose inclusion was unclear, were obtained in full text. The reviewers examined the studies in full

text to determine their inclusion. Further information was requested from authors of included studies during the process.

## ***OUTCOMES***

The primary outcomes of this systematic review were: a) hospital readmission and b) mortality. The secondary outcomes were: a) functional exercise capacity measured using any validated exercise field test such as six minute walking test (6MWT) or shuttle walk test; b) health related quality of life measured using generic or disease specific questionnaires; c) adverse events either during the intervention period, such as musculoskeletal injury, falls, and need for ventilation support measures (invasive or non-invasive); or adverse events reported in the follow-up period, eg. hospitalisation and death. Both short-term and long-term outcomes were analysed. Short-term outcomes were those where results were reported during the program or immediately after finishing the rehabilitation program; while long-term outcomes were those where results were reported at follow up.

To answer the question regarding the effect of program characteristics, results were compared between subgroups based on characteristics of the program: i) Program mode (exercise training only vs exercise training plus education); ii) Length (< 3 weeks, 3-12 weeks or >12 weeks), with the lower cutoff chosen because exercise training studies have frequently shown benefits with a duration of three weeks or more; iii) Commencement (inpatient vs after discharge); iv) Frequency (1/week or  $\geq 2$ /week); v) Location (inpatient, outpatient or a combination of both); vi) Supervision (supervised vs unsupervised).

## ***RISK OF BIAS ASSESSMENT***

The quality assessment of the studies included in this review was performed based on The Cochrane risk of bias tool <sup>11</sup>. The studies were assessed for bias under the following headings: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias.

We considered as high-quality evidence studies that were classified as having low risk of bias for random sequence generation, allocation concealment, and incomplete outcome data.

## ***DATA EXTRACTION AND ANALYSIS***

Data were extracted from the included studies onto a purpose-designed data extraction form. When similarities were found between studies regarding intervention, patient characteristics and analysed variables, a meta-analysis was conducted. The data for mean and standard deviation or mean and standard error of the studies included in the meta-analysis were extracted and converted into weighted mean differences (treatment effect) and 95% confidence intervals (95% CI) to allow comparison across studies using different metrics. The statistical homogeneity of the studies was assessed using the  $I^2$  value and if the  $I^2$  value was over 25%, the meta-analysis was performed using the random effects model in the software package Review Manager (RevMan) (Version 5.2, Copenhagen, Denmark).

## **RESULTS**

### ***DESCRIPTION OF STUDIES***

The electronic database searches identified a total of 14,162 citations after duplicates removed. From the total, 14,000 citations were excluded after screening titles and abstracts, leaving 162 studies for detailed evaluation. Forty citations met the inclusion criteria; however, 11 were conference abstracts of studies already published in full and therefore, the results from abstracts and published manuscript were considered as one citation and data was collected from the main publication. A total of 30 studies meet the inclusion criteria (Figure 1), the characteristics of included studies are presented on Table 1.

### ***EXERCISE PROGRAM CHARACTERISTICS***

The exercise program component characteristics of the 30 included studies are described on Table 2. Not all included studies had detailed information about program characteristics. Exercise training alone was delivered in 40% (n=12) of studies and 53% (n=16) delivered exercise training plus education. Program duration varied from length of hospital stay to 12 weeks. Over one-third of studies (n=11; 37%) had a program duration of less than 3 weeks; 50% (n=15) had duration between 3 and 12 weeks; and 7% (n=2) of the programs were longer than 12 weeks. Intervention frequency varied from daily exercises to once a week, with 87% (n=26) of the studies delivering exercise two or more times per week. The interventions began as early as within 24 hours of hospitalisation for acute exacerbation, up to two weeks after discharge; 60% (n=18) started the exercise program during hospitalisation and 37% (n=11) started after hospital discharge. Interventions were conducted in the hospital (inpatients) (40%; n=12), as outpatients (37%; n=11) or combination of inpatient program followed by outpatient (20%; n=6). Regarding supervision, 87% (n=24) of studies delivered supervised programs.

## ***RISK OF BIAS***

Summary data for risk of bias are presented in Table 3. Included studies generally had low risk of bias for random sequence generation and selective reporting domains, and higher risk for allocation concealment. Blinding was expected to be poorly reported due the nature of the intervention where researchers involved in the interventions and patients cannot be blinded.

## ***PRIMARY OUTCOMES – HOSPITAL READMISSIONS AND MORTALITY***

### ***PROGRAM MODE (EXERCISE TRAINING ONLY OR EXERCISE TRAINING PLUS EDUCATION)***

In 12 studies the intervention was exercise training only<sup>12-23</sup> and in 16 studies the intervention was an exercise program plus an education component<sup>24-39</sup>. Two studies were unclear regarding program mode<sup>40,41</sup>.

### ***Hospital readmission***

Risk of hospital readmission was generally reduced in studies that compared exercise training plus education to usual care<sup>29,31,33-35,37,38</sup>, although this was statistically significant in only two studies (Table 4). Pooled results comparing exercise training plus education to usual care found significantly lower readmissions (RR 0.6; 95% CI 0.4 to 0.9;  $I^2=49\%$ ) at end of program<sup>33,37,38</sup>, but this effect was no longer significant at 12 months (RR 0.8; 95% CI 0.6 to 1.0;  $I^2=72\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figures B1 and B2). Of note, heterogeneity was high in both analyses. Studies that delivered exercise training only could not be combined due to heterogeneous time points measured (Table 4), thus no effect was

evident<sup>13,23</sup>. Relative risk for hospital readmission of included studies for program mode are presented in Table 4.

### ***Mortality***

There was no significant effect on mortality regardless of program mode, with substantial variability between studies. Two studies of exercise training only pulmonary rehabilitation delivered at the hospital were able to be pooled and showed a relative risk for mortality of 0.8 (95% CI 0.1 to 4.5;  $i^2=31\%$ ) (Supplemental Digital Content B – Figure B3) at one month after hospital discharge<sup>13,23</sup>.

For studies delivering exercise training plus education, pooled results reported a relative risk for mortality of 0.5 (95% CI 0.1 to 1.6;  $i^2=0\%$ ) at three months after discharge<sup>33,35,37,38</sup> and of 0.8 (95% CI 0.3 to 1.8;  $i^2=0\%$ ) at 12 months after discharge<sup>34,35</sup> (Supplemental Digital Content B – Figures B4 and B5). The remaining studies could not be combined due to the heterogeneous time points measured<sup>29,31,34</sup> (Table 5). Of note, one large study of exercise and education reported increased risk of mortality at 12 months (RR 2.1; 95%CI 1.1 to 4.0)<sup>31</sup>.

### ***PROGRAM LENGTH (<3 WEEKS, 3-12 WEEKS OR >12 WEEKS)***

In 11 studies the intervention length was less than three weeks<sup>13-15,17,18,20-23,32,36</sup>, 15 studies were between 3 and 12 weeks<sup>16,24-31,33-35,37-39</sup> and four were more than 12 weeks<sup>12,30,39,40</sup>.

Two studies were unclear regarding program length<sup>18,19,41</sup>.

### ***Hospital readmission***

No effect on hospital readmission was evident for studies that delivered <3 weeks of intervention<sup>13,23</sup>. Studies that delivered >12 weeks of intervention did not report hospital readmission. Risk of hospital admission was generally reduced in studies that delivered 3-12 weeks program length<sup>29,31,33-35,37,38</sup> (Table 4). Of note, these studies all delivered exercise and education, so it is not possible to determine whether the program mode or program length was responsible for this effect.

Meta-analysis results favoured the intervention group with length between 3 and 12 weeks at the end of the program (RR 0.6; 95% CI 0.4 to 0.9;  $I^2=49\%$ )<sup>33,37,38</sup>, but not at 12 months after discharge (RR 0.8; 95% CI 0.6 to 1.0;  $I^2=72\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figures B6 and B7).

### ***Mortality***

Mortality was reported in two studies with program length less than 3 weeks<sup>13,23</sup>, seven with programs between 3 and 12 weeks<sup>29,31,33-35,37,38</sup> and two with more than 12 weeks<sup>12,23</sup>.

Included studies reported no effect on mortality regardless of program length.

Pooled results for program length <3 weeks demonstrated no effect on mortality at one month after discharge (RR 0.8; 95% CI 0.1 to 4.5;  $i^2=31\%$ )<sup>13,23</sup> (Supplemental Digital Content B – Figure B8). Likewise, the effect on mortality for length of program between 3-12 weeks was non-significant at three months (RR 0.5; 95% CI 0.1 to 1.6;  $i^2=0\%$ )<sup>33,35,37,38</sup> and at 12 months after discharge (RR 0.8; 95% CI 0.3 to 1.8;  $i^2=0\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figures B9 and B10). Risk ratios for the studies that could not be combined due heterogeneous time points are presented on Table 5.



### ***PROGRAM FREQUENCY ( $\leq 1$ SESSION/WEEK OR $\geq 2$ SESSIONS/WEEKS)***

Four studies were unclear regarding session frequency<sup>18,28,40,41</sup>. All other studies included in the review delivered interventions at least twice a week<sup>12-17,19-27,29-39,42</sup>. One study delivered face-to-face intervention only four times during the study period and participants were asked to perform the exercises independently in between sessions; making it unclear exactly how many times per week the intervention was delivered<sup>39</sup>. As a result, we were not able to evaluate the effects of program frequency on outcomes.

### ***PROGRAM COMMENCEMENT (INPATIENT OR AFTER DISCHARGE)***

Eighteen studies delivered exercises starting during inpatient period<sup>12-15,17-24,29-32,36,39</sup> and 11 started after discharge<sup>16,25-27,33-35,37,38,40,43</sup>. One study was unclear regarding program commencement<sup>41</sup>.

### ***Hospital Readmission***

Overall, hospital readmission seemed to be lower in studies that started the program after discharge<sup>33-35,37,38,44</sup> (Table 4). These studies generally used both exercise and education, and had a length between 3 and 12 weeks. Studies, which started the exercise program during the inpatient period, were too heterogeneous to be combined in a meta-analysis and had variable effect on readmissions (Table 4)<sup>13,23,29,31</sup>. Pooled results of studies that delivered rehabilitation starting after discharge favoured intervention at end of program (RR 0.6; 95% CI 0.4 to 0.9;  $I^2=49\%$ )<sup>33,37,38</sup>, but were non-significant at 12 months (RR 0.79; 95% CI 0.6 to 1.0;  $I^2=72\%$ )<sup>34,35</sup>. Moreover, heterogeneity was high in the analyses (Supplemental Digital Content B – Figures B11 and B12).

## ***Mortality***

Mortality was reported in seven studies that started during the inpatient period<sup>13,23,29,31,40,45</sup> and six that started after discharge<sup>33-35,37,38</sup>. Included studies generally showed no effect on mortality regardless of the time of program commencement.

Two studies commencing intervention during the inpatient period could be combined and a non-significant result was observed at one month after discharge (RR 0.8; 95% CI 0.1 to 4.5;  $i^2=31\%$ )<sup>13,23</sup> and after end of program (RR 1.8, 95%CI 0.4 to 8.4;  $i^2=0\%$ )<sup>29,31</sup>

(Supplemental Digital Content B – Figures B13 and B14). For long-term, one study commenced during the inpatient period reported a trend towards reduced risk of death in the exercise training group after four years (Table 5)<sup>40</sup>.

Five studies starting the program after discharge reported no effect on mortality at 3 months (RR 0.5; 95% CI 0.1 to 1.6;  $i^2=0\%$ )<sup>33,35,37,38</sup> or at 12 months (RR 0.8; 95% CI 0.3 to 1.8;  $i^2=0\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figure B15 and B16).

## ***PROGRAM LOCATION (INPATIENT, OUTPATIENT, COMBINATION OF INPATIENT AND OUTPATIENT)***

In 11 studies exercise programs was delivered in the inpatient setting<sup>13-15,17-23,32,36</sup>, 11 studies were delivered as outpatient programs<sup>16,25-28,33-35,37,38,40</sup> and six delivered a combination of an inpatient program followed by an outpatient program<sup>12,24,29-31,39</sup>. One study was unclear regarding program location<sup>41</sup>.

## ***Hospital Readmission***

Two studies had programs located in an inpatient facility, however they could not be combined due to heterogeneous time points measured<sup>13,23</sup>. Results are not conclusive about the effect of program location on hospital readmission due to the wide confidence intervals of results<sup>13,23</sup> (Table 4).

For programs located as outpatient services, the results favored the intervention at 3 months (RR 0.6; 95% CI 0.4 to 0.9;  $I^2=49\%$ )<sup>33,37,38</sup>, but were non-significant at 12 months (RR 0.8; 95% CI 0.6 to 1.0;  $I^2=72\%$ )<sup>34,35</sup>. However, heterogeneity was high in the analyses (Supplemental Digital Content B – Figure B17 and B18).

Two studies that had a combination of location (inpatient and outpatient) could not be combined<sup>29,31</sup>. One study reported a reduced risk of readmission at 3 months<sup>29</sup> while the other study reported a higher relative risk of readmission at 12 months<sup>31</sup> (Table 4).

## **Mortality**

Effects on mortality were varied and generally non-significant (Table 5), with the exception of one trial (combination of inpatient and outpatient) that reported increased mortality at 12 months<sup>31</sup>. Programs delivered as outpatients had a non-significant relative risk for mortality at one month (RR 0.8 95%CI 0.1 to 4.5), at 3 months (RR 0.5; 95% CI 0.1 to 1.6), and at 12 months (RR 0.8; 95%CI 0.4 to 1.7) (Supplemental Digital Content B – Figures B19, B20 and B21).

## ***PROGRAM SUPERVISION (SUPERVISED OR UNSUPERVISED)***

Twenty-six studies delivered supervised programs<sup>12-29,32-39</sup>, one delivered unsupervised programs<sup>30</sup> and one delivered a supervised program as inpatients followed by unsupervised

program after discharge<sup>31</sup>. The remaining studies were unclear regarding program supervision<sup>40,41</sup>.

### ***Hospital readmission***

Effects of pulmonary rehabilitation on hospital admission were varied and generally non-significant (Table 4). Eight studies delivered supervised programs<sup>13,23,29,33-35,37,38</sup>, and some were sufficiently similar to be pooled in a meta-analysis with results favoring the intervention at end of program (RR 0.6; 95% CI 0.4 to 0.9;  $I^2=49\%$ )<sup>33,37,38</sup> and non-significant at 12 months (RR 0.8; 95% CI 0.6 to 1;  $I^2=72\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figures B22 and B23). Also, heterogeneity was high in the analyses.

### ***Mortality***

Studies that delivered supervised programs and were sufficient similar regarding intervention and time points measured were combined<sup>13,23,33-35,37,38</sup>. Effects on mortality were non-significant at one month after discharge (RR 0.8; 95% CI 0.1 to 4.5;  $i^2=31\%$ )<sup>13,23</sup>, at three months (RR 0.5; 95% CI 0.1 to 1.6;  $i^2=0\%$ )<sup>33,35,37,38</sup>, and at 12 months (RR 0.8; 95% CI 0.3 to 1.8;  $i^2=0\%$ )<sup>34,35</sup> (Supplemental Digital Content B – Figures B24, Figure B25 and Figure B26). The remaining studies could not be combined due heterogeneous time points measured and results were non-significant at three months<sup>29</sup>, six weeks<sup>31</sup> and 12 months after the program<sup>31</sup> (Table 5). One study delivered an unsupervised home-based component of the program that followed discharge and reported increased risk of death at 6 weeks and significant higher mortality risk after 12 months (Table 5)<sup>31</sup>.

## ***SECONDARY OUTCOMES***

Secondary outcomes (functional capacity, quality of life and adverse events) are reported in the Supplemental Digital Content C. For the secondary outcomes of functional capacity and quality of life, the mean difference of the pooled results exceeded the minimum important difference regardless of program characteristics. Four studies that presented data for adverse events had no adverse events during the intervention period<sup>23,24,32,37</sup>. The only study that reported adverse events during the study delivered exercise program started as inpatients for less than 3 weeks<sup>19</sup>. Tang et al.<sup>19</sup> reported 13 adverse events, seven non-serious, five nonserious study related and not expected and one serious and study related<sup>19</sup>. The study reported that a participant with previous history of heart condition developed chest pain that lasted two minutes while exercising in low-intensity; the adverse event was resolved within one hour without medical intervention<sup>19</sup>.

## **DISCUSSION**

The present systematic review analysed the efficacy of each characteristic of pulmonary rehabilitation programs delivered following an exacerbation of COPD on clinical outcomes. None of the included studies made a direct comparison of program characteristics, so subgroup analysis was used to compare the benefits of different program characteristics to usual care. Reductions in hospital readmissions were seen where programs had a duration between 3-12 weeks, delivered exercise training plus education, or started after discharge. There was no influence of program characteristics on mortality risk. Functional capacity and quality of life presented clinically significant improvements regardless of the characteristics of the program delivered.

Programs starting after discharge with longer duration and that have education associated with the exercises had lower risk of hospital readmission. These characteristics are similar to those supported by pulmonary rehabilitation guidelines and management strategies for stable COPD patients <sup>7,46</sup>. However, we could not indicate which of the three characteristics were most important for positive outcomes since many of the same studies were included in the analyses for length, mode and commencement. This is a common challenge with complex interventions, where the critical components are often not clear <sup>47</sup>. In the study of early pulmonary rehabilitation (combined inpatient and outpatient) after exacerbation by Greening et al.<sup>31</sup>, a high mortality rate was reported in the intervention group at one year after pulmonary rehabilitation <sup>31</sup>. However, the complexity of the intervention makes it difficult to detect the component within the program design that may have contributed to this outcome and how that could be altered <sup>31</sup>. Future research should focus on documenting program characteristics in order to improve reproducibility, and make direct comparisons of different program characteristics in clinical trials, to allow identification of possible contributors to outcomes <sup>47</sup>. A systematic review assessing outcomes of early pulmonary rehabilitation found significant decrease in mortality (OR 0.28; 95% CI 0.10 to 0.84) after the program <sup>8</sup>. In the present review we report mortality risk was not influenced by any of the rehabilitation program characteristics. The evidence syntheses presented in the two systematic reviews provide evidence contrasting with the increased mortality risk reported in the study by Greening et al. <sup>31</sup> and suggest that early rehabilitation is likely safe. However, the present review did not consider patient characteristics, such as disease severity. It is possible that mortality risk may be related to COPD phenotype <sup>48</sup>, suggesting that future randomised controlled trials of pulmonary rehabilitation early after exacerbation should stratify for

frequent-exacerbators phenotype, which may better help identify contributors to mortality risk.

Puhan et al.<sup>8</sup> reported high quality evidence that early pulmonary rehabilitation increased functional capacity and quality of life in people with COPD after exacerbation<sup>8</sup>. The present review reported that functional capacity and quality of life increase with early pulmonary rehabilitation regardless of the program characteristics. Reported results correspond to the body of literature, stating that decreasing inactivity improve functional capacity and quality of life in people with COPD<sup>49,50</sup>. Starting exercises early after exacerbation of COPD would break the inactivity cycle that starts after onset of exacerbation and can result in prolonged recovery<sup>50</sup>. Thus, starting exercises early after exacerbation of COPD is effective on increasing outcomes that would possibly be affected by the recovery process.

Although the present review identified some program characteristics associated with positive outcomes, many included studies were too heterogeneous regarding program characteristics to be combined in a meta-analysis. When meta-analysis was possible several analyses found high I-squared values (between 50-90%), representing substantial heterogeneity and suggesting that even when results shown statistical significance they were inconsistent<sup>51</sup>. This suggests unexplained variation across the studies that could be related to program characteristics, participant characteristics or other unidentified features of these complex intervention packages. Another potential limitation is the lack of details to describe the programs delivered in the studies, such as supervision or blinding. Future studies should thoroughly describe the intervention so it can be reproduced and comprehensively analysed.

## **APPLICATION TO PRACTICE**

This review confirms the safety and efficacy of early pulmonary rehabilitation for people after exacerbation of COPD, and suggests that program characteristics may influence readmission risk. In clinical practice, supervised early pulmonary rehabilitation programs that commence after discharge, combine exercises with education, and with more than three weeks of length may be optimal to minimize hospital readmission.

## **SUMMARY**

Hospital readmission was reduced following supervised pulmonary rehabilitation programs that delivered exercise training associated with education, started after discharge from hospital or lasted for longer than three weeks. Mortality risk was not related to program characteristics. Functional capacity and quality of life improved after early pulmonary rehabilitation independent of program characteristics. Studies of early pulmonary rehabilitation after exacerbation are heterogeneous regarding program characteristics. Future studies should consider a direct comparison of early pulmonary rehabilitation characteristics, allowing the most effective components to be understood.

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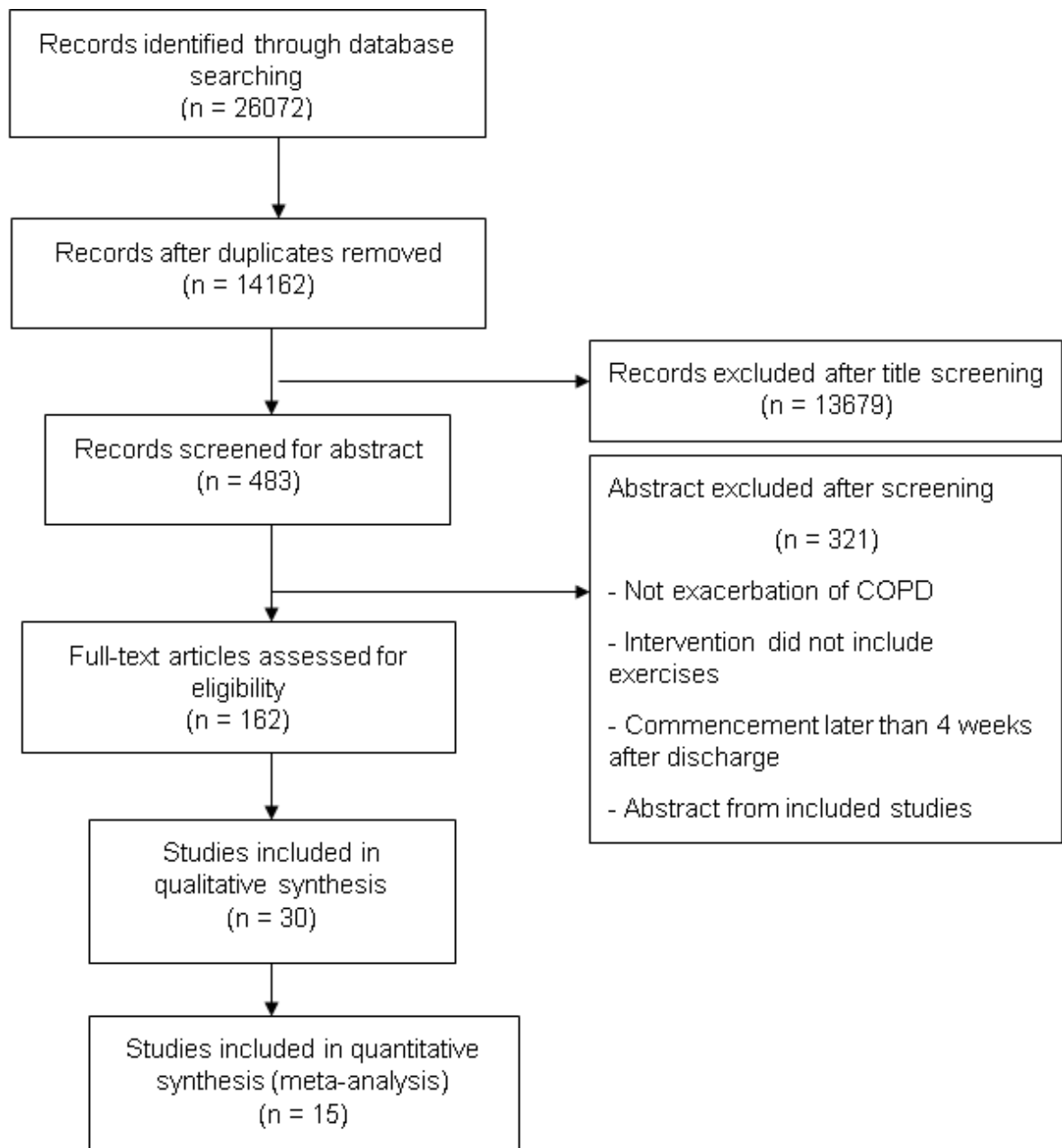
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**Figure and tables**



**Figure 1.** PRISMA flow diagram of study screening and selection <sup>10</sup>. PRISMA flow diagram used in study selection and screening. Thirty studies were included for review whereas the rest of the studies were excluded

**Table 1.** Characteristics of included studies

Reference	Year	Country	Type	Single or Multicentre	Number of participants	Outcomes	Intervention duration	Assessment time points	Funding
Ali et al. (12)	2014	India	Full report	S	30	6MWD, SF-36	Hospital stay + 3 weeks (outpatient)	Baseline, end intervention	Not stated
Behnke et al. (17)	2000	Germany	Full report	S	46	6MWD treadmill, CRQ	10 days (hospital) + 6 months (outpatient)	Day 1 and 10, Months 1, 2,3, end intervention	Yes
Borges et al. (18)	2014	Brazil	Full report	S	46	6MWD, SGRQ	Mean of 9 days (hospital stay)	Baseline, discharge, day 30	Yes
Dabbis et al. (29)	2017	Egypt	Full report	S	45	6MWD, SGRQ	8 weeks	Baseline, end intervention	Not stated
Deepak et al. (30)	2014	India	Full report	S	60	6MWD, SGRQ	12 weeks	Baseline, end intervention	Not stated
Eaton et al. (31)	2009	New Zealand	Full report	S	97	Hospital readmission, 6MWD, CRQ, SF-36	Hospital stay + 8 weeks (outpatient)	Baseline, 3 months	Yes
Ghanem et al. (32)	2010	Egypt	Full report	S	39	6MWD, CRQ, SF-36	Hospital stay + 2 months (outpatient)	Baseline, end intervention	No
Greening et al. (33)	2014	United Kingdom	Full report	M	389	Hospital readmission, Mortality, ISWT, ESWT, SGRQ	Median of 5 days (hospital stay) + 6 weeks (outpatient)	Baseline, discharge, end intervention, months 3 and 12	Yes
He et al. (13)	2015	China	Full report	S	101	6MWD, CRQ	Mean of 10 days (hospital stay)	Baseline, discharge	Yes

Johnson-Warrington et al. (34)	2016	United Kingdom	Full report	M	78	Hospital readmission, Mortality, ISWT, ESWT, CRQ	3 months	Baseline, end intervention	Yes
Kjærgaard et al. (28)	2020	Denmark	Full report	S	150	ISWT, ESWT	7 weeks	Baseline, end intervention	Yes
Kirsten et al. (19)	1998	Germany	Full report	S	29	6MWD treadmill	Hospital stay	Baseline, day 1, 5, 10 and 11	Yes
Knaut et al. (20)	2014	Brazil	Abstract	Not stated	11	6MWD, SGRQ	Hospital stay	Baseline, 1 month	Not stated
Ko et al. (36)	2011	Hong Kong	Full report	S	60	Hospital readmission, Mortality, 6MWD, SGRQ, SF-36	8 weeks	Baseline, months 3, 6, 9 and 12	Yes
Ko et al. (35)	2017	Hong Kong	Full report	S	180	Hospital readmission, Mortality, 6MWD, SGRQ	8 weeks	Baseline, 12 months	Not stated
Liao et al. (37)	2015	Taiwan	Full report	M	62	6MWD	4 days (hospital stay)	Baseline, end intervention	Yes
Man et al. (14)	2004	United Kingdom	Full report	S	42	Hospital readmission, Mortality, ISWT, SGRQ, CRQ, SF-36	8 weeks	Baseline, 3 months	Yes
Murphy et al. (21)	2005	Ireland	Full report	S	31	ISWT, SGRQ	6 weeks	Baseline, end intervention	Not stated
Probst et al. (22)	2005	Not stated	Abstract	Not stated	21	Outcomes not related to the review question	7 days (hospital stay)	Baseline, end intervention	Not stated

Revitt et al. (27)	2018	United Kingdom	Short report	S	36	ISWT, ESWT	6 weeks	Baseline, 7 weeks	No
Seymour et al. (38)	2010	United Kingdom	Full report	M	60	Hospital readmission, Mortality, ISWT, ESWT, CRQ, SGRQ	8 weeks	Baseline, 3 months	Yes
Song et al. (39)	2014	Korea	Full report	S	40	6MWD, SGRQ	2 months	Baseline, end intervention	Yes
Tahirah et al. (23)	2015	Australia, Malaysia	Abstract	Not stated	38	Outcomes not related to the review question	Hospital stay	Baseline, end intervention	Not stated
Tang et al. (16)	2012	Australia	Full report	Not stated	32	Adverse events	Hospital stay	End intervention	Not stated
Torres-Sánchez et al. (26)	2014	Spain	Abstract	Not stated	60	Outcomes not related to the review question	Mean of 8 days (hospital stay)	Baseline, end intervention	Not stated
Torres-Sánchez et al. (25)	2016	Spain	Full report	M	49	Outcomes not related to the review question	Mean of 9 days (hospital stay)	Baseline, end intervention	Yes
Torres-Sánchez et al. (24)	2017	Spain	Full report	M	58	Outcomes not related to the review question	Mean of 11 days (hospital stay)	Baseline, end intervention	Yes
Troosters et al. (40)	2002	Belgium	Abstract	Not stated	48	Survival	6 months	4 years	Not stated
Troosters et al. (15)	2010	Belgium, Brazil	Full report	S	40	Hospital readmission, Mortality, 6MWD	7 days (hospital stay)	Baseline, end intervention, 1 month	Yes
Wu et al. (41)	2015	China	Abstract	Not stated	90	6MWD	Unclear	Baseline, end intervention	Not stated

Table Legend: S: Single centre study; M: Multicentre study; 6MWD: Six-minute walking distance; SF-36: The Short Form-36; CRQ: Chronic Respiratory Disease Questionnaire; SGRQ: Saint George's Respiratory Questionnaire; ISWT: Incremental shuttle walk test; ESWT: Endurance shuttle walk test.






































































































































































**Table 2.** Pulmonary rehabilitation program characteristics

<b>Study</b>	<b>Comparison</b>	<b>Mode</b>	<b>Length</b>	<b>Frequency</b>	<b>Commencement</b>	<b>Location/Setting</b>	<b>Supervision</b>
Ali et al. 2014 (12)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	Inpatient	Combination	Yes
Behnke et al. 2000 (17)	PR x UC	Exercise only	>12 weeks	$\geq 2x/\text{week}$	Inpatient	Combination	Yes
Borges et al. 2014 (18)	PRx UC	Exercise only	<3 weeks	$\geq 2x/\text{week}$	Inpatient	Inpatient	Yes
Dabbis et al. 2017 (29)	CT x ET x UC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	After discharge	Outpatient	Yes
Deepak et al. 2014 (30)	PRxUC	Exercise + education	3-12 weeks	?	After discharge	Outpatient	Yes
Eaton et al. 2009 (31)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	Inpatient	Combination	Yes
Ghanem et al. 2010 (32)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	Inpatient	Combination	No
Greening et al. 2014 (33)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	Inpatient	Combination	Yes/ No
He et al. 2015 (13)	PRxUC	Exercise + education	<3 weeks	$\geq 2x/\text{week}$	Inpatient	Inpatient	Yes
Johnson-Warrington et al. 2016 (34)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	After discharge	Outpatient	Yes
Kjærgaard et al. 2020 (28)	Early PR x Late PR	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	After discharge	Outpatient	Yes
Kirsten et al. 1998 (19)	PRxUC	Exercise only	<3 weeks	$\geq 2x/\text{week}$	Inpatient	Inpatient	Yes
Knaut et al. 2014 (20)	PRxUC	Exercise only	<3 weeks	$\geq 2x/\text{week}$	Inpatient	Inpatient	Yes
Ko et al. 2011 (36)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	After discharge	Outpatient	Yes
Ko et al. 2017 (35)	PRxUC	Exercise + education	3-12 weeks	$\geq 2x/\text{week}$	After discharge	Outpatient	Yes
Liao et al. 2015 (37)	PRxUC	Exercise + education	<3 weeks	$\geq 2x/\text{week}$	Inpatient	Inpatient	Yes











































Man et al. 2004 (14)	PRxUC	Exercise + education	3-12 weeks	≥2x/week	After discharge	Outpatient	Yes
Murphy et al. 2005 (21)	Early PR x Late PR	Exercise only	3-12 weeks	≥2x/week	After discharge	Outpatient	Yes
Probst et al. 2005 (22)	PRxUC	Exercise only	<3 weeks	≥2x/week	Inpatient	Inpatient	Yes
Revitt et al. 2018 (27)	Early PR x Late PR	Exercise + education	3-12 weeks	≥2x/week	After discharge	Outpatient	Yes
Seymour et al. 2010 (38)	PRxUC	Exercise + education	3-12 weeks	≥2x/week	After discharge	Outpatient	Yes
Song et al. 2014 (39)	PRxUC	Exercise + education	3-12 weeks	≥2x/week	Inpatient	Combination	Yes
Tahirah et al. 2015 (23)	PRxUC	Exercise only	<3 weeks	?	Inpatient	Inpatient	Yes
Tang et al. (16)	LI-PR x HI-PR x UC	Exercise only	?	≥2x/week	Inpatient	Inpatient	Yes
Torres-Sánchez et al. 2014 (26)	PRxUC	Exercise only	<3 weeks	≥2x/week	Inpatient	Inpatient	Yes
Torres-Sánchez et al. 2016 (25)	PRxUC	Exercise only	<3 weeks	≥2x/week	Inpatient	Inpatient	Yes
Torres-Sánchez et al. 2017 (24)	PRxUC	Exercise only	<3 weeks	≥2x/week	Inpatient	Inpatient	Yes
Troosters et al. 2002 (40)	PRxUC	?	>12 weeks	?	After discharge	Outpatient	?
Troosters et al. 2010 (15)	PRxUC	Exercise only	<3 weeks	≥2x/week	Inpatient	Inpatient	Yes
Wu et al. 2015 (41)	PRxUC	?	?	?	?	?	?

Table Legend: PR: pulmonary rehabilitation program; UC: usual care; CT: Combined training; ET: Endurance training; LI-PR: low-intensity pulmonary rehabilitation; HI-PR: high-intensity pulmonary rehabilitation; ?: unclear

**Table 3.** Risk of bias summary: review authors' judgments about each risk of bias item for each included study

	Random sequence generation	Allocation concealment	Blinding of assessors (Quality of life)	Blinding of assessors (functional capacity)	Incomplete outcome data	Selective reporting	Other (peer-reviewed before published)
 Low Risk of Bias  High Risk of Bias  Unclear  Not Applicable							
Ali et al. 2014(12)							
Behnke et al. 2000 (17)							
Borges et al. 2014 (18)							
Daabis et al. 2017 (29)							
Deepak et al. 2014 (30)							
Eaton et al. 2009 (31)							
Ghanem et al. 2010 (32)							
Greening et al. 2014 (33)							
He et al. 2015 (13)							
Johnson-Warrington et al. 2016 (34)							
Kjærgaard 2020 (28)			 				
Kirsten et al. 1998 (19)							
Knaut et al. 2014 (20)							
Ko et al. 2011 (36)							
Ko et al. 2017 (35)							
Liao et al. 2015 (37)							
Man et al. 2004 (14)							
Murphy et al. 2005 (21)							
Probst et al. 2005 (22)							
Revitt 2018 (27)							
Seymour et al. 2010 (38)							
Song et al. 2014 (39)							
Tahirah et al							



Tang et al. (16)						
Torres-Sánchez et al. 2014 (26)						
Torres-Sánchez et al. 2016 (25)						
Torres-Sánchez et al. 2017 (24)						
Troosters et al. 2002 (40)						
Troosters et al. 2010 (15)						
Wu et al. 2015 (41)						

**Table 4.** Hospital readmission relative risk for each program characteristics

<b>Hospital Readmission Relative Risk for Program Mode</b>				
Study	Time point <sup>a</sup>	Relative Risk	95% CI	P value
<b>Exercise only vs Usual care</b>				
Borges 2014 (18)	1 month	3.6	0.2 to 82.7	0.43
Troosters 2010 (15)	6 months	1.2	0.7 to 2.4	0.43
<b>Exercise plus education vs Usual care</b>				
Eaton 2009 (31)	3 months	0.7	0.4 to 1.4	0.35
Man 2004 (14)	3 months	0.6	0.3 to 1.3	0.19
Seymour 2010 (38)	3 months	0.2	0.1 to 0.8	0.03
Johnson-Warrington 2016 (34)	3 months	0.8	0.5 to 1.4	0.50
Greening 2014 (33)	12 months	1.1	0.9 to 1.3	0.34
Ko 2011 (36)	12 months	1.2	0.7 to 2.1	0.44
Ko 2017 (35)	12 months	0.7	0.4 to 1.0	0.03
<b>Hospital Readmission Relative Risk for Program Length</b>				
<b>&lt; 3 weeks</b>				
Borges 2014 (18)	1 month	3.6	0.15 to 82.7	0.43
Troosters 2010 (15)	6 months	1.2	0.7 to 2.4	0.43
<b>3-12 weeks</b>				
Eaton 2009 (31)	3 months	0.7	0.4 to 1.4	0.35
Man 2004 (14)	3 months	0.6	0.3 to 1.3	0.19
Seymour 2010 (38)	3 months	0.2	0.1 to 0.8	0.03
Johnson-Warrington 2016 (34)	3 months	0.8	0.5 to 1.4	0.50
Greening 2014 (33)	12 months	1.1	0.9 to 1.3	0.34
Ko 2011 (36)	12 months	1.2	0.7 to 2.1	0.44
Ko 2017 (35)	12 months	0.7	0.4 to 1.0	0.03
<b>Hospital Readmission Relative Risk for Program Commencement</b>				
<b>Inpatient</b>				
Borges 2014 (18)	1 month	3.6	0.2 to 82.7	0.43
Eaton 2009 (31)	3 months	0.7	0.4 to 1.4	0.35
Troosters 2010 (15)	6 months	1.2	0.7 to 2.4	0.43
Greening 2014 (33)	12 months	1.1	0.9 to 1.3	0.34
<b>After discharge</b>				
Man 2004 (14)	3 months	0.6	0.3 to 1.3	0.19
Seymour 2010 (38)	3 months	0.2	0.1 to 0.8	0.03
Johnson-Warrington 2016 (34)	3 months	0.8	0.5 to 1.4	0.50
Ko 2011 (36)	12 months	1.2	0.7 to 2.1	0.44
Ko 2017 (35)	12 months	0.7	0.4 to 1.0	0.03
<b>Hospital Readmission Relative Risk for Program Location</b>				
<b>Inpatient</b>				
Borges 2014 (18)	1 month	3.6	0.2 to 82.7	0.43
Troosters 2010 (15)	6 months	1.3	0.7 to 2.4	0.43

	<b>Outpatient</b>			
Man 2004 (14)	3 months	0.6	0.3 to 1.3	0.19
Seymour 2010 (38)	3 months	0.2	0.1 to 0.8	0.03
Johnson-Warrington 2016 (34)	3 months	0.8	0.5 to 1.4	0.50
Ko 2011 (36)	12 months	1.2	0.7 to 2.1	0.44
Ko 2017 (35)	12 months	0.7	0.4 to 1.0	0.03
	<b>Combination of inpatient and outpatient program</b>			
Eaton 2009 (31)	3 months	0.7	0.4 to 1.4	0.35
Greening 2014 (33)	12 months	1.1	0.9 to 1.3	0.34
<b>Hospital Readmission Relative Risk for Program Supervision</b>				
	<b>Supervised</b>			
Borges 2014 (18)	1 month	3.6	0.2 to 82.7	0.43
Eaton 2009 (31)	3 months	0.7	0.4 to 1.4	0.35
Man 2004 (14)	3 months	0.6	0.3 to 1.3	0.19
Seymour 2010 (38)	3 months	0.2	0.1 to 0.8	0.03
Johnson-Warrington 2016 (34)	3 months	0.8	0.5 to 1.4	0.50
Troosters 2010 (15)	6 months	1.0	0.5 to 2.0	0.02
Ko 2011 (36)	12 months	1.2	0.7 to 2.1	0.44
Ko 2017 (35)	12 months	0.7	0.4 to 1.0	0.03
	<b>Supervised and unsupervised</b>			
Greening 2014 (33)	12 months	1.1	0.9 to 1.3	0.34

Table Legend: <sup>a</sup>Months after hospital discharge

**Table 5.** Mortality relative risk for each program characteristics

<b>Mortality Relative Risk for Program Mode</b>				
Study	Time point <sup>a</sup>	Relative risk	95% CI	P value
<b>Exercise training only vs Usual care</b>				
Borges 2014 (18)	1 month	0.2	0.01 to 4.7	0.23
Troosters 2010 (15)	1 month	3.3	0.1 to 76.8	0.43
Behnke (17)	6 months	1.0	0.1 to 15.0	1.0
<b>Exercise training plus education vs Usual care</b>				
Greening 2014 (33)	6 weeks	1.5	0.3 to 8.8	0.67
Eaton 2009 (31)	3 months	3.2	0.1 to 76.4	0.47
Man 2004 (14)	3 months	0.5	0.1 to 5.1	0.55
Seymour 2010 (38)	3 months	3.0	0.1 to 70.8	0.46
Johnson-Warrington 2016 (34)	3 months	0.1	0.01 to 2.7	0.10
Ko 2011 (36)	3 months	0.4	0.01 to 8.1	0.46
Greening 2014 (33)	12 months	2.1	1.1 to 4.0	0.03
Ko 2011 (36)	12 months	0.3	0.01 to 7.9	0.44
Ko 2017 (35)	12 months	0.8	0.3 to 2.0	0.65
<b>Mortality Relative Risk for Program Length</b>				
<b>&lt; 3 weeks</b>				
Borges 2014 (18)	1 month	0.2	0.01 to 4.7	0.23
Troosters 2010 (15)	1 month	3.3	0.1 to 76.8	0.43
<b>3-12 weeks</b>				
Greening 2014 (33)	6 weeks	1.5	0.3 to 8.8	0.67
Eaton 2009 (31)	3 months	3.2	0.1 to 76.4	0.47
Man 2004 (14)	3 months	0.5	0.1 to 5.1	0.55
Seymour 2010 (38)	3 months	3.0	0.1 to 70.8	0.46
Johnson-Warrington 2016 (34)	3 months	0.1	0.01 to 2.7	0.10
Ko 2011 (36)	3 months	0.4	0.01 to 8.1	0.46
Greening 2014 (33)	12 months	2.1	1.1 to 4.0	0.03
Ko 2011 (36)	12 months	0.3	0.01 to 7.9	0.44
<b>&gt;12 weeks</b>				
Behnke 2000 (17)	6 months	1.0	0.1 to 15.0	1.0
Troosters 2002 (40)	4 years	0.6	0.3 to 1.1	0.07
<b>Mortality Relative Risk for Program Commencement</b>				
<b>Inpatient</b>				
Greening 2014 (33)	6 weeks	1.5	0.3 to 8.9	0.67
Borges 2014 (18)	1 month	0.2	0.01 to 4.7	0.23
Troosters 2010 (15)	1 month	3.3	0.1 to 76.8	0.43
Eaton 2009 (31)	3 months	3.2	0.1 to 76.4	0.47
Behnke 2000 (17)	6 months	1.0	0.1 to 15.0	1.0
Greening 2014 (33)	12 months	2.1	1.1 to 4.0	0.03
Troosters 2002 (40)	4 years	0.6	0.3 to 1.1	0.07
<b>After discharge</b>				
Man 2004 (14)	3 months	0.5	0.05 to 5.1	0.55

Seymour 2010	3 months	3.0	0.13 to 70.8	0.46
Johnson-Warrington 2016	3 months	0.1	0.01 to 2.7	0.10
Ko 2011 (36)	3 months	0.4	0.01 to 8.1	0.46
Ko 2011 (36)	12 months	0.3	0.01 to 7.9	0.44
Ko 2017 (35)	12 months	0.8	0.33 to 2.0	0.65

#### **Mortality Relative Risk for Program Location**

<b>Inpatient</b>				
Borges 2014 (18)	1 month	0.2	0.01 to 4.7	0.23
Troosters 2010 (15)	1 month	3.3	0.1 to 76.8	0.43
<b>Outpatient</b>				
Man 2004 (14)	3 months	0.5	0.1 to 5.1	0.55
Seymour 2010 (38)	3 months	3.0	0.1 to 70.8	0.46
Johnson-Warrington 2016 (34)	3 months	0.1	0.01 to 2.7	0.10
Ko 2011 (36)	3 months	0.4	0.01 to 8.1	0.46
Ko 2011 (36)	12 months	0.3	0.01 to 7.9	0.44
Ko 2017 (35)	12 months	0.8	0.3 to 2.0	0.65
Troosters 2002 (40)	4 years	0.6	0.3 to 1.1	0.07
<b>Combination of inpatient and outpatient program</b>				
Eaton 2009 (31)	3 months	3.2	0.1 to 76.4	0.47
Behnke 2000 (17)	6 months	1.0	0.1 to 15.0	1.0
Greening 2014 (33)	6 weeks	1.5	0.3 to 8.8	0.67
Greening 2014 (33)	12 months	2.1	1.1 to 4.0	0.03

#### **Mortality Relative Risk for Program Supervision**

<b>Supervised</b>				
Borges 2014 (18)	1 month	0.2	0.01 to 4.7	0.23
Troosters 2010 (15)	1 month	3.3	0.1 to 76.8	0.43
Eaton 2009 (31)	3 months	3.2	0.1 to 76.4	0.47
Man 2004 (14)	3 months	0.5	0.1 to 5.1	0.55
Seymour 2010 (38)	3 months	3.0	0.1 to 70.8	0.46
Johnson-Warrington 2016 (34)	3 months	0.1	0.01 to 2.7	0.10
Ko 2011 (36)	3 months	0.4	0.01 to 8.1	0.46
Behnke 2000 (17)	6 months	1.0	0.1 to 15.0	1.0
Ko 2011 (36)	12 months	0.3	0.01 to 7.9	0.44
Ko 2017 (35)	12 months	0.8	0.3 to 2.0	0.65
<b>Supervised and unsupervised</b>				
Greening 2014 (33)	6 weeks	1.5	0.3 to 8.8	0.67
Greening 2014 (33)	12 months	2.1	1.1 to 4.0	0.03

Table Legend: <sup>a</sup>Time after hospital discharge

## 4.4 Supplemental Material

### Supplemental Digital Content A – Search strategy model

#### MEDLINE STRATEGY

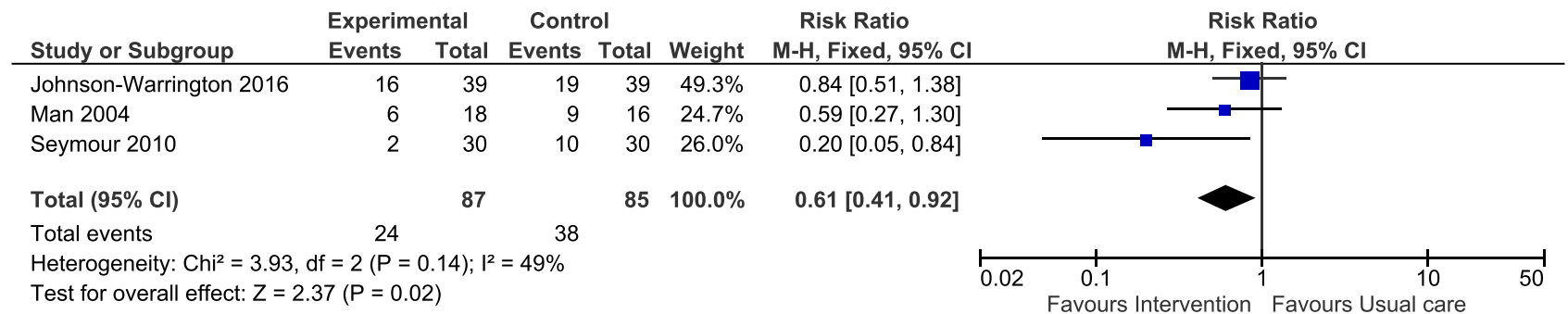
```
1   exp Pulmonary Disease, Chronic Obstructive/
2   exp Lung Diseases, Obstructive/
3   Chronic obstructive pulmonary disease.mp.
4   chronic obstructive lung disease.mp.
5   COPD.mp.
6   Pulmonary emphysema.mp.
7   Pulmonary Emphysema/
8   Emphysema*.mp.
9   ((chronic airflow or chronic airway or chronic lung or chronic bronchopulmonary or chronic
10  pulmonary or chronic respiratory) adj3 obstruct*).mp.
11  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
12  exp Rehabilitation/
13  (Rehabilitation or physiotherap* or physical therap* or Kinesiotherap*).mp.
14  exp Physical Therapy Modalities/
15  (Pulmonar* or respiratory) adj2 Rehab*.mp.
16  exp Exercise Movement Techniques/
17  exp Exercise/
18  Chest physio*.mp.
19  (Chest adj3 exercis*).mp.
20  (comprehensive adj1 therap*).mp.
21  exp Physical Endurance/
22  resistance Training/
23  (chest adj2 therap*).mp.
24  (exercise* or endurance or resistance training).mp.
25  ((strength or aerobic* or flexibility or stretch*) adj2 (exercis* or training or routine*)).mp.
26  (home-based adj2 (rehab* or exercise*)).mp.
27  (early adj2 (rehab* or exercise*)).mp.
28  exp Breathing Exercises/
29  Breathing exercises.mp.
30  muscle training.mp.
31  Exercise Test/
32  11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or
33  27 or 28 or 29 or 30
34  10 and 31
35  exp Pulmonary Disease, Chronic Obstructive/rh [Rehabilitation]
36  (COPD adj4 (exercise* or rehab* or therapy or physiotherap*)).mp.
37  32 or 33 or 34
38  randomized controlled trial.pt.
39  controlled clinical trial.pt.
40  randomized.ab.
41  placebo.ab.
42  clinical trials as topic.sh.
43  randomly.ab.
```

42	trial.ti.
43	36 or 37 or 38 or 39 or 40 or 41 or 42
44	exp animals/ not humans.sh.
45	43 not 44
46	35 and 45

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM MODE** (*Exercise training only or Exercise training plus education*)

### *Hospital Readmission*



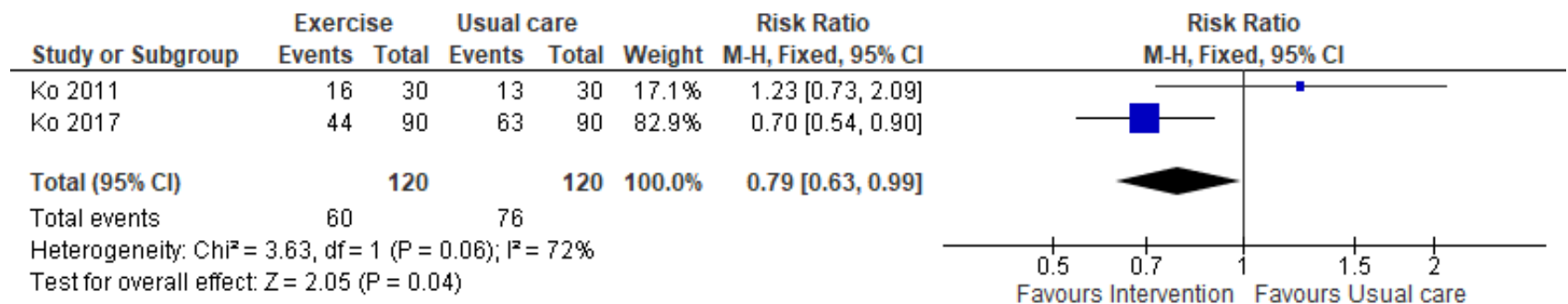
**Figure B1.** Metanalysis of hospital readmission at 3 months for studies that delivered exercise training plus education.



## Supplemental Digital Content B – Primary outcomes forest plots

*PROGRAM MODE (Exercise training only or Exercise training plus education)*

### *Hospital Readmission*

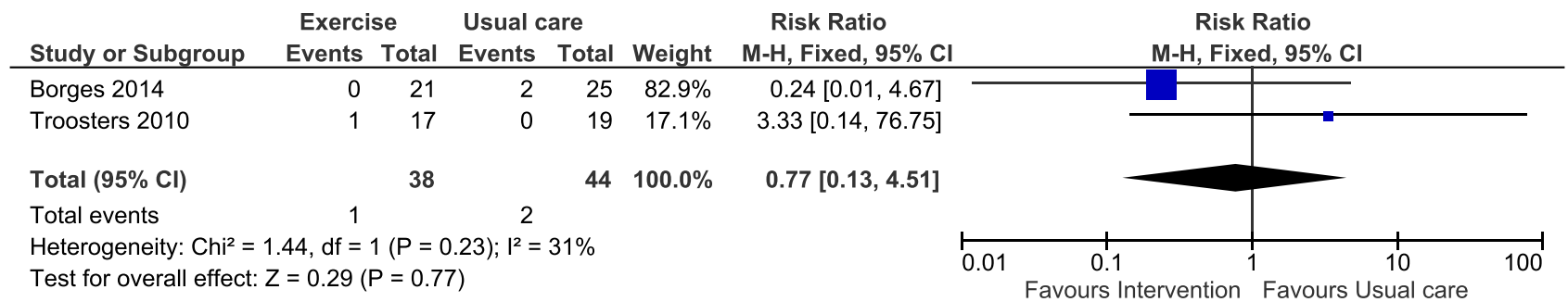


**Figure B2.** Metanalysis of hospital readmission at 12 months for studies that delivered exercise training plus education

## Supplemental Digital Content B – Primary outcomes forest plots

*PROGRAM MODE (Exercise training only or Exercise training plus education)*

### *Mortality*

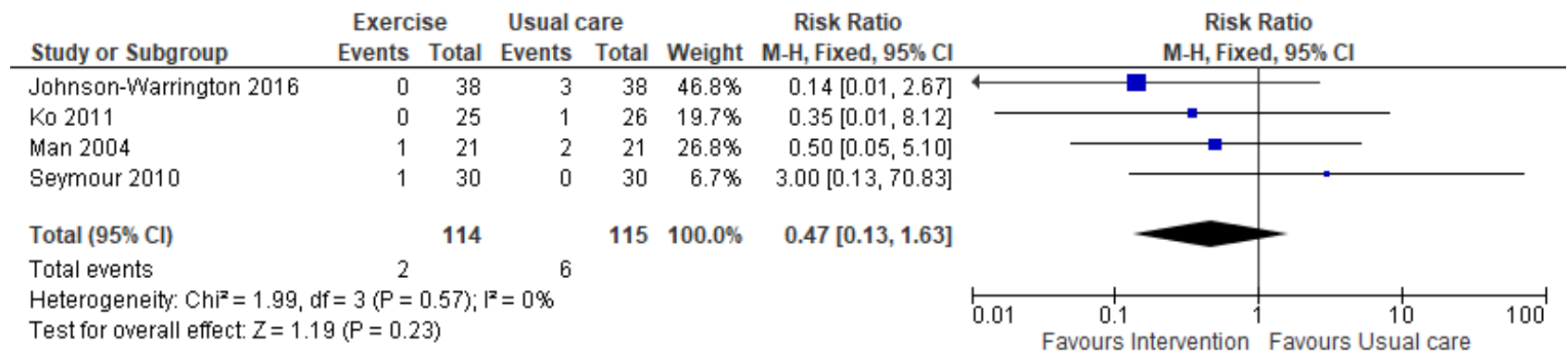


**Figure B3.** Metanalysis of mortality relative risk for studies that delivered exercise training only one months after discharge

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM MODE** (*Exercise training only or Exercise training plus education*)

### Mortality

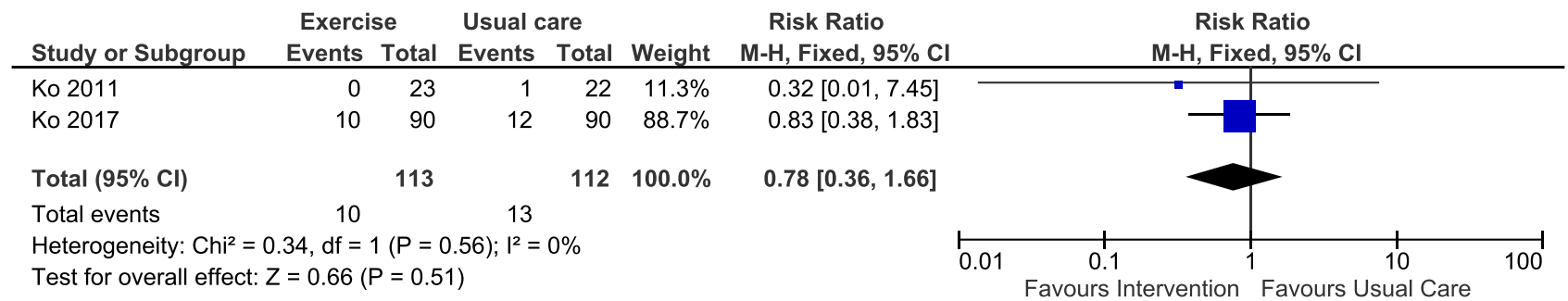


**Figure B4.** Metanalysis of mortality relative for studies that delivered exercise training plus education at 3 months

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM MODE** (*Exercise training only or Exercise training plus education*)

### Mortality

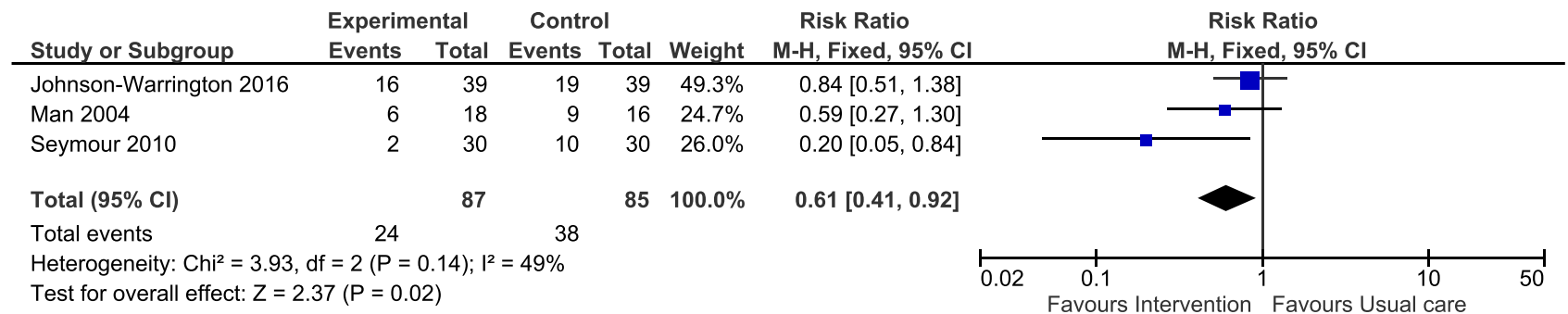


**Figure B5.** Metanalysis of mortality relative risk for studies that delivered exercise training plus education at 12 months

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM LENGTH** (<3 weeks; 3-12 weeks or >12 weeks)

### *Hospital readmission*

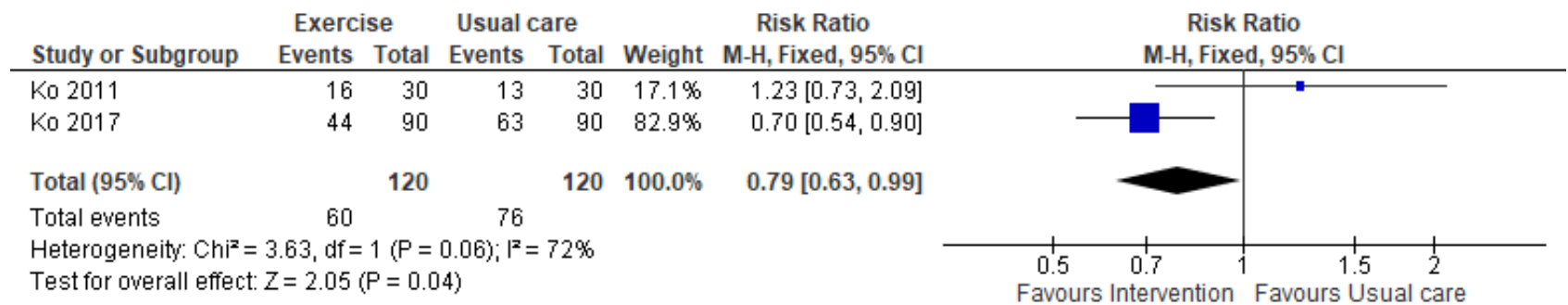


**Figure B6.** Metanalysis of hospital readmission relative risk at 3 months for studies that delivered program length between 3 and 12 weeks

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM LENGTH** (<3 weeks; 3-12 weeks or >12 weeks)

### *Hospital readmission*

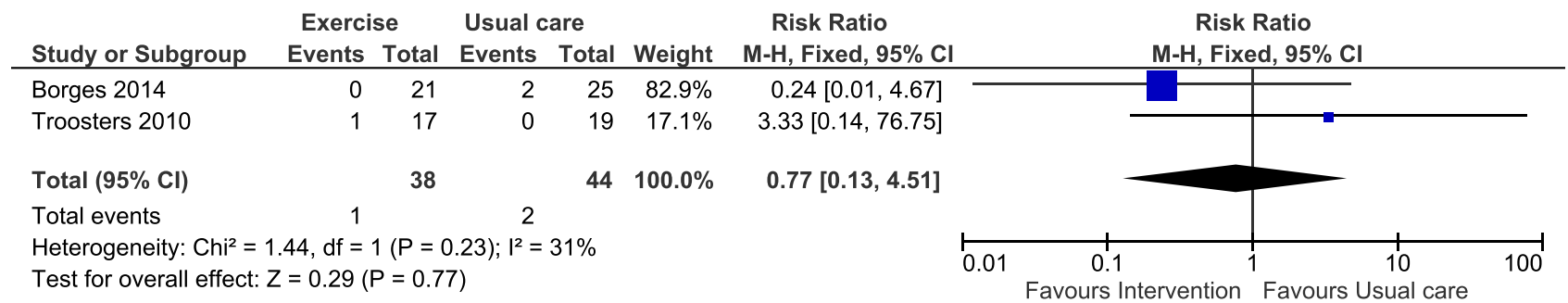


**Figure B7.** Metanalysis of hospital readmission relative risk at 12 months for studies that delivered program length between 3 and 12 weeks

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM LENGTH (<3 weeks; 3-12 weeks or >12 weeks)**

### Mortality

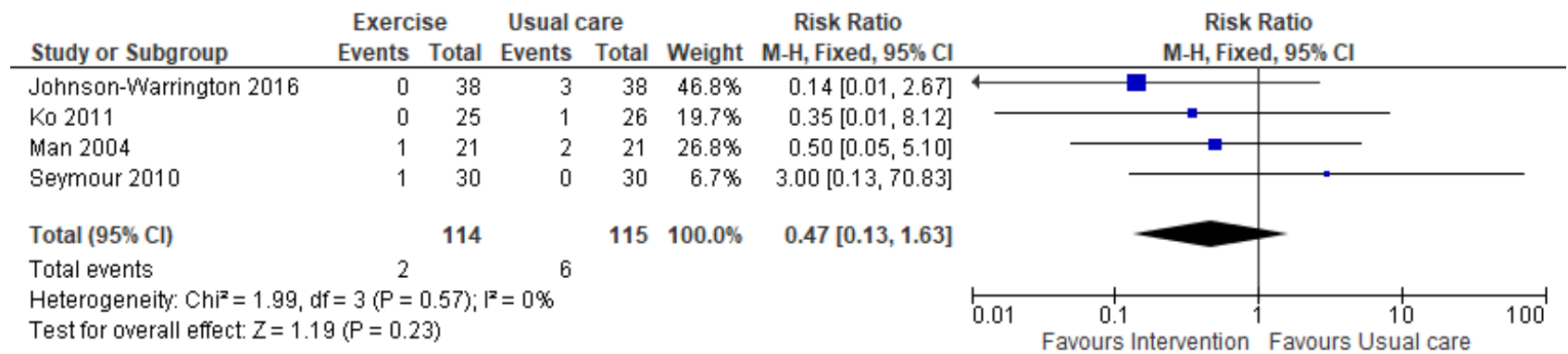


**Figure B8.** Metanalysis of mortality relative risk at 1 months after discharge for studies that delivered program length of <3 weeks

## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM LENGTH** (<3 weeks; 3-12 weeks or >12 weeks)

### Mortality



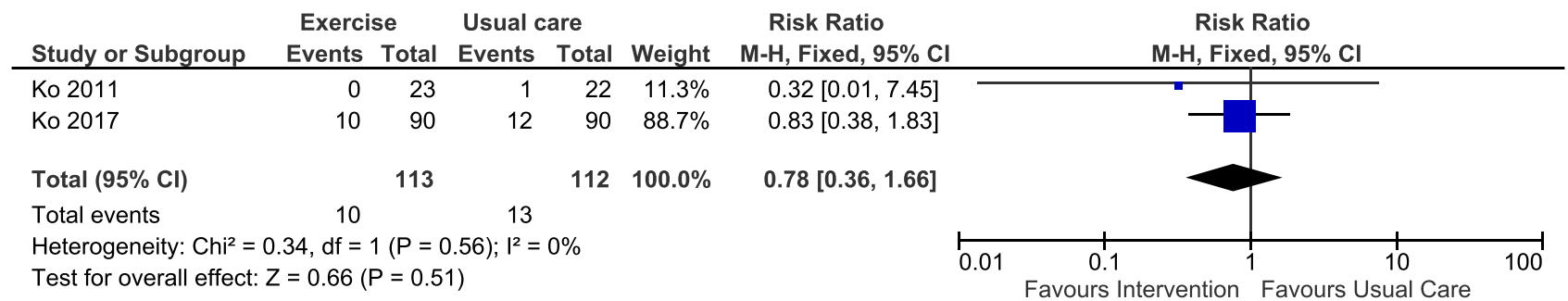
**Figure B9.** Metanalysis of mortality relative risk at 3 months after discharge for studies that delivered program length between 3 and 12 weeks



## Supplemental Digital Content B – Primary outcomes forest plots

**PROGRAM LENGTH** (<3 weeks; 3-12 weeks or >12 weeks)

### Mortality

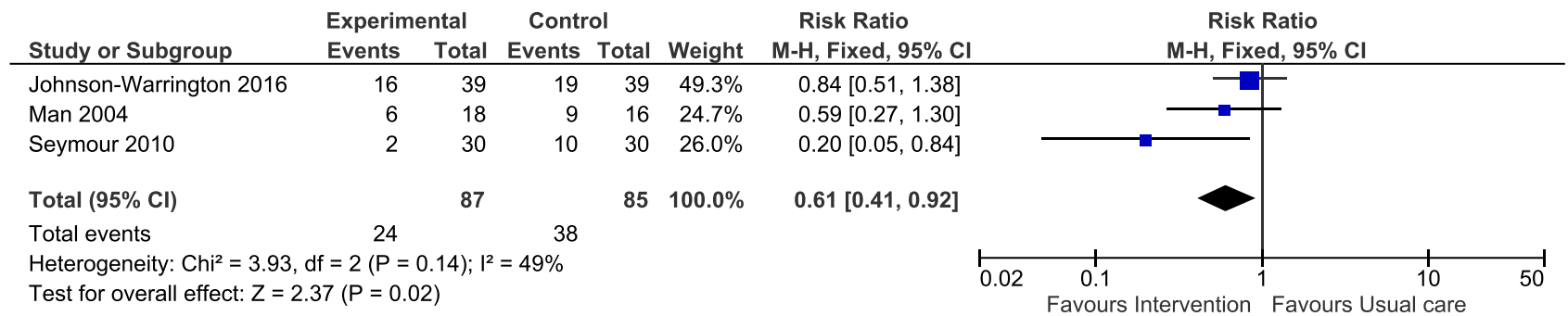


**Figure B10.** Metanalysis of mortality relative risk at 12 months after discharge for studies that delivered program length between 3 and 12 weeks

## Supplemental Digital Content B – Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Hospital Readmission*

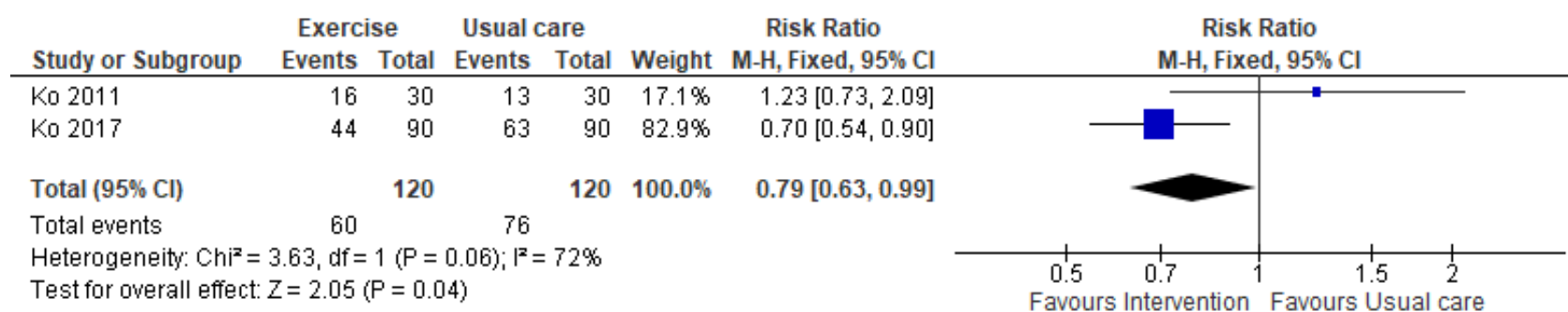


**Figure B11.** Metanalysis of hospital readmission relative risk at 3 months for studies with program starting after discharge

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Hospital Readmission*

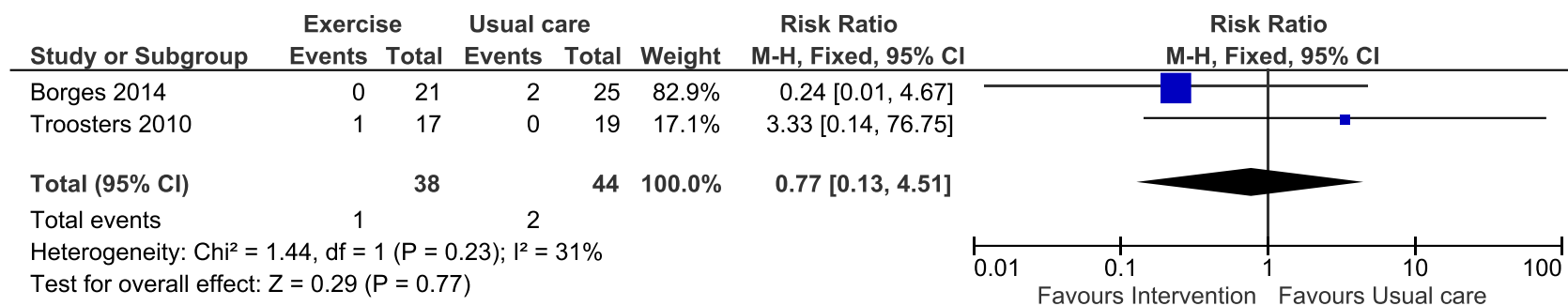


**Figure B12.** Metanalysis of hospital readmission relative risk at 12 months for studies with program starting after discharge

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Mortality*



**Figure B13.** Metanalysis of mortality relative risk at 1 months after discharge for studies with program starting during inpatient period

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Mortality*

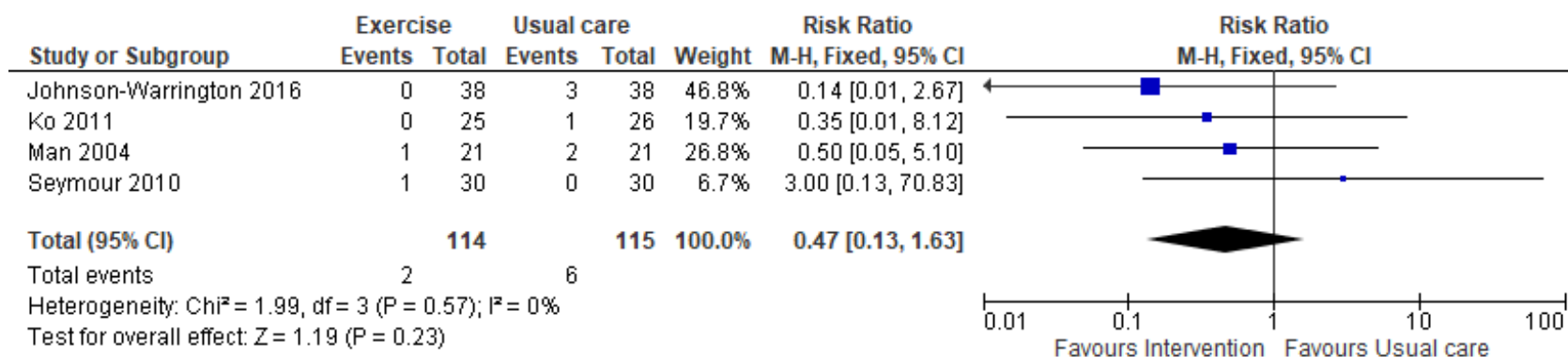


**Figure B14.** Metanalysis of mortality relative risk at end program for studies with program starting after discharge

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Mortality*

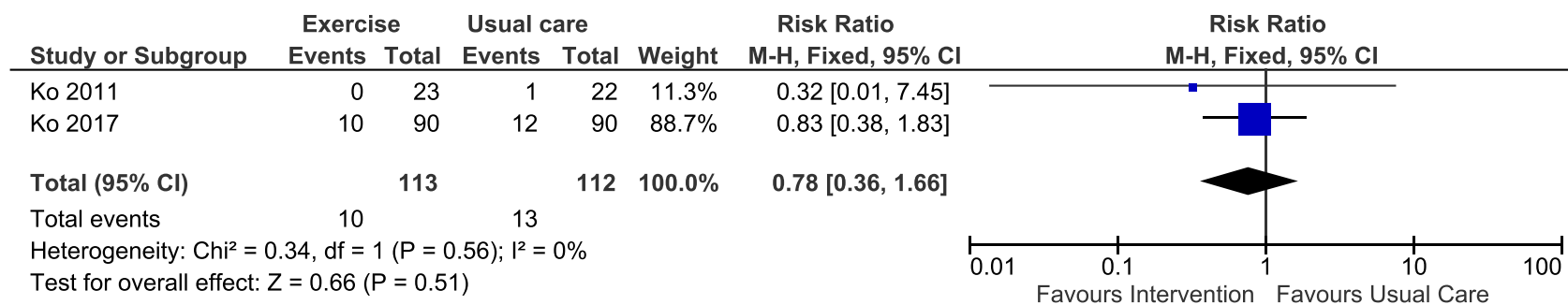


**Figure B15.** Metanalysis of mortality relative risk at 3 months after discharge for studies with program starting after discharge

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM COMMENCEMENT (Inpatient or After discharge)*

#### *Mortality*



**Figure B16.** Metanalysis of mortality relative risk at 12 months after discharge for studies with program starting after discharge

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM LOCATION (Inpatient, outpatient, combination of inpatient and outpatient)*

#### *Hospital Readmission*



**Figure B17.** Metanalysis of hospital readmission relative risk at 3 months for studies that delivered programs at a centre



## Supplemental Digital Content B– Primary outcomes forest plots

**PROGRAM LOCATION** (*Inpatient, outpatient, combination of inpatient and outpatient*)

### *Hospital Readmission*

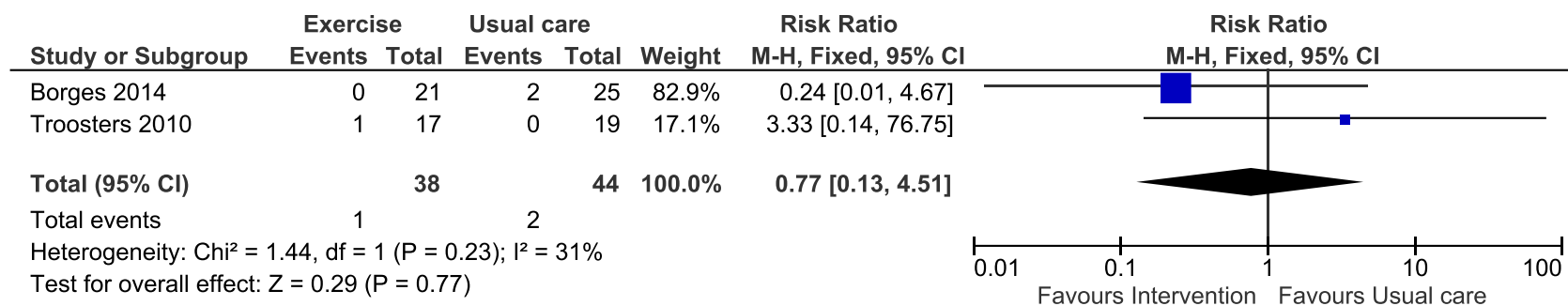


**Figure B18.** Metanalysis of hospital readmission relative risk at 12 months for studies that delivered programs at a centre

## Supplemental Digital Content B– Primary outcomes forest plots

**PROGRAM LOCATION** (*Inpatient, outpatient, combination of inpatient and outpatient*)

### Mortality

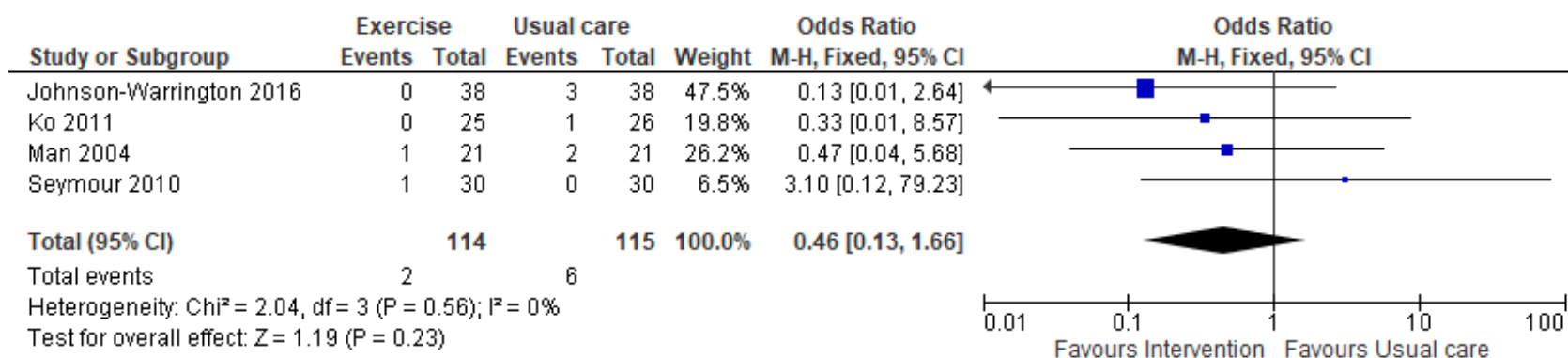


**Figure B19.** Metanalysis of mortality relative risk at 1 months after discharge for studies that delivered program at the hospital

## Supplemental Digital Content B– Primary outcomes forest plots

**PROGRAM LOCATION** (*Inpatient, outpatient, combination of inpatient and outpatient*)

### Mortality

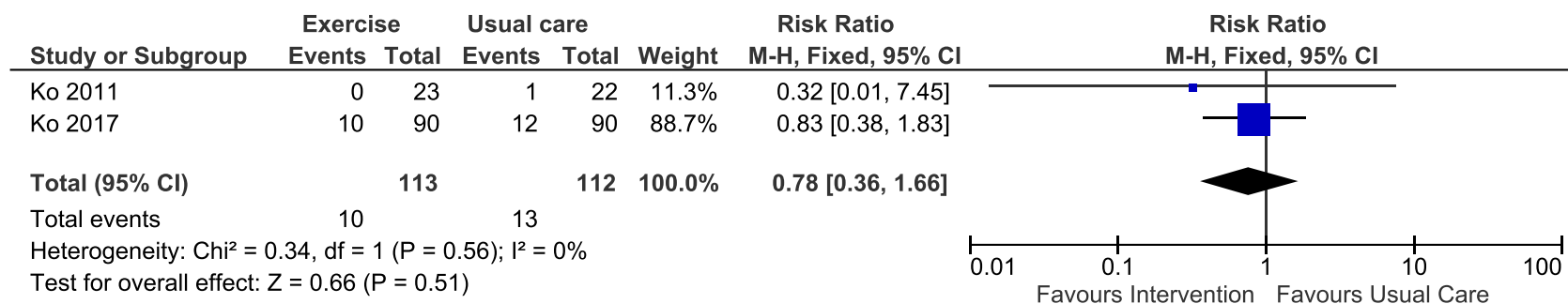


**Figure B20.** Metanalysis of mortality relative risk at 3 months for studies that delivered program centre-based

## Supplemental Digital Content B– Primary outcomes forest plots

**PROGRAM LOCATION** (*Inpatient, outpatient, combination of inpatient and outpatient*)

### Mortality



**Figure B21.** Metanalysis of mortality relative risk at 12 months for studies that delivered program centre-based and at 12 months

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM SUPERVISION (Supervised, unsupervised)*

#### *Hospital Readmission*

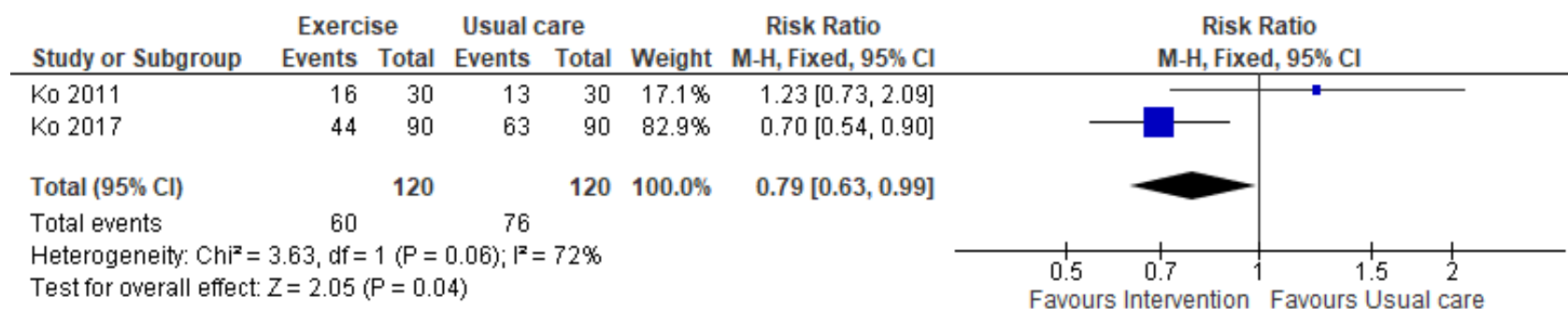


**Figure B22.** Metanalysis of hospital readmission relative risk at 3 months for studies that delivered supervised

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM SUPERVISION (Supervised, unsupervised)*

#### *Hospital Readmission*

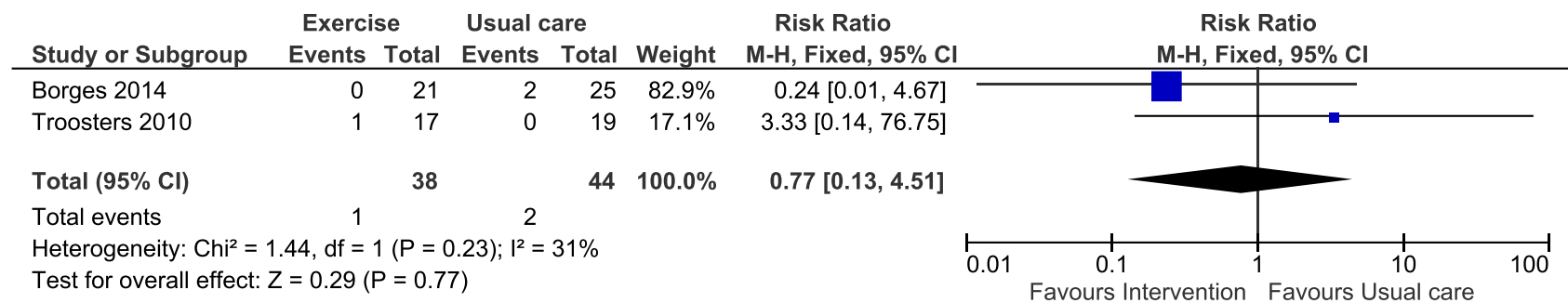


**Figure B23.** Metanalysis of hospital readmission relative risk at 12 months for studies that delivered supervised program

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM SUPERVISION (Supervised, unsupervised)*

### *Mortality*

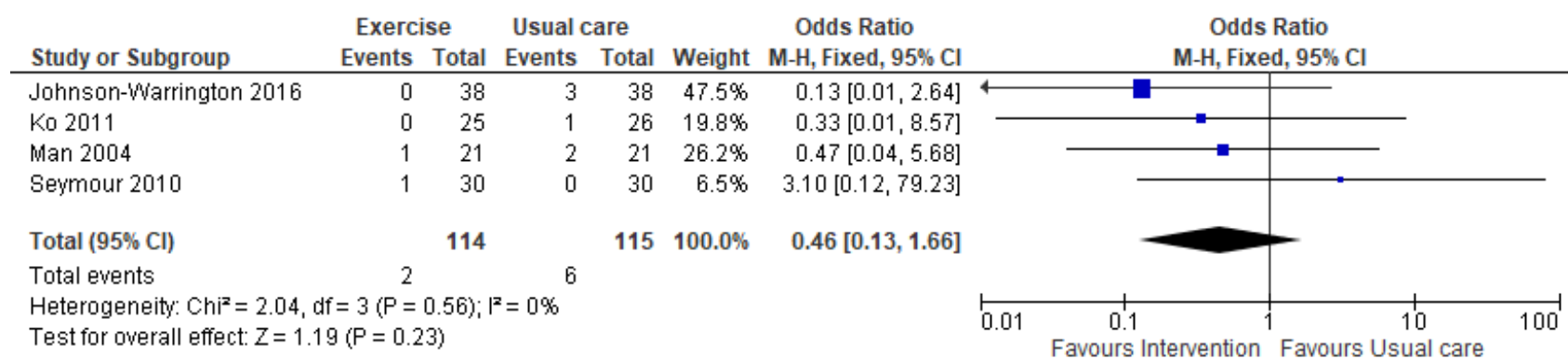


**Figure B24.** Metanalysis of mortality relative risk at 1 months after discharge for studies that delivered supervised program

## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM SUPERVISION (Supervised, unsupervised)*

### *Mortality*



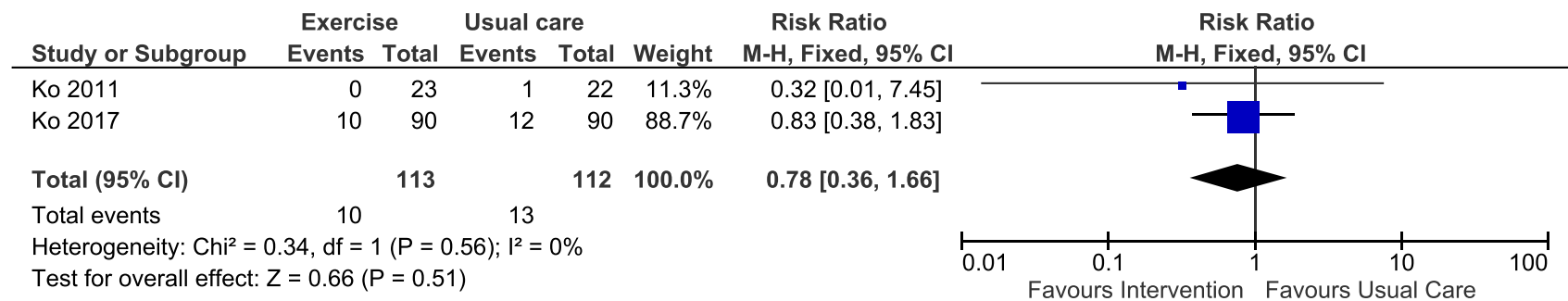
**Figure B25.** Metanalysis of mortality relative risk at 3 months after discharge for studies that delivered supervised program



## Supplemental Digital Content B– Primary outcomes forest plots

### *PROGRAM SUPERVISION (Supervised, unsupervised)*

### *Mortality*



**Figure B26.** Metanalysis of mortality relative risk at 12 months after discharge for studies that delivered supervised program

***PROGRAM MODE (EXERCISE TRAINING ONLY OR EXERCISE TRAINING PLUS EDUCATION)***

***Functional capacity***

A total of 17 included studies measured the six-minute walk distance (6MWD), seven delivered exercises training only <sup>1-7</sup> and ten delivered exercises training plus education <sup>8-17</sup>. The average change in 6MWD exceeded the minimum important distance (Table C1) regardless of whether the program was exercise alone or exercise in combination with education. Thus, both program modes seemed to be effective in improving functional capacity.

From the exercise training only studies, three measured functional capacity using the 6MWD, had a similar intervention and could be pooled in a meta-analysis. The results of this meta-analysis favoured exercise training only, when undertaken during the hospital stay, as compared to usual care (Mean Difference 191.0 metres; 95% CI 114.1 to 268.1;  $i^2=60\%$ ) (Figure C1) <sup>1,2,18</sup>. Only one study of exercise training alone measured functional capacity using incremental shuttle walk test (ISWT) with no significant difference in ISWT distance when compared usual care (Table C2) <sup>19</sup>.

For studies that delivered exercise training plus education, combined results for 6MWD favoured exercise training plus education compared to usual care at end of intervention (2 months) (Mean Difference 51.6 metres; 95% CI 1.0 to 102.1;  $i^2=76\%$ ) (Figure C2) <sup>12,17</sup>;

however this difference not significant in studies when assessed at end of intervention (3 months) (Mean Difference 54.9 metres; 95% CI -26.3 to 136.1;  $i^2=80\%$ ) (Figure C3) <sup>9,15</sup>.

**Table C1.** Functional capacity (6MWD) difference between groups from studies that delivered exercise training only or exercise training plus education compared to usual care

<b>Functional capacity for exercise training only and exercise training plus education groups – 6MWD (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Exercise training only vs Usual care</b>				
Borges 2014 <sup>1</sup>	At discharge	139.0	55.0 to 223.0	0.003
Kirsten 1998 <sup>2</sup>	At discharge	165.0	67.1 to 262.9	0.003
Knaut 2014 <sup>3</sup>	1 months <sup>b</sup>	83.0	0.1 to 166.0	0.08
Troosters 2010 <sup>5</sup>	1 months <sup>b</sup>	27.0	-4.4 to 79.0	0.3
Behnke 2000 <sup>18</sup>	6 months	259.0	185.3 to 332.7	<0.0001
<b>Exercise training plus education vs Usual care</b>				
He 2015 <sup>13</sup>	At discharge	17.3	9.1 to 25.5	<0.0001
Dabbis 2017 <sup>9</sup>	2 months	98.5	40.8 to 156.2	0.002
Ko 2011 <sup>15</sup>	3 months	15.5	-29.0 to 60.1	0.5
Ghanem 2010 <sup>12</sup>	2 months	73.2	9.8 to 92.3	<0.0001
Song 2014 <sup>17</sup>	2 months	20.8	-26.1 to 67.7	0.4
Ali 2014 <sup>8</sup>	3 weeks <sup>b</sup>	0.5	0.0 to 1.0	0.05
Deepak 2014 <sup>10</sup>	3 months	80.5	31.5 to 129.4	0.002
Eaton 2009 <sup>11</sup>	3 months	3.0	-50.6 to 55.0	0.9
Ko 2011 <sup>15</sup>	12 months	36.0	-23.0 to 95.0	0.2
Ko 2017 <sup>14</sup>	12 months <sup>b</sup>	12.5	-6.9 to 31.9	0.2

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked. 6MDW: six-minute walk distance; m: metres.

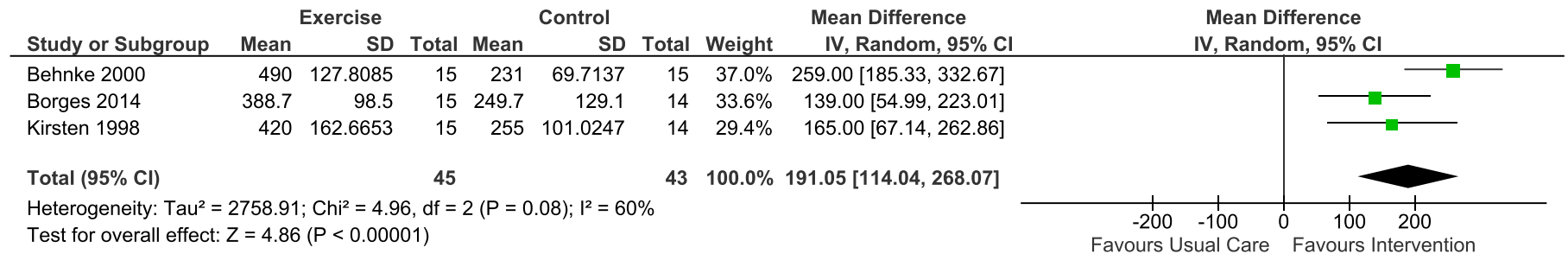
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups

**Table C2.** Functional capacity (ISWT) difference between groups for studies that delivered exercise training only or exercise training plus education compared to usual

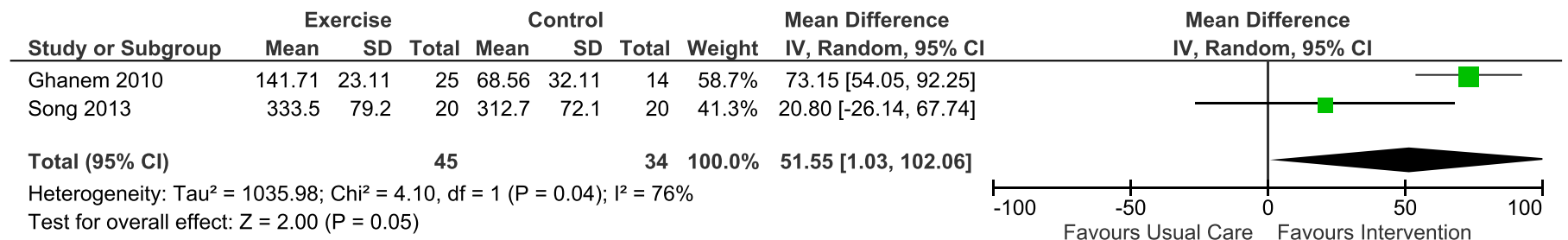
<b>Functional capacity for exercise training only and exercise training plus education groups – ISWT (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Exercise training only vs Usual care</b>				
Murphy 2005 <sup>19</sup>	6 weeks	89.0	-25.9 to 203.9	0.1
<b>Exercise training plus education vs Usual care</b>				
Kjaergaard 2020 <sup>20</sup>	2 months	33.9	4.2 to 63.7	0.02
Man 2004 <sup>21</sup>	3 months	60.0 <sup>c</sup>	26.6 to 93.4	0.0002
Seymour 2010 <sup>22</sup>	3 months	33.0	-30.8 to 96.8	0.3
Johnson-Warrington 2016 <sup>23</sup>	3 months <sup>b</sup>	-7.5	-67.4 to 52.4	0.8

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked. ISWT: incremental shuttle walk test; m: metres.

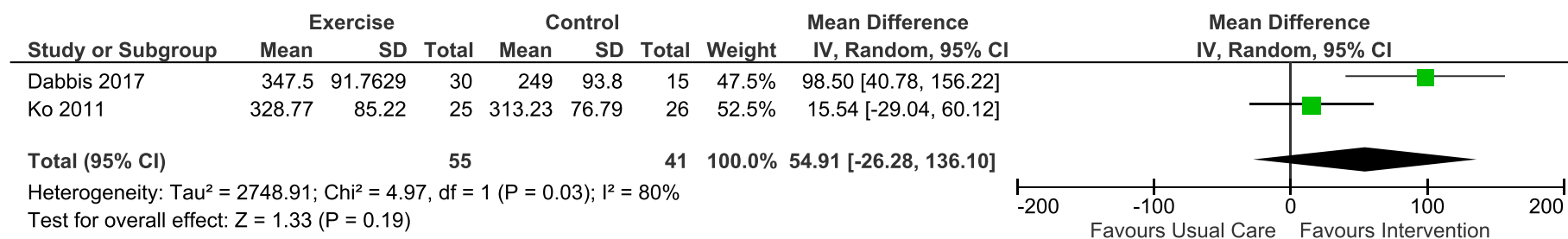
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C1.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that delivered exercise training only one month after discharge



**Figure C2.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that delivered exercise training plus education assessed at 2 months



**Figure C3.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that delivered exercise training plus education assessed at 3 months

### ***Health related quality of life***

The average of change in health-related quality of life (HRQoL) following pulmonary rehabilitation for both programs of exercise training alone or exercise training in addition to education were clinically important. This suggests both program modes seemed to be effective in improving HRQoL.

#### ***Chronic Respiratory Questionnaire (CRQ)***

One study of exercise training only assessed HRQoL using the CRQ. Behnke et al.<sup>18</sup> showed a significant difference between the exercise training intervention group and usual care at 3 months after hospital discharge for the dyspnoea, fatigue and mastery domains; and on the emotion domain at 6 months after discharge (Table C3)<sup>18</sup>.

Four studies of exercise training plus education used the CRQ to assess HRQoL. Three of these studies could be pooled in a metanalysis<sup>21-23</sup>. The pooled results favoured the intervention in all domains except mastery of disease at 3 months (Std. Mean Difference; Dyspnoea: 0.8; 95% CI 0.5 to 1.1;  $i^2=0\%$ / Fatigue: 0.4; 95% CI 0.0 to 0.7;  $i^2=0\%$ / Emotion: 0.5; 95% CI 0.1 to 0.8;  $i^2=0\%$ ) (Figure C4)<sup>21-23</sup>.

#### ***Saint George Respiratory Questionnaire (SGRQ)***

Two studies that delivered exercise training only assessed HRQoL using SGRQ. The results could not be pooled due to heterogeneous interventions and timepoint measured and are presented in Table C4.

From five studies delivered exercises training plus education, three could be pooled in a metanalysis with results favouring the exercise training plus education in most domains

except symptoms (Mean Difference; Activities: -10.3; 95% CI -17.0 to 3.8;  $i^2=0\%$ /

Impacts: -10.3; 95% CI -20.4 to 0.2;  $i^2=66\%$ / Total: -9.2; 95% CI -16.3 to -2.0;  $i^2=47\%$ )

(Figure C5) <sup>21-23</sup>.



**Table C3.** Health-related quality of life (CRQ) for a study that compared exercise training only and usual care at 3 and 6 months after discharge

<b>Health-related quality of Life for exercise training only and exercise training plus education groups – CRQ</b>					
Study	Time point <sup>a</sup>	Domain	Intervention (n=15)	Usual care (n=15)	P value between groups
<b>Exercise training only vs Usual care</b>					
Behnke 2000 <sup>18</sup>	3 months	dyspnoea	22.1±1.4	15.7±1.6	<0.01
Behnke 2000 <sup>18</sup>		fatigue	20.7±1.1	15.7±1.2	<0.01
Behnke 2000 <sup>18</sup>		mastery	23.5±1.2	18.9±1.2	<0.01
Behnke 2000 <sup>18</sup>	6 months	emotion	42.1±1.7	31.0±2.5	<0.001

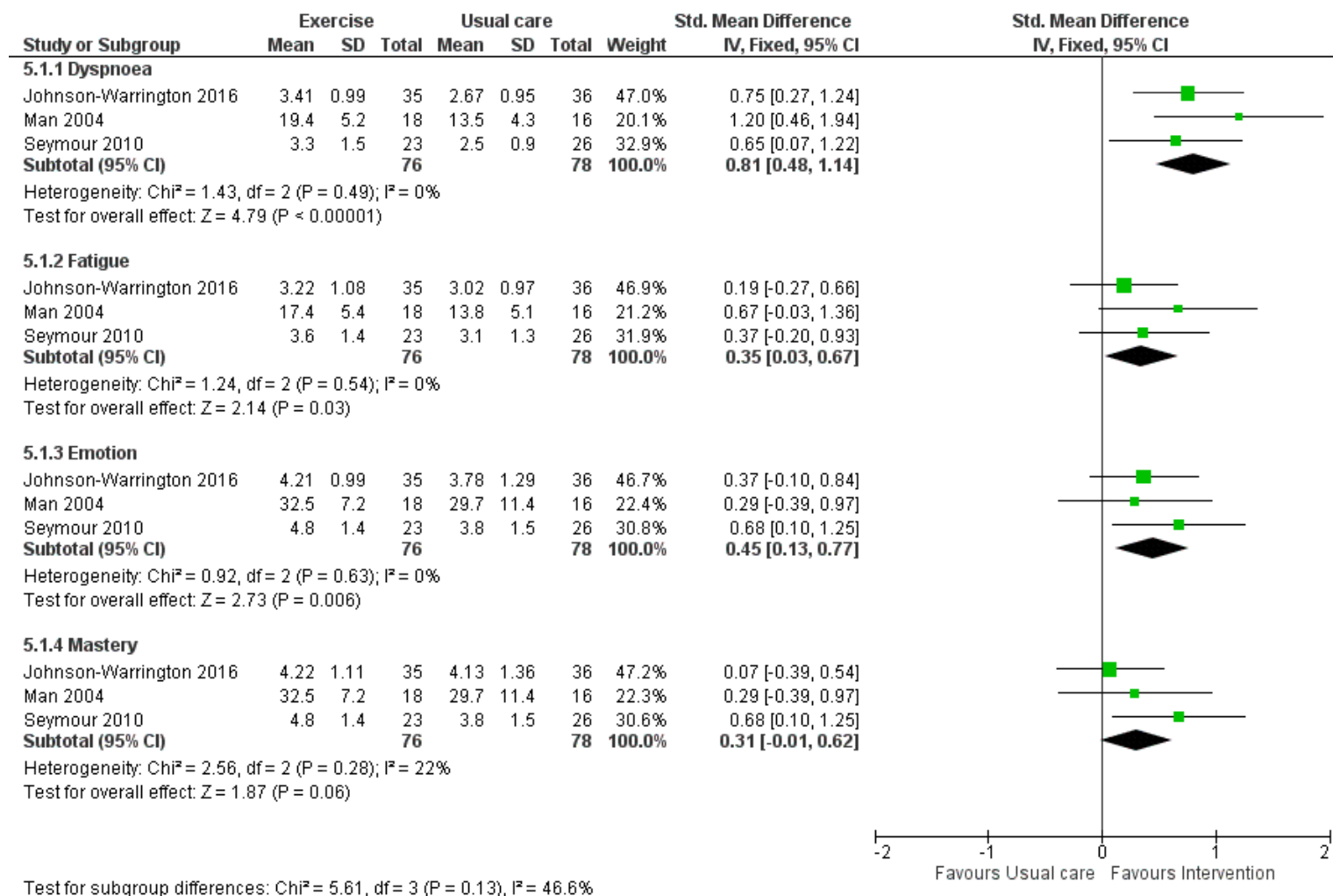
Table legend: <sup>a</sup>Time after hospital discharge. Data presented are Mean±SEM.

**Table C4.** Health-related quality of life (SGRQ) for studies that compared exercise training only or exercise training plus education to usual care

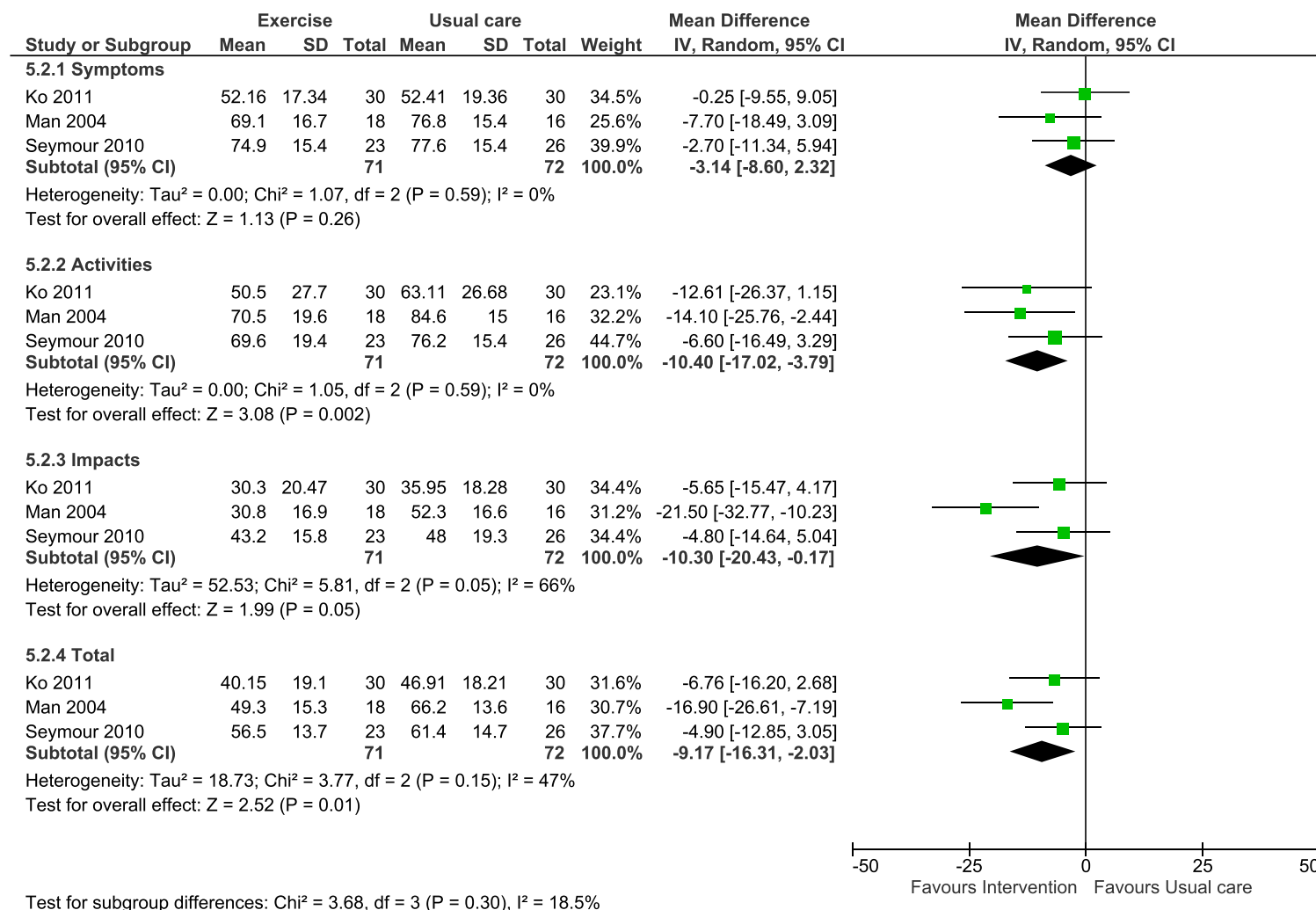
<b>Health-related quality of Life for exercise training only and exercise training plus education groups – SGRQ total</b>				
Study	Time point <sup>a</sup>	Mean difference between groups (m)	95% CI	P value
<b>Exercise training only vs Usual care</b>				
Borges 2014 <sup>1</sup>	At discharge	-8.3 <sup>c</sup>	-20.2 to 3.6	0.2
Borges 2014 <sup>1</sup>	1 months	-23.4 <sup>c</sup>	-31.8 to -14.9	<0.0001
Murphy 2005 <sup>21</sup>	6 weeks	-4.1	-18.3 to 10.1	0.6
<b>Exercise training plus education vs Usual care</b>				
Song 2014 <sup>17</sup>	2 months	-24.5	-29 to -20.0	<0.0001
Deepak 2014 <sup>10</sup>	3 months	-23.4	-31.8 to -14.9	<0.0001
Ko 2017 <sup>14</sup>	12 months	-6.8 <sup>c</sup>	-11.1 to -2.5	0.002

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked.

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C4.** Metanalysis of health-related quality of life (CRQ) standardised mean difference between groups for studies of exercise training plus education at end intervention



**Figure C5.** Metanalysis of health-related quality of life (SGRQ) mean difference between groups for studies that delivered exercise training plus education at end intervention

### *Adverse events*

Studies which presented data for adverse events reported no adverse events during the interventions <sup>5,8,13,21</sup>. The only study that reported adverse events during the study delivered exercise training only <sup>4</sup>. Tang et al. <sup>4</sup> reported 13 adverse events, seven non-serious, five nonserious study related and not expected and one serious and study related <sup>4</sup>. The study reported that a participant with previous history of heart condition developed chest pain that lasted two minutes while exercising in low-intensity; the adverse event was resolved within one hour without medical intervention <sup>4</sup>.

## ***PROGRAM LENGTH (<3 WEEKS; 3-12 WEEKS OR >12 WEEKS)***

### ***Functional capacity***

Five studies delivered an exercise program less than 3 weeks in duration <sup>1-3,5,13</sup>; seven studies delivered programs of 3-12 weeks duration <sup>8-12,14,15,17</sup>; and one study contained a pulmonary rehabilitation program of longer than 12 weeks <sup>18</sup>. The average change in 6MWD generally exceeded the minimum important difference for all program lengths (Table C5).

Of studies that delivered a pulmonary rehabilitation program less than 3 weeks in duration, results favoured the intervention group at discharge from hospital, but were not significant (Mean Difference 99.3 metres; 95% CI -8.7 to 207.3;  $i^2=88\%$ ) (Figure C6) <sup>1,2,13</sup>. One month after hospital discharge the difference in 6MWD between groups ranged from 83 to 27 metres favouring the intervention group <sup>3,5</sup>. A program delivered in hospital during 3 weeks also reported results favouring exercise group at end program with significant change between groups at three weeks (Table C5) <sup>8</sup>.

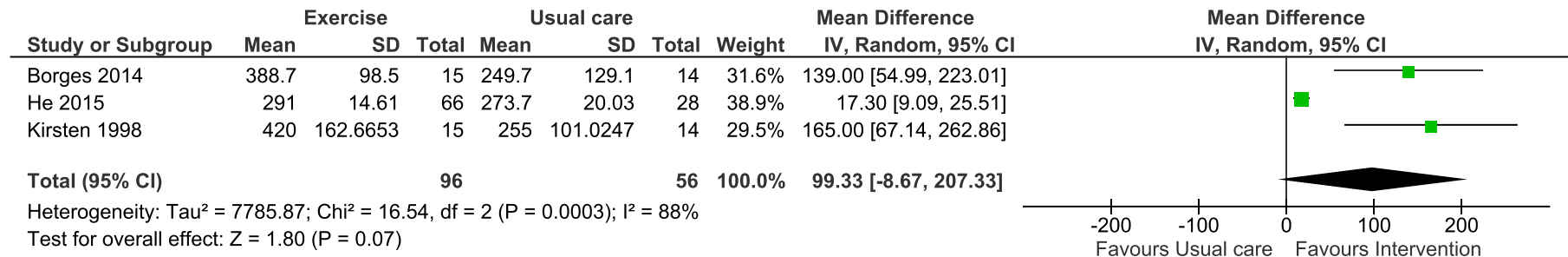
For studies with a program duration of between 3 and 12 weeks the improvement in 6MWD favoured pulmonary rehabilitation (Mean Difference 54.9 metres; 95% CI -26.3 to 136.1;  $i^2=80\%$ ) (Figure C7) <sup>9,15</sup>. Two studies delivered education during inpatient period and an exercise program afterwards, with a total length of two months <sup>12,17</sup>. Results of these two studies favoured intervention group at end intervention for 6MWD (Mean Difference 51.6 metres; 95% CI 1.0 to 102.1;  $i^2=76\%$ ) (Figure C8) <sup>12,17</sup>.

**Table C5.** Functional capacity difference assessed by 6MWD between groups from studies based on program length

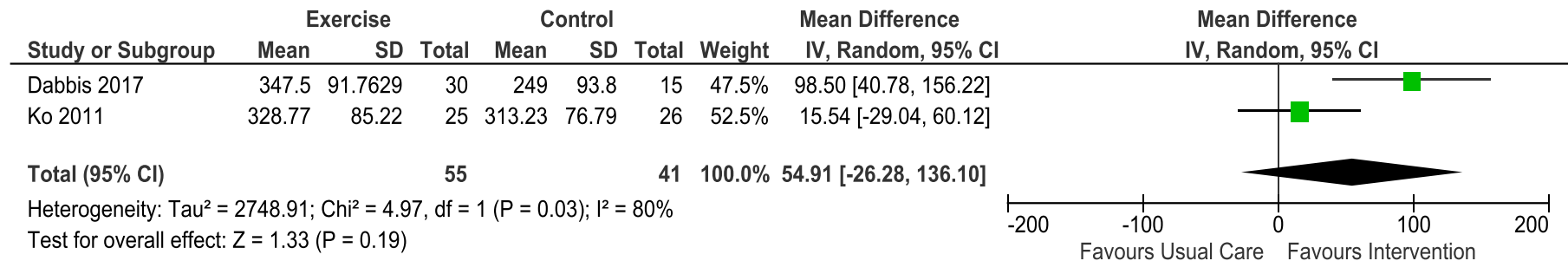
<b>Functional capacity for Program Length – 6MWD (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>&lt;3 weeks</b>				
Borges 2014 <sup>1</sup>	At discharge	139.0	55.0 to 223.0	0.003
Kirsten 1998 <sup>2</sup>	At discharge	165.0	67.1 to 262.9	0.003
He 2015 <sup>13</sup>	At discharge	17.3	9.1 to 25.5	<0.0001
Knaut 2014 <sup>3</sup>	1 month <sup>b</sup>	83.0 <sup>b</sup>	0.1 to 166.0	0.08
Troosters 2010 <sup>5</sup>	1 month <sup>b</sup>	27.0 <sup>b</sup>	-4.4 to 79.0	0.3
<b>3-12 weeks</b>				
Ali 2014 <sup>8</sup>	3 weeks <sup>b</sup>	0.5 <sup>b</sup>	0.0 to 1.0	0.05
Dabbis 2017 <sup>9</sup>	2 months	98.5	40.8 to 156.2	0.002
Ghanem 2010 <sup>12</sup>	2 months	73.2	9.8 to 92.3	<0.0001
Song 2014 <sup>17</sup>	2 months	20.8	-26.1 to 67.7	0.4
Ko 2011 <sup>15</sup>	3 months	15.5	-29.0 to 60.1	0.5
Deepak 2014 <sup>10</sup>	3 months	80.5	31.5 to 129.4	0.002
Eaton 2009 <sup>11</sup>	3 months	3.0	-50.6 to 55.0	0.9
Ko 2011 <sup>15</sup>	12 months	36.0	-23.0 to 95.0	0.2
Ko 2017 <sup>14</sup>	12 months <sup>b</sup>	12.5 <sup>b</sup>	-6.9 to 31.9	0.2
<b>&gt;12 weeks</b>				
Behnke 2000 <sup>18</sup>	6 months	259.0	185.3 to 332.7	<0.0001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

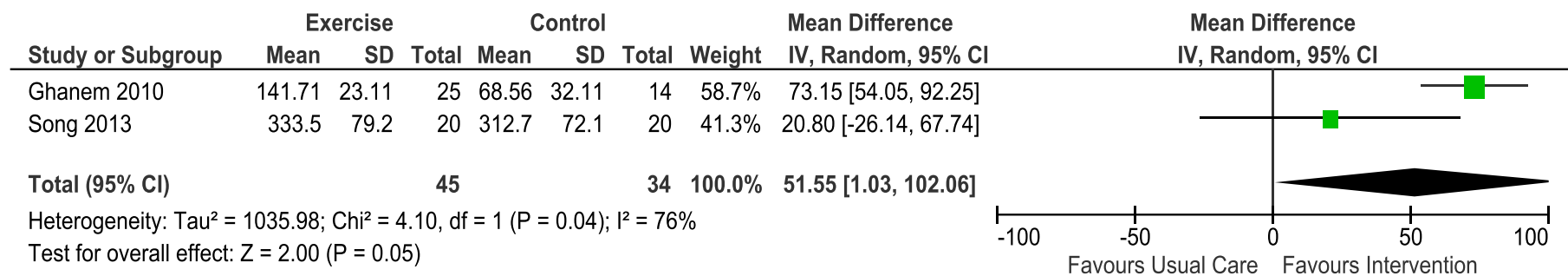
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C6.** Metanalysis of functional capacity (6MWD) mean difference at the end of intervention for studies that delivered a program length <3 weeks



**Figure C7.** Metanalysis of functional capacity (6MWD) mean difference at the end of intervention for studies that delivered program length between 3 and 12 weeks



**Figure C8.** Metanalysis of functional capacity (6MWD) mean difference at the end of intervention for studies that delivered program length between 3 and 12 weeks



### ***Health-related quality of life***

Six studies with a pulmonary rehabilitation program length less than three weeks; eleven with a program between 3 and 12 weeks, and three programs with length longer than 12 weeks assessed HRQoL. The average of change in HRQoL following pulmonary rehabilitation for all program lengths exceeded the minimum clinically difference; suggesting that pulmonary rehabilitation programs following exacerbation of COPD, irrespective of program length, are effective in improving HRQoL.

#### ***Chronic Respiratory Questionnaire (CRQ)***

Three studies delivered programs between 3 to 12 weeks and were sufficiently similar to be combined for analysis. CRQ combined results favoured intervention on all domains except mastery of disease at 3 months (Std. Mean Difference; Dyspnoea: 0.8; 95% CI 0.5 to 1.1;  $i^2=0\%$ / Fatigue: 0.4; 95% CI 0.0 to 0.7;  $i^2=0\%$ / Emotion: 0.5; 95% CI 0.1 to 0.8;  $i^2=0\%$ ) (Figure C9) <sup>15,21,22</sup>. Studies that delivered an exercise program for longer than 12 weeks could not be pooled in a metanalysis, however they reported significant improvement in HRQoL at end of program and 6 months after discharge <sup>18</sup> (Table C6).

#### ***Saint George Respiratory Questionnaire (SGRQ)***

Studies that delivered an exercise program with less than 3 weeks of length could not be combined due heterogenous assessment tools and time points. Borges et al. delivered exercises during the inpatient period and found significantly improved HRQoL on SGRQ one month after hospital discharge (Table C7) <sup>1</sup>. Knaut et al. measured percentage change of the SGRQ score and found a difference between groups of  $83\% \pm 44.19$  (mean $\pm$ SD,  $p=0.09$ ) at one month after discharge favouring the intervention group <sup>3</sup>. Other studies

included used different tools to measure HRQoL, all with improvements favouring the intervention group<sup>8,24,25</sup>.

Pooled results of studies that delivered an exercise program between 3 and 12 weeks favoured the intervention for SGRQ, with the exception of the symptoms domain (Mean Difference; Activities: -10.3; 95% CI -17.0 to 3.8;  $i^2 = 0\%$  / Impacts: -10.3; 95% CI -20.4 to 0.2;  $i^2 = 66\%$  / Total: -9.2; 95% CI -16.3 to -2.0;  $i^2 = 47\%$ ) (Figure C10). For the SF-36 there was no significant difference between exercise programs of between 3 and 12 weeks and usual care (Mean Difference; Physical: 7.5; 95% CI -0.5 to 15.4;  $i^2 = 0\%$  / Mental: 3.3; -5.6 to 12.2;  $i^2 = 0\%$ ) (Figure C11)<sup>15,21</sup>. Three studies that could not be included on the meta-analysis assessed HRQoL via SGRQ however and reported results favouring the intervention group at the end of the program<sup>10,19</sup> and 12 months (Table C7)<sup>14</sup>.

**Table C6.** Health-related quality of life difference between groups assessed via CRQ  
based on program length

**Health-related quality of Life for Program >12 weeks of Length – CRQ**

Study	Time point <sup>a</sup>	Domain	Intervention (n=15)	Usual care (n=15)	P value between groups
<b>&gt;12 weeks</b>					
Behnke 2000 <sup>18</sup>	3 months	dyspnoea	22.1±1.4	15.7±1.6	<0.01
Behnke 2000 <sup>18</sup>		fatigue	20.7±1.1	15.7±1.2	<0.01
Behnke 2000 <sup>18</sup>		mastery	23.5±1.2	18.9±1.2	<0.01
Behnke 2000 <sup>18</sup>	6 months	emotion	42.1±1.7	31.0±2.5	<0.001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented in Mean±SEM.

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups

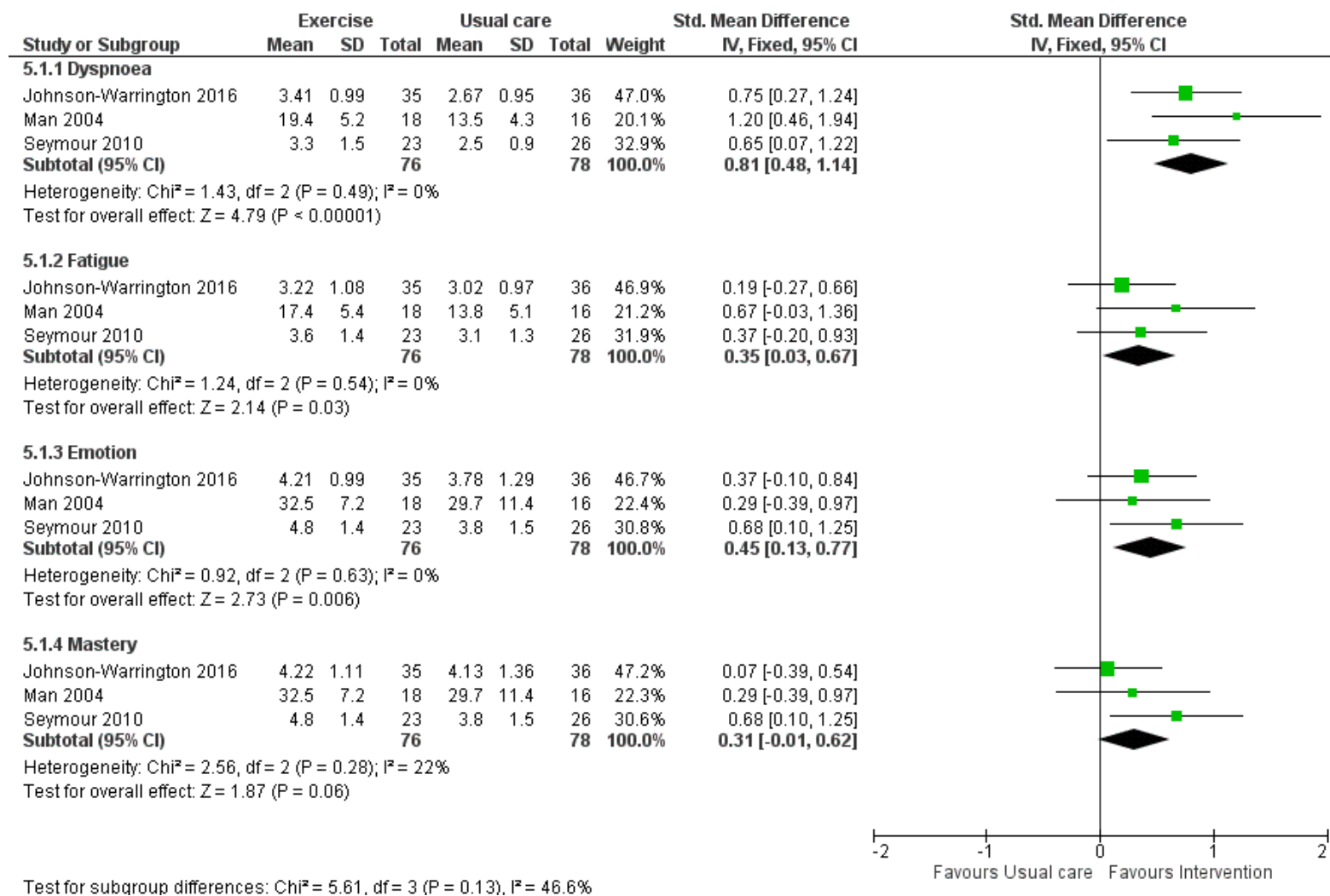
**Table C7.** Health-related quality of life difference between groups assessed via SGRQ  
from studies based on program length

**Health-related quality of Life for Program Length– SGRQ total**

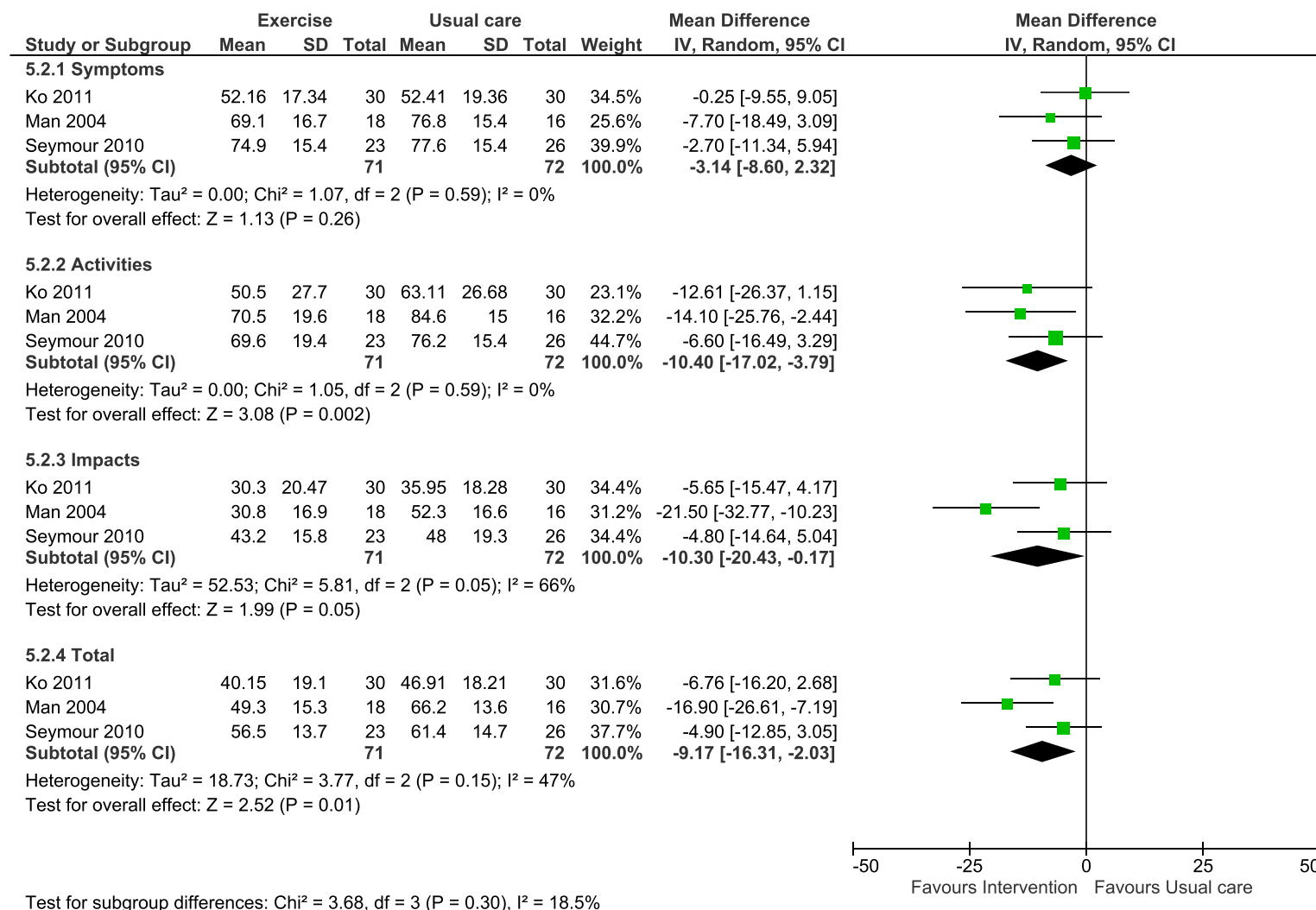
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>&lt;3 weeks</b>				
Borges 2014 <sup>1</sup>	At discharge	-8.3 <sup>c</sup>	-20.2 to 3.6	0.2
Borges 2014 <sup>1</sup>	1 months	-23.4 <sup>c</sup>	-31.8 to -14.9	<0.0001
<b>3-12 weeks</b>				
Murphy 2005 <sup>21</sup>	6 weeks	-4.1	-18.3 to 10.1	0.6
Deepak 2014 <sup>10</sup>	3 months	-23.4	-31.8 to -14.9	<0.0001
Ko 2017 <sup>14</sup>	12 months	-6.8 <sup>c</sup>	-11.1 to -2.5	0.002
<b>&gt;12 weeks</b>				
Song 2014 <sup>17</sup>	2 months	-24.5	-29 to -20.0	<0.0001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked.

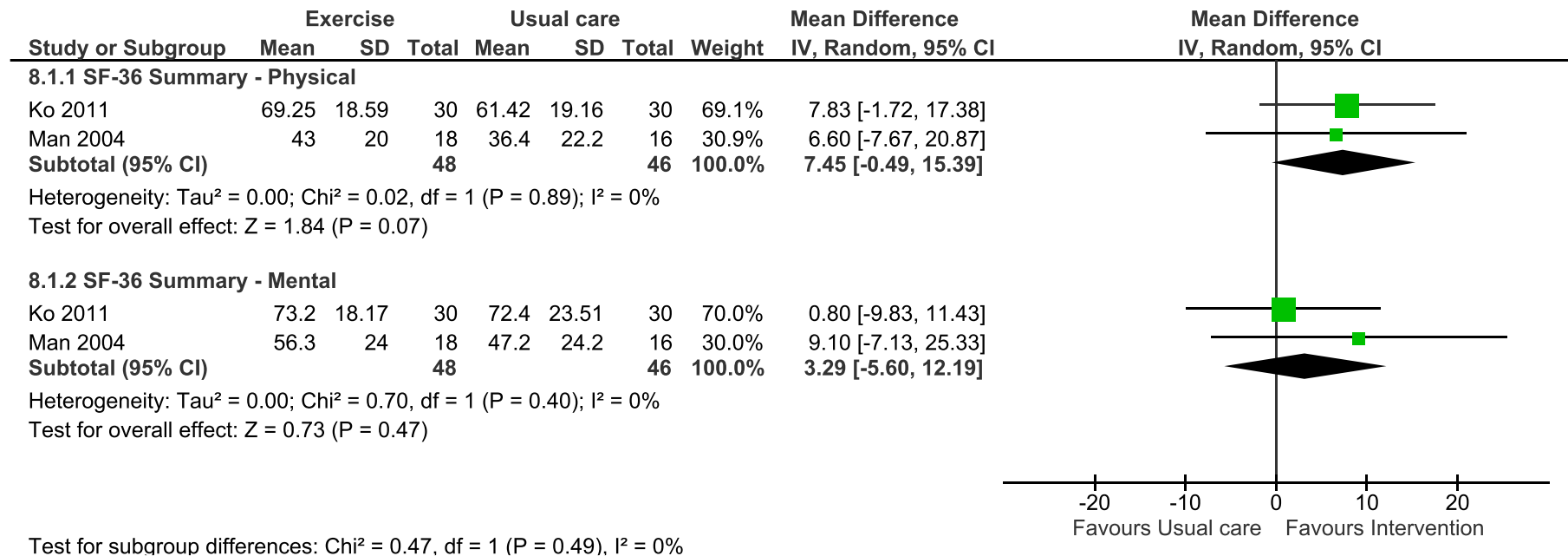
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C9.** Metanalysis of health-related quality of life (CRQ) standardised mean difference between groups for studies that delivered a program length between 3 and 12 weeks at end intervention



**Figure C10.** Metanalysis of health-related quality of life (SGRQ) mean difference between groups for studies that delivered program length between 3 and 12 weeks at end intervention



**Figure C11.** Metanalysis of health-related quality of life (SF-36) physical and mental component scores mean difference between groups for studies that delivered program length between 3 and 12 weeks at end intervention

### ***Adverse Events***

Four studies presented data for adverse events and had no adverse events during the study period<sup>5,8,13,21</sup>.

## ***PROGRAM COMMENCEMENT (INPATIENT OR AFTER DISCHARGE)***

### ***Functional capacity***

Eleven studies that started an exercise program during the inpatient period reported functional capacity <sup>1-3,5,8,11-13,17-19</sup> and seven reported program commencement after discharge <sup>9,10,14,15,21-23</sup>. The average of change in 6MWD exceeded the minimum important difference for both studies of programs commenced in the inpatient period, and those commenced after discharge (Table C8 and C9). This suggests functional capacity can improve regardless of timing of program commencement.

Studies starting during the inpatient period that assessed functional capacity with the 6MWD and were similar enough to be combined presented results favouring exercise group during hospital compared to usual care at hospital discharge (Mean Difference 99.3 metres; 95% CI -8.7 to 207.3;  $i^2=88\%$ ) (Figure C12) <sup>1,2,13</sup>; and at the end of intervention (2 months) (Mean Difference 51.6 metres; 95% CI 1.0 to 102.1;  $i^2=76\%$ ) (Figure C13) <sup>12,17</sup>.

Studies starting the program after hospital discharge that could be combined showed significant but heterogenic improvement on 6MWD at the end of intervention (2-3 months) compared to usual care (Mean Difference 54.9 metres; 95% CI -26.3 to 136.1;  $i^2=80\%$ ) (Figure C14) <sup>9,15</sup>.



**Table C8.** Functional capacity assessed via 6MWD of studies based on timing of program commencement

<b>Functional capacity for Program Commencement – 6MWD (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Inpatient</b>				
Borges 2014 <sup>1</sup>	At discharge	139.0	55.0 to 223.0	0.003
Kirsten 1998 <sup>2</sup>	At discharge	165.0	67.1 to 262.9	0.003
He 2015 <sup>13</sup>	At discharge	17.3	9.1 to 25.5	<0.0001
Ali 2014 <sup>8</sup>	3 weeks <sup>b</sup>	0.5	0.0 to 1.0	0.05
Knaut 2014 <sup>3</sup>	1 months <sup>b</sup>	83.0	0.1 to 166.0	0.08
Troosters 2010 <sup>5</sup>	1 months <sup>b</sup>	27.0	-4.4 to 79.0	0.3
Ghanem 2010 <sup>12</sup>	2 months	73.2	9.8 to 92.3	<0.0001
Song 2014 <sup>17</sup>	2 months	20.8	-26.14 to 67.7	0.39
Eaton 2009 <sup>11</sup>	3 months	3.0	-50.6 to 55.0	0.9
Behnke 2000 <sup>18</sup>	6 months	259.0	185.3 to 332.7	<0.0001
<b>After discharge</b>				
Dabbis 2017 <sup>9</sup>	2 months	98.5	40.8 to 156.2	0.002
Ko 2011 <sup>15</sup>	3 months	15.5	-29.0 to 60.1	0.5
Deepak 2014 <sup>10</sup>	3 months	80.5	31.5 to 129.4	0.002
Ko 2011 <sup>15</sup>	12 months	36.0	-23.0 to 95.0	0.2
Ko 2017 <sup>14</sup>	12 months <sup>b</sup>	12.5	-6.9 to 31.9	0.20

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

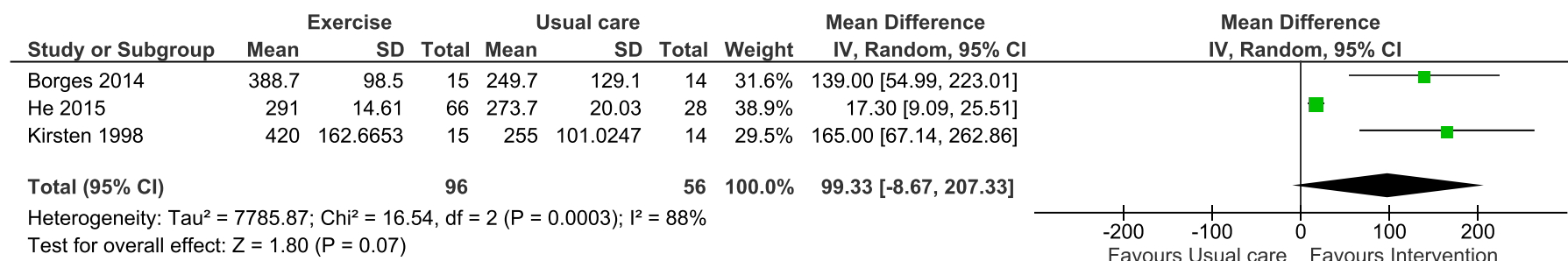
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups

**Table C9.** Functional capacity assessed via ISWT of studies based on timing of program commencement

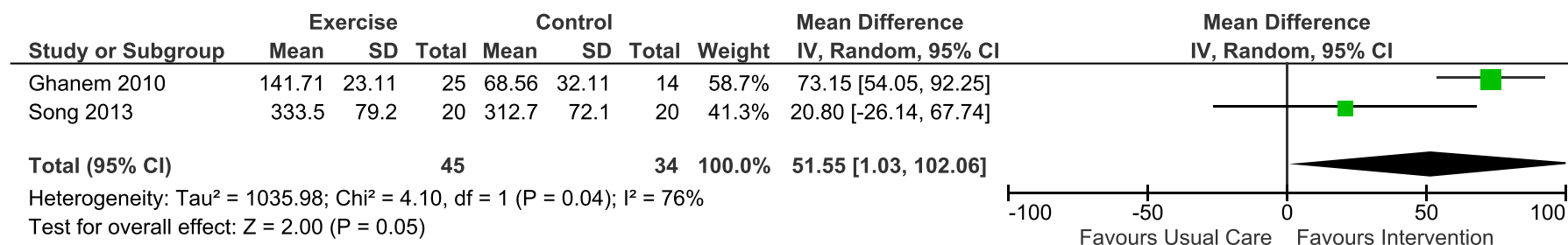
<b>Functional capacity for Program Commencement – ISWT (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Inpatient</b>				
Murphy 2005 <sup>19</sup>	6 weeks	89.0	-25.9 to 203.9	0.1
<b>After discharge</b>				
Kjaergaard 2020 <sup>20</sup>	2 months	33.9	4.2 to 63.7	0.02
Man 2004 <sup>21</sup>	3 months	60.0 <sup>c</sup>	26.6 to 93.4	0.0002
Seymour 2010 <sup>22</sup>	3 months	33.0	-30.8 to 96.8	0.3
Johnson-Warrington 2016 <sup>23</sup>	3 months <sup>b</sup>	-7.5	-67.4 to 52.4	0.8

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

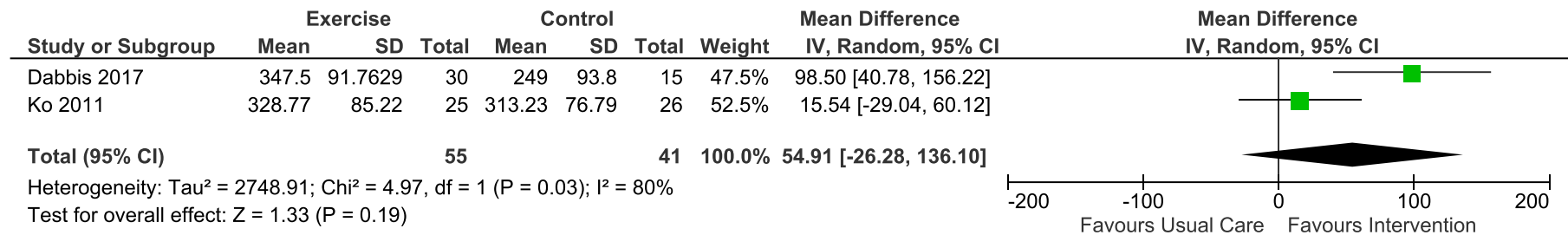
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C12.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that started during inpatient at one month after discharge



**Figure C13.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that started as inpatient at 2 months



**Figure C14.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that started after discharge at end intervention (2-3 months)

## ***Health-related quality of life***

### *Chronic Respiratory Questionnaire (CRQ)*

Two studies that could not be combined assessed HRQOL via CRQ and delivered exercises programs starting during the inpatient period. Ghanem et al. reported significant improvement between groups favouring intervention groups in CRQ dyspnoea ( $p=0.003$ ), fatigue ( $p=0.004$ ) and emotion ( $p=0.008$ ) domains at the end of rehabilitation (2 months) <sup>12</sup>. Eaton et al. reported significant change within both groups for the CRQ fatigue and mastery domains, however not between groups <sup>11</sup>.

Three studies that started the exercises program after discharge could be combined in a metaanalysis <sup>21-23</sup>. Exercise programs commenced after discharge resulted in improved CRQ scores favouring the intervention when assessed at 3 months, for all domains except mastery of disease (Std. Mean Difference; Dyspnoea: 0.8; 95% CI 0.5 to 1.1;  $i^2=0\%$ / Fatigue: 0.4; 95% CI 0.0 to 0.7;  $i^2=0\%$ / Emotion: 0.5; 95% CI 0.1 to 0.8;  $i^2=0\%$ ) (Figure C15) <sup>21-23</sup>.

### *Saint George Respiratory Questionnaire (SGRQ)*

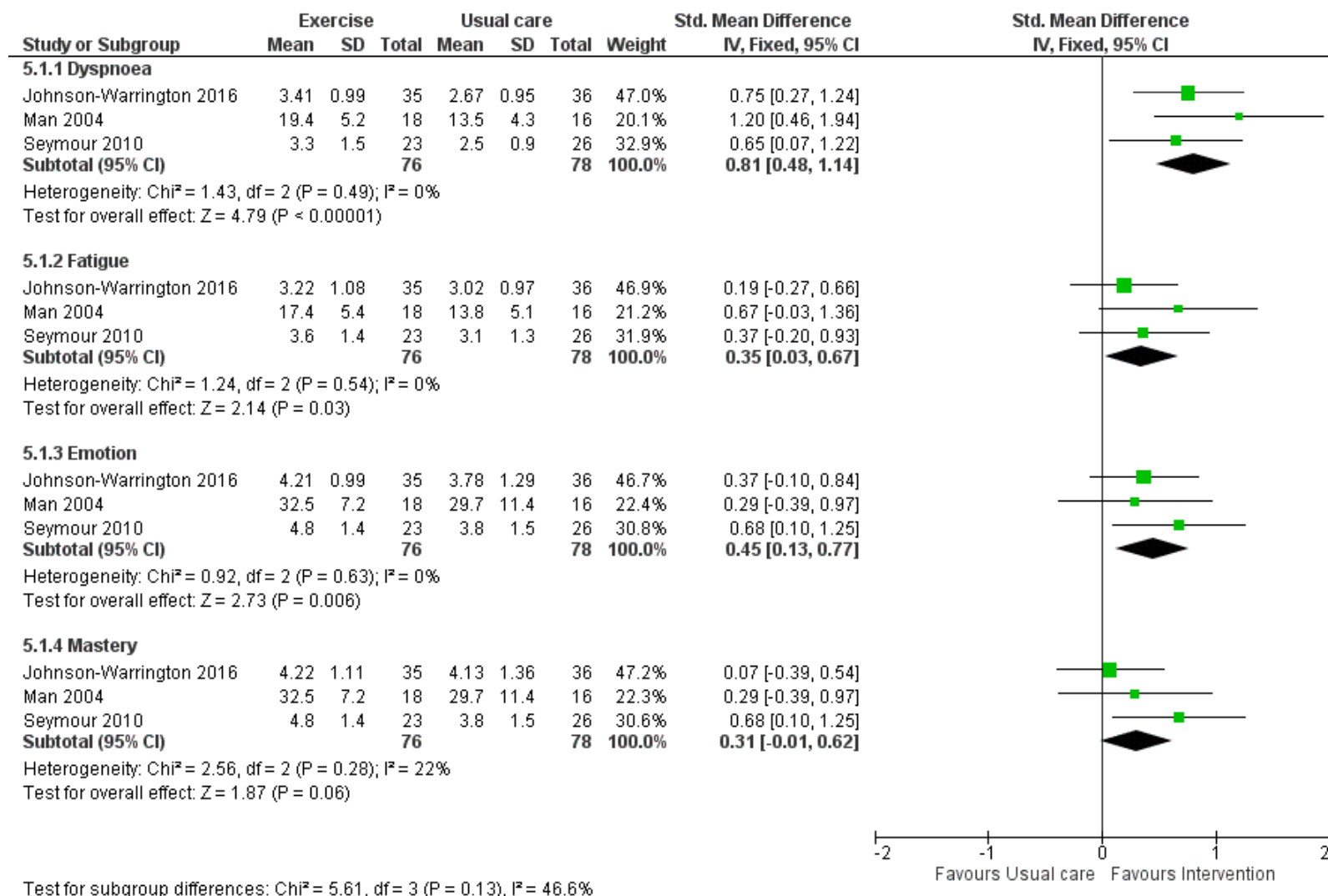
Data from included studies suggested improvement in HRQoL regardless of program length (Table C10). Three studies that started the exercise program after discharge could be combined in a metaanalysis <sup>15,21,22</sup>. Exercise programs commenced after discharge showed improvement in the SQRG favouring the intervention when assessed at 3 months, with the exception of the symptom domain (Mean Difference; Activities: -10.3; 95% CI -17.0 to -3.8;  $i^2=0\%$ / Impacts: -10.3; 95% CI -20.4 to 0.2;  $i^2=66\%$ / Total: -9.2; 95% CI -16.3 to -2.0;  $i^2=47\%$ ) (Figure C16) <sup>15,21,22</sup>.

**Table C10.** Health-related quality of life of studies based on commencement

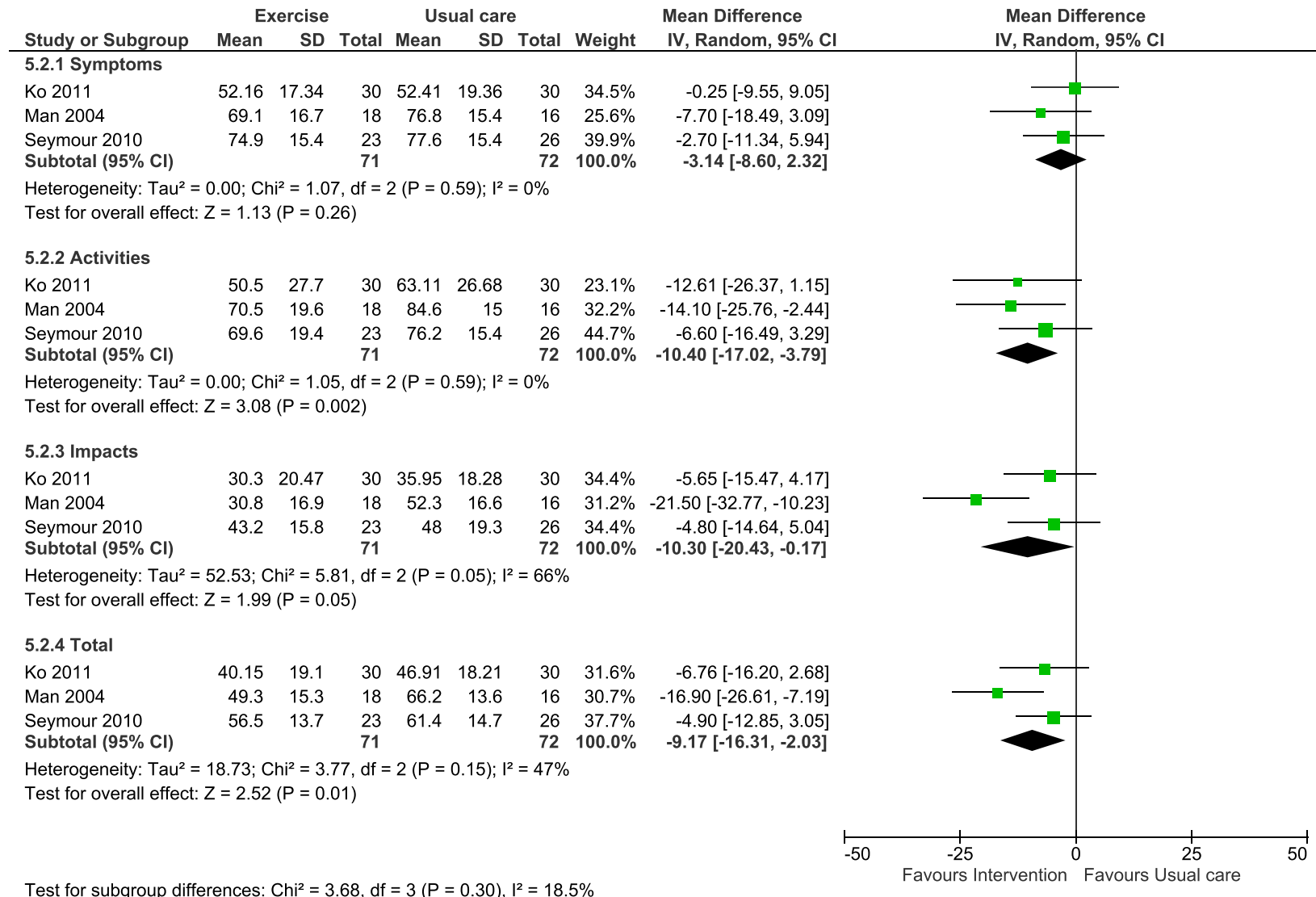
<b>Health-related quality of Life for Program Commencement – SGRQ total</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Inpatient</b>				
Borges 2014 <sup>1</sup>	At discharge	-8.3 <sup>c</sup>	-20.2 to 3.6	0.2
Borges 2014 <sup>1</sup>	1 months	-23.4 <sup>c</sup>	-31.8 to -14.9	<0.0001
Murphy 2005 <sup>21</sup>	6 weeks	-4.1	-18.3 to 10.1	0.6
Song 2014 <sup>17</sup>	2 months	-24.5	-29 to -20.0	<0.0001
<b>After discharge</b>				
Deepak 2014 <sup>10</sup>	3 months	-23.4	-31.8 to -14.9	<0.0001
Ko 2017 <sup>14</sup>	12 months	-6.8 <sup>c</sup>	-11.1 to -2.5	0.002

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked.

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C15.** Metanalysis of health-related quality of life (CRQ) standardised mean difference between groups for studies that started after discharge



**Figure C16.** Metanalysis of health-related quality of life (SGRQ) mean difference between groups for studies that started after discharge



### ***Adverse events***

Only one study reported having adverse events during the study period delivered exercises starting during inpatient period<sup>4</sup>. Tang et al.<sup>4</sup> reported 13 adverse events, seven non-serious, five nonserious study related and not expected and one serious and study related<sup>4</sup>. The study reported that a participant with previous history of heart condition developed chest pain that lasted two minutes while exercising in low-intensity; the adverse event was resolved within one hour without medical intervention<sup>4</sup>.

## ***PROGRAM LOCATION (INPATIENT, OUTPATIENT, COMBINATION OF INPATIENT AND OUTPATIENT)***

### ***Functional Capacity***

Seven studies <sup>1-3,5,8,13,19</sup> reporting functional capacity delivered the program entirely during the inpatient stay; four as outpatient <sup>9,10,14,15,20</sup> and four delivered a combination of inpatient and outpatient location <sup>11,12,17,18</sup>. The average of change for all groups exceeded minimum important distance (Table C11 and C12).

Three studies that delivered their program in the inpatient location assessed functional capacity via 6MWD and could be pooled in a metanalysis. The results favoured intervention group at discharge from hospital but did not reach statistical significance (Mean Difference 99.3 metres; 95% CI -8.7 to 207.3;  $i^2=88\%$ ) (Figure C17) <sup>1,2,13</sup>. One month after discharge the difference between groups ranged from 83 to 27 <sup>3,5</sup> (Table C11). An inpatient program of 3 weeks also reported results favouring exercise group at end of the program with significant difference between groups at three weeks (Table C11) <sup>8</sup>.

For studies located in outpatient centres the combined results assessed via 6MWD were not significant at 3 months (Mean Difference 54.9 metres; 95% CI -26.3 to 136.1;  $i^2=80\%$ ) (Figure C18) <sup>9,15</sup>

**Table C11.** Functional capacity assessed via 6MWD based on program location

<b>Functional capacity for Program Location – 6MWD (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Inpatient</b>				
Borges 2014 <sup>1</sup>	At discharge	139.0	55.0 to 223.0	0.003
Kirsten 1998 <sup>2</sup>	At discharge	165.0	67.1 to 262.9	0.003
He 2015 <sup>13</sup>	At discharge	17.3	9.1 to 25.5	<0.0001
Ali 2014 <sup>8</sup>	3 weeks <sup>b</sup>	0.52	0.02 to 1.0	0.05
Knaut 2014 <sup>3</sup>	1 months <sup>b</sup>	83.0	0.05 to 166.0	0.08
Troosters 2010 <sup>5</sup>	1 months <sup>b</sup>	27.0	-4.4 to 79.0	0.3
<b>Outpatient</b>				
Dabbis 2017 <sup>9</sup>	2 months	98.5	40.8 to 156.2	0.002
Ko 2011 <sup>15</sup>	3 months	15.5	-29.0 to 60.1	0.5
Deepak 2014 <sup>10</sup>	3 months	80.5	31.5 to 129.4	0.002
Ko 2011 <sup>15</sup>	12 months	36.0	-23.0 to 95.0	0.2
Ko 2017 <sup>14</sup>	12 months <sup>b</sup>	12.5	-6.9 to 31.9	0.20
<b>Combination of inpatient and outpatient program</b>				
Ghanem 2010 <sup>12</sup>	2 months	73.2	9.8 to 92.3	<0.0001
Song 2014 <sup>17</sup>	2 months	20.8	-26.1 to 67.7	0.4
Eaton 2009 <sup>11</sup>	3 months	3.0	-50.6 to 55.0	0.9
Behnke 2000 <sup>18</sup>	6 months	259.0	185.3 to 332.7	<0.0001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

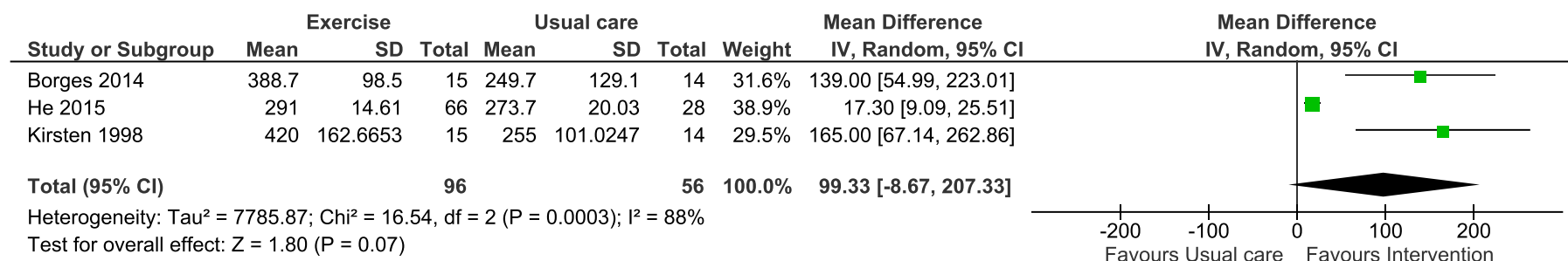
<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups

**Table C12.** Functional capacity assessed via ISWT based on program location

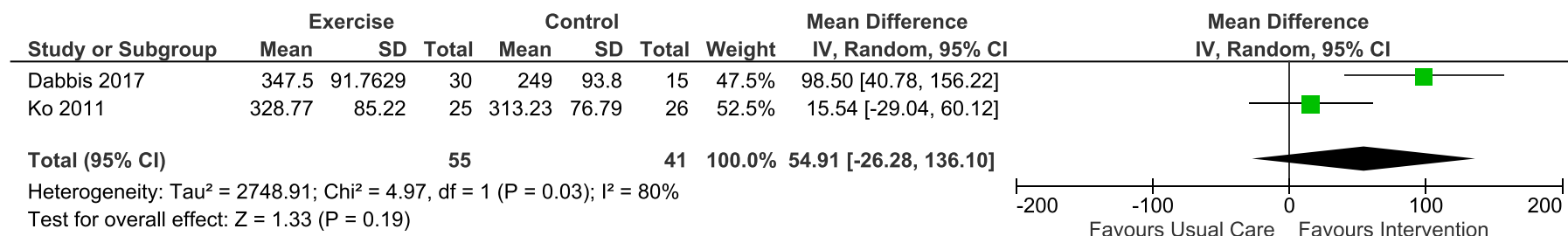
<b>Functional capacity for Program Location – ISWT (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Outpatient</b>				
Kjaergaard 2020 <sup>20</sup>	2 months	33.9	4.2 to 63.7	0.02
Man 2004 <sup>21</sup>	3 months	60.0 <sup>c</sup>	26.6 to 93.4	0.0002
Seymour 2010 <sup>22</sup>	3 months	33.0	-30.8 to 96.8	0.3
Johnson-Warrington 2016 <sup>23</sup>	3 months <sup>b</sup>	-7.5	-67.4 to 52.4	0.8
Murphy 2005 <sup>19</sup>	6 weeks	89.0	-25.9 to 203.9	0.1

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C17.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that delivered programs as inpatient at one month after discharge



**Figure C18.** Metanalysis of functional capacity (6MWD) mean difference between groups for studies that delivered programs as inpatient at end intervention (2-3 months)

## ***Health related quality of life***

### ***Chronic Respiratory Questionnaire (CRQ)***

Three studies delivered outpatient programs combined results was significant for the intervention compared to at 3 months in all domains except mastery of disease (Std. Mean Difference; Dyspnoea: 0.8; 95% CI 0.5 to 1.1;  $i^2=0\%$ / Fatigue: 0.4; 95% CI 0.0 to 0.7;  $i^2=0\%$ / Emotion: 0.5; 95% CI 0.1 to 0.8;  $i^2=0\%$ ) (Figure C19) <sup>21,22,26</sup>.

### ***Saint George Respiratory Questionnaire (SGRQ)***

Data from five included studies suggested improvement in HRQoL on the SGRQ regardless of program location (Table C13). Studies delivering outpatient programs combined results favoured the intervention at 3 months in all domains except symptoms (Mean Difference; Activities: -10.3; 95% CI -17.0 to 3.8;  $i^2=0\%$ / Impacts: -10.3; 95% CI -20.4 to 0.2;  $i^2=66\%$ / Total: -9.2; 95% CI -16.3 to -2.0;  $i^2=47\%$ ) (Figure C20) <sup>21-23</sup>.

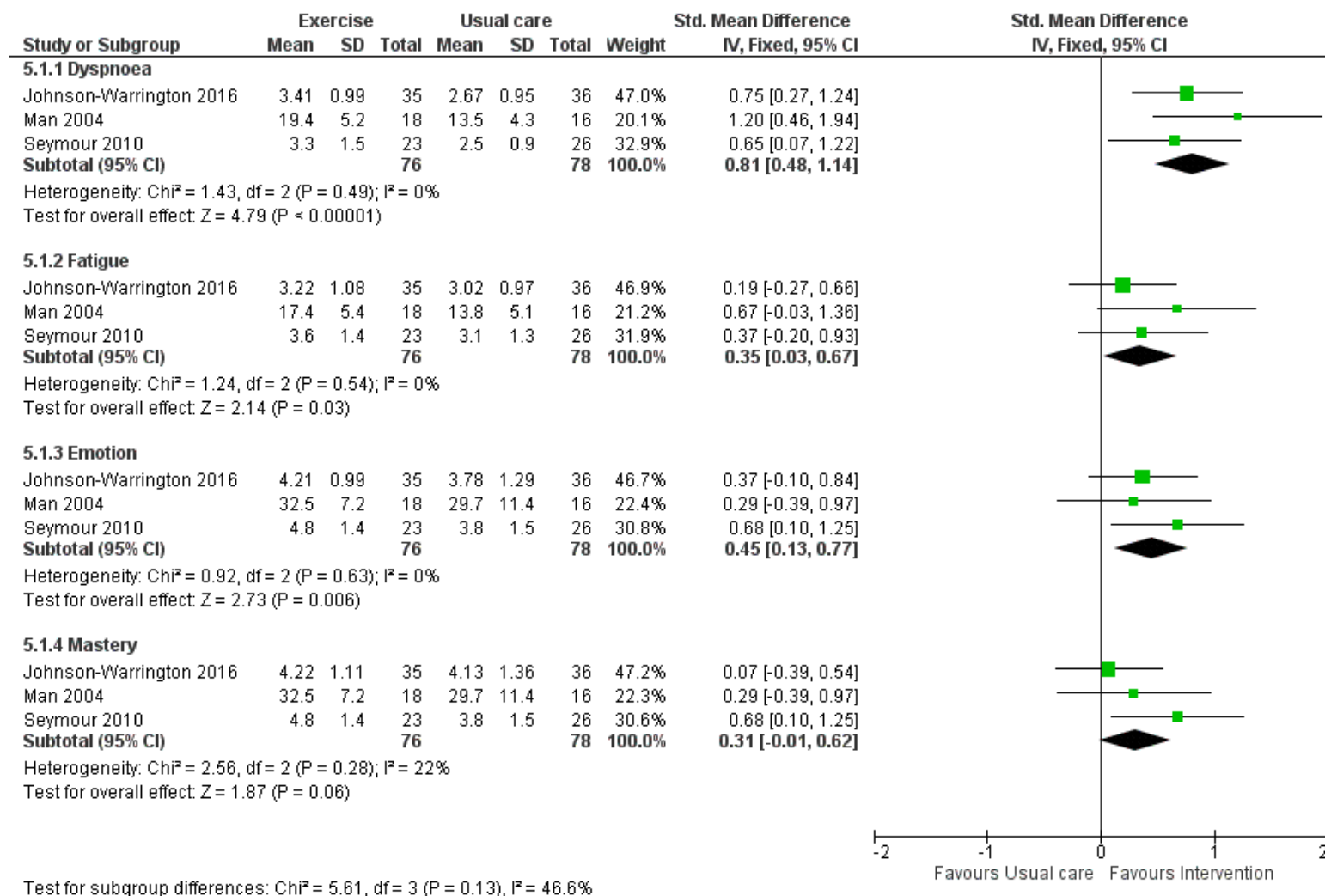
Programs that were delivered in a combination of inpatient and outpatient locations <sup>17,19</sup> reported improvement in HRQoL on the SGRQ (total score) (Table C13).

**Table C13.** Health-related quality of life on studies based on program location

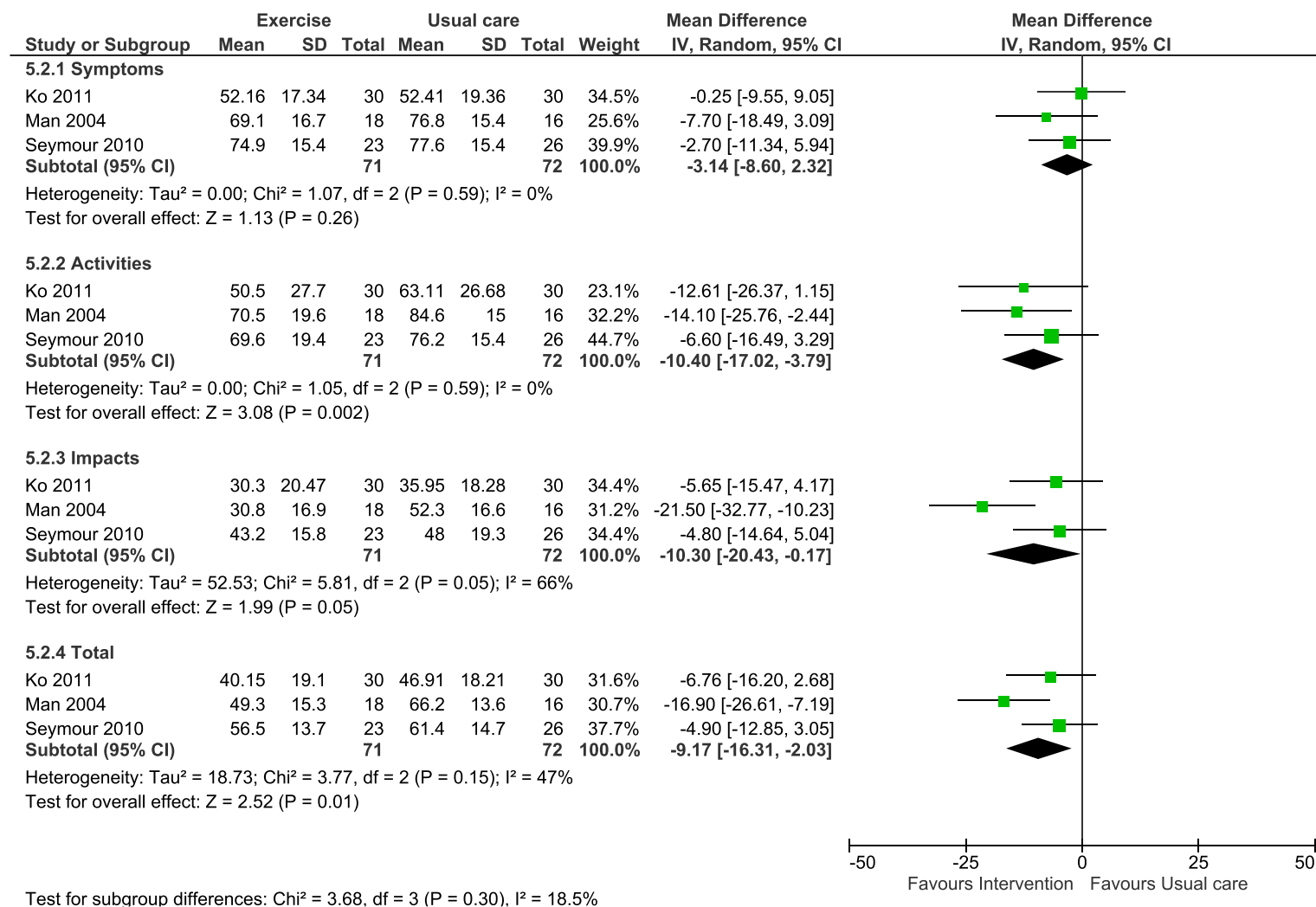
<b>Health-related quality of Life for Program Location – SGRQ total</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Inpatient</b>				
Borges 2014 <sup>1</sup>	At discharge	-8.3 <sup>c</sup>	-20.2 to 3.6	0.2
Borges 2014 <sup>1</sup>	1 months	-23.4 <sup>c</sup>	-31.8 to -14.9	<0.0001
<b>Outpatient</b>				
Deepak 2014 <sup>10</sup>	3 months	-23.4	-31.8 to -14.9	<0.0001
Ko 2017 <sup>14</sup>	12 months	-6.8 <sup>c</sup>	-11.1 to -2.5	0.002
<b>Combination of inpatient and outpatient program</b>				
Murphy 2005 <sup>21</sup>	6 weeks	-4.1	-18.3 to 10.1	0.6
Song 2014 <sup>17</sup>	2 months	-24.5	-29 to -20.0	<0.0001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C19.** Metanalysis of health-related quality of life (CRQ) standardized mean difference between groups for studies that delivered program as an outpatient



**Figure C20.** Metanalysis of St George Respiratory Questionnaire score mean difference between groups for studies that delivered program as an outpatient



### ***Adverse Events***

Four studies presented data for adverse events and reported no adverse events during the study period <sup>5,8,13,21</sup>. Only one study reported having adverse events during the study period located as inpatient period <sup>4</sup>. Tang et al. <sup>4</sup> reported 13 adverse events, seven non-serious, five nonserious study related and not expected and one serious and study related <sup>4</sup>. The study reported that a participant with previous history of heart condition developed chest pain that lasted two minutes while exercising in low-intensity; the adverse event was resolved within one hour without medical intervention <sup>4</sup>.

## ***PROGRAM SUPERVISION (SUPERVISED, UNSUPERVISED)***

### ***Functional capacity***

Thirteen studies that delivered supervised programs measured functional capacity <sup>1-3,5,8,9,11,13-15,17,18</sup>, and one which delivered unsupervised program <sup>12</sup>. The average of change for both groups exceeded the minimum important distance (Table C14).

Five studies of supervised programs reported results favouring the intervention, three at discharge from hospital (Mean Difference 99.3 metres; 95% CI -8.7 to 207.3;  $i^2=88\%$ ) (Figure C21) <sup>1,2,13</sup>, and two at end of intervention (3 months) compared to usual care (Mean Difference 54.9 metres; 95% CI -26.3 to 136.1;  $i^2=80\%$ ) (Figure C22) <sup>9,15</sup>. The remaining supervised studies favoured exercise group with mean difference between groups range from 3 to 259 metres (Table C14).

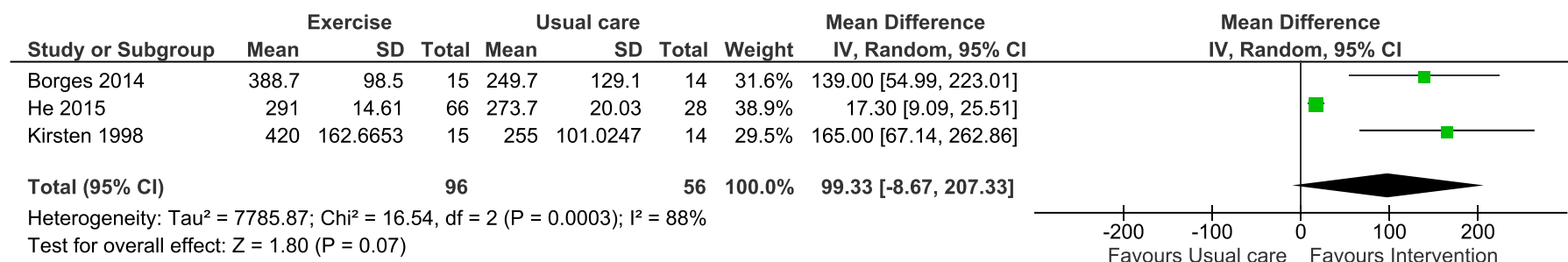
One study delivered an unsupervised program and reported significant increased 6MWD between groups favouring the intervention group compared to usual care (Table C14).

**Table C14.** Functional capacity in studies based on program supervision

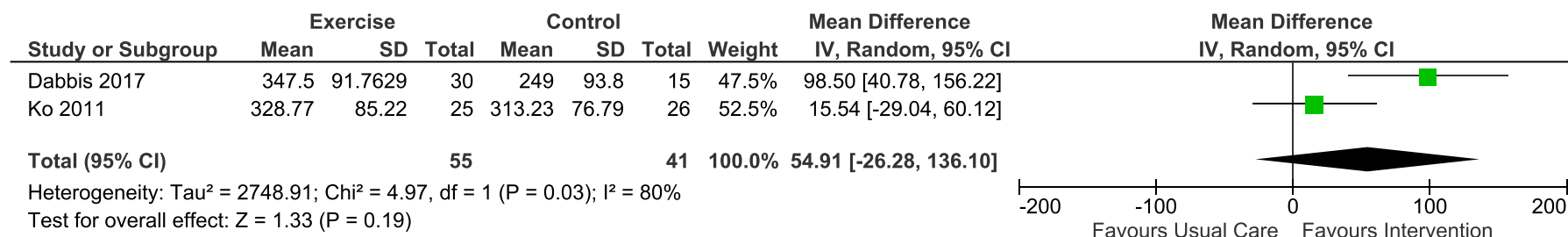
<b>Functional capacity for Program Supervision – 6MWD (m)</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Supervised</b>				
Borges 2014 <sup>1</sup>	At discharge	139.0	55.0 to 223.0	0.003
Kirsten 1998 <sup>2</sup>	At discharge	165.0	67.1 to 262.9	0.003
He 2015 <sup>13</sup>	At discharge	17.3	9.1 to 25.5	<0.0001
Ali 2014 <sup>8</sup>	3 weeks <sup>b</sup>	0.5	0.02 to 1.0	0.05
Knaut 2014 <sup>3</sup>	1 months <sup>b</sup>	83.0	0.05 to 166.0	0.08
Troosters 2010 <sup>5</sup>	1 months <sup>b</sup>	27.0	-4.4 to 79.0	0.3
Dabbis 2017 <sup>9</sup>	2 months	98.5	40.8 to 156.2	0.002
Kjaergaard 2020 <sup>20</sup>	2 months	33.9	4.2 to 63.7	0.02
Man 2004 <sup>21</sup>	3 months	60.0 <sup>c</sup>	26.6 to 93.4	0.0002
Seymour 2010 <sup>22</sup>	3 months	33.0	-30.8 to 96.8	0.3
Johnson-Warrington 2016 <sup>23</sup>	3 months <sup>b</sup>	-7.5	-67.4 to 52.4	0.8
Ko 2017 <sup>14</sup>	12 months <sup>b</sup>	12.5	-6.9 to 31.9	0.20
Behnke 2000 <sup>18</sup>	6 months	259.0	185.3 to 332.7	<0.0001
Song 2014 <sup>17</sup>	2 months	20.8	-26.1 to 67.7	0.4
<b>Unsupervised</b>				
Ghanem 2010 <sup>12</sup>	2 months	73.2	9.8 to 92.3	<0.0001

Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups



**Figure C22.** Metanalysis of functional capacity (6MWD) mean difference for studies that delivered a supervised program at one month after discharge



**Figure C23.** Metanalysis of functional capacity (6MWD) mean difference for studies that delivered a supervised program at end intervention (2-3 months)

## Health-related quality of life

Twelve studies that assessed HRQoL delivered supervised programs <sup>1,3,10,11,14,15,17-19,21-23</sup> and one delivered an unsupervised program <sup>12</sup>. The average improvement with rehabilitation exceeded the minimum important difference (Table 15).

### *Chronic Respiratory Questionnaire (CRQ)*

Studies of supervised programs that used the CRQ to assess HRQoL presented significant improvement at 3 months in all domains except mastery of disease (Std. Mean Difference; Dyspnoea: 0.8; 95% CI 0.5 to 1.1;  $i^2=0\%$ / Fatigue: 0.4; 95% CI 0.0 to 0.7;  $i^2=0\%$ / Emotion: 0.5; 95% CI 0.1 to 0.8;  $i^2=0\%$ ) (Figure C24) <sup>21-23</sup>. One study delivered an unsupervised program and reported significant change between groups on all CRQ domains (Mean [95%CI]; Dyspnoea 5.5 [3 to 9]; Fatigue 5.3 [1.9 to 9.8]; Emotion 8.7 [2.5 to 15]) <sup>12</sup>.

### *Saint George Respiratory Questionnaire (SGRQ)*

Studies of supervised programs presented significant improvement in all domains except symptoms on the SGRQ at three months (Mean Difference; Activities: -10.3; 95% CI -17.0 to -3.8;  $i^2=0\%$ / Impacts: -10.3; 95% CI -20.4 to 0.2;  $i^2=66\%$ / Total: -9.2; 95% CI -16.3 to -2.0;  $i^2=47\%$ ) (Figure C25) <sup>21-23</sup>.

### *Other HRQoL measurements*

Studies that assessed HRQoL via SF-36 favoured intervention however without significant result (Mean Difference; Physical: 7.5; 95% CI -0.5 to 15.4;  $i^2=0\%$ / Mental:

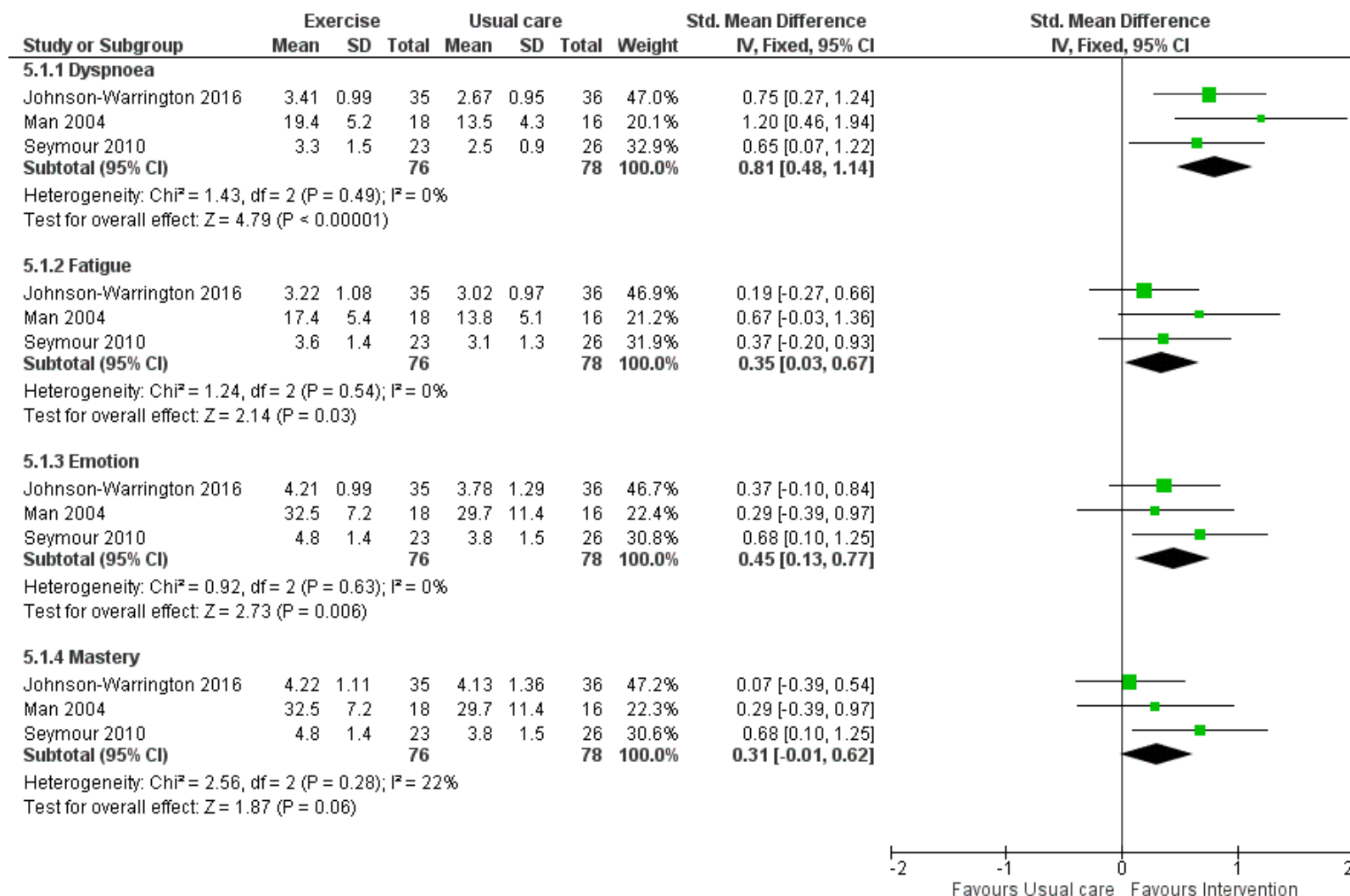
3.3; -5.6 to 12.2;  $i^2 = 0\%$ ) (Figure C26). Other studies measured used different tool to measure HRQoL, all with improvements favouring the intervention group  
8,9,11,12,15,21,22,24,25 .

**Table 15.** Health-related quality of life in studies based on program supervision

<b>Health-related quality of Life for Program Location – SGRQ total</b>				
Study	Time point <sup>a</sup>	Mean difference between groups	95% CI	P value
<b>Supervised</b>				
Borges 2014 <sup>1</sup>	At discharge	-8.3 <sup>c</sup>	-20.2 to 3.6	0.2
Borges 2014 <sup>1</sup>	1 months	-23.4 <sup>c</sup>	-31.8 to -14.9	<0.0001
Deepak 2014 <sup>10</sup>	3 months	-23.4	-31.8 to -14.9	<0.0001
Ko 2017 <sup>14</sup>	12 months	-6.8 <sup>c</sup>	-11.1 to -2.5	0.002
Murphy 2005 <sup>21</sup>	6 weeks	-4.1	-18.3 to 10.1	0.6
Song 2014 <sup>17</sup>	2 months	-24.5	-29 to -20.0	<0.0001

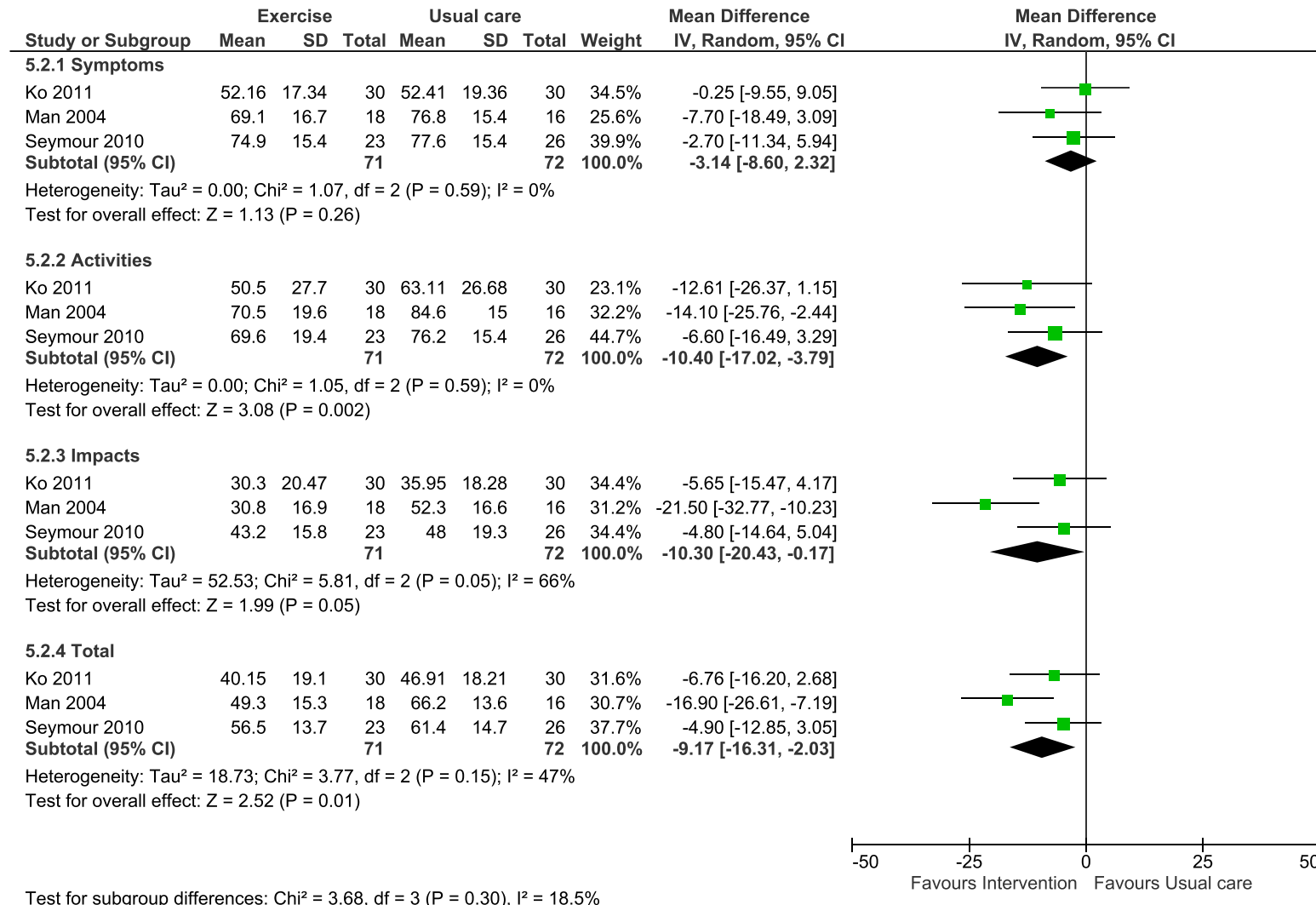
Table legend: <sup>a</sup>Time after hospital discharge. Data presented is change between groups at time point measured unless otherwise marked

<sup>b</sup>change from baseline at time point measured. <sup>c</sup>median difference between groups

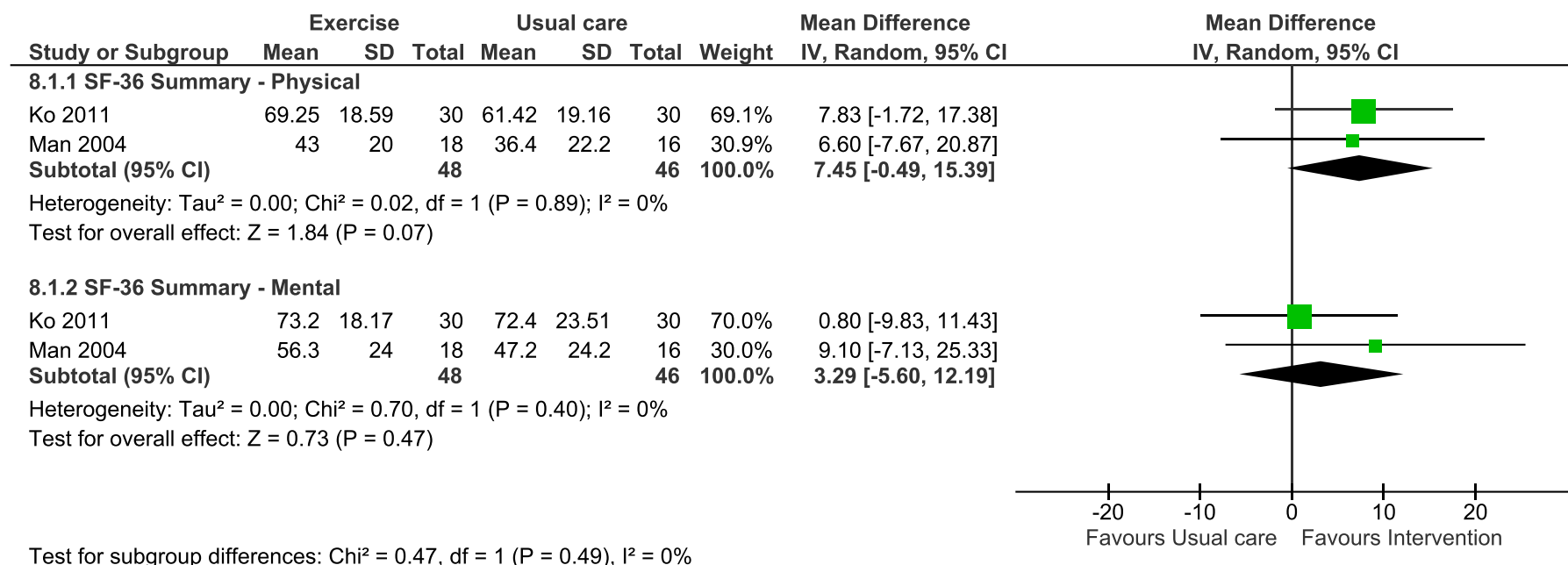




**Figure C24.** Metanalysis of health-related quality of life (CRQ) standardised mean difference between groups for studies that delivered supervised programs



**Figure C25.** Metanalysis of health-related quality of life (SGRQ) mean difference between groups for studies that delivered a supervised program



**Figure C26.** Metanalysis of health-related quality of life (SF-36) physical and mental component scores mean difference between groups for studies that delivered a supervised program

## **Adverse events**

Four studies presented data for adverse events and reported no adverse events during the study period <sup>5,8,13,21</sup>. Only one study reported having adverse delivered exercise training with supervision <sup>4</sup>. Tang et al. <sup>4</sup> reported 13 adverse events, seven non-serious, five nonserious study related and not expected and one serious and study related <sup>4</sup>. The study reported that a participant with previous history of heart condition developed chest pain that lasted two minutes while exercising in low-intensity; the adverse event was resolved within one hour without medical intervention <sup>4</sup>.

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# CHAPTER FIVE


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*Early home-based pulmonary rehabilitation  
following acute exacerbation of COPD: A  
feasibility study using an action research approach*

## 5.1 Declaration of Authorship – Chapter Five


### Student's Declaration

The nature and extent of contributions to Chapter Five of this thesis are as follows:

Name	Nature of contribution	Contribution	Signature
Bruna Wageck	Study concept, protocol development, ethics application, data collection, data analysis, writing and review of manuscript	60%	
Anne E Holland	Study concept, protocol development, data analysis, writing and review of manuscript	20%	
Narelle S Cox	Study concept, protocol development, data analysis, writing and review of manuscript	10%	
Janet Bondarenko	Data collection and review of manuscript	2.5%	
Monique Corbett	Data collection and review of manuscript	2.5%	
Amanda Nichols	Delivery of intervention and review of manuscript	2.5%	
Rosemary Moore	Delivery of intervention and review of manuscript	2.5%	

### Supervisor's Declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter Five of this thesis by the student and all listed

Supervisor name	Signature
Professor Anne E Holland	

## 5.2 Preface

The review presented in Chapter Four analysed the effect of the characteristics of pulmonary rehabilitation programs on clinical outcomes. Programs of longer duration, those that delivered exercise training in association with education, and those that started after hospital discharge were all associated with reduced risk of hospital readmission.

Pulmonary rehabilitation is commonly offered at a healthcare facility on an outpatient basis (centre-based). There are numerous well documented barriers experienced by patients with being able to take up an offer of centre-based pulmonary rehabilitation, and attend the centre for sessions. Alternative models of pulmonary rehabilitation, including home-based, have been developed in an effort to overcome barriers to attending a centre-based program, and allow more people with COPD to experience the benefits of pulmonary rehabilitation. In people with stable COPD the 'HomeBase' model of pulmonary rehabilitation has been shown to deliver similar clinical outcomes to centre-based pulmonary rehabilitation. The aim of the study presented in Chapter Five was to inform the feasibility of an early, home-based, pulmonary rehabilitation program for people who were hospitalised due exacerbation of COPD. The study was designed as a three-phase action research protocol to enable continuous learning and problem solving in order to improve the model.

Action research was applied with the aim of developing a program that would fulfill the needs of people with COPD after discharge from hospital. Phase I tested our first design and although the protocol achieved promising clinical outcomes, many hospitalised patients with COPD did not meet eligibility criteria, including many of whom had a co-

morbid condition that impacted safety of home-based exercise. Phase II analysed barriers to the delivery and uptake of a home-based pulmonary rehabilitation early after hospital discharge using qualitative methods. Phase III incorporated earlier findings to determine if program accessibility could be enhanced.

The manuscript arising from this study was submitted for publication to *Chronic Respiratory Disease* on 12<sup>th</sup> March 2020 and is currently under review. The journal has an impact factor of 2.885.

As the methods in the manuscript had to be shortened to fulfill journal requirements, the following extended methods section provides more details on the development of each Phase of the study.

## Chronic Respiratory Disease

**Early home-based pulmonary rehabilitation following acute exacerbation of COPD: A feasibility study using an action research approach**

Journal:	<i>Chronic Respiratory Disease</i>
Manuscript ID	CRD-20-0028
Manuscript Type:	Original Paper
Date Submitted by the Author:	12-Mar-2020
Complete List of Authors:	Wageck, Bruna; La Trobe University, School of Allied Health, Human Services and Sport Cox, Narelle; La Trobe University; Institute for Breathing and Sleep; Monash University Central Clinical School Bondarenko, Janet; Alfred Health, Department of Physiotherapy Corbett, Monique; Alfred Health, Department of Physiotherapy Nichols, Amanda; Monash University Central Clinical School; Monash Health, Department of Physiotherapy Moore, Rosemary; Austin Health, Institute for Breathing and Sleep; Austin Hospital, Department of Physiotherapy Holland, Anne; La Trobe University, School of Allied Health, Human Services and Sport; Institute for Breathing and Sleep; Monash University Central Clinical School; Alfred Health, Department of Physiotherapy
Keywords:	Home-based, pulmonary Rehabilitation, Exacerbation, COPD, feasibility
Abstract:	Objective: Pulmonary rehabilitation (PR) improves function, reduces symptoms and decreases healthcare usage in people with chronic obstructive pulmonary disease (COPD) following an acute exacerbation (AECOPD). However, rehabilitation uptake rates are low. This study aimed to address barriers to uptake and completion of PR following AECOPD using an action research approach. Methods and Results: Phase I tested a home-based PR program started early after AECOPD. From 97 screened patients, 26 were eligible and 10 (38%) started home-based PR. Eight participants undertook $\geq 70\%$ of PR sessions, achieving clinically meaningful improvement in 6minute walk distance (mean (SD) change 76(60)m) and chronic respiratory disease questionnaire (CRQ) total score (15(21) units). Phase II identified potential barriers to uptake of home-based PR including access issues, confidence to exercise, and lack of information about PR benefits. Phase III involved re-testing the program with changes to recruitment and assessment strategies. From 77 screened patients, 23 were eligible and five (22%) started the program. Discussion: Home-based PR improved clinical outcomes, but program eligibility and uptake remain challenging. Efforts should be made to ensure PR program eligibility criteria are broad enough to accommodate patient needs, and new ways of engaging patients are needed to improve PR uptake after AECOPD.

<http://mc.manuscriptcentral.com/crd>

## 5.3 Extended Methods – Chapter Five

The study was approved by the The Alfred Human Research Ethics Committee 475/15 and La Trobe University Human Research Ethics Committee, and written informed consent was obtained from all participants. Each phase was added to the ethics protocol and approved as the research evolved.

### **PHASE 1 – FEASIBILITY STUDY**

The aim of this feasibility study was to inform the planning of a definitive multicentre randomised controlled trial. In the current study we explored key trial processes, and the feasibility and acceptability of an early home-based pulmonary rehabilitation intervention for people with COPD following an exacerbation. Participants were recruited during hospital admission in the respiratory and general medicine wards of the Alfred Hospital, Melbourne, Australia.

#### **Inclusion Criteria:**

- Confirmed diagnosis of COPD;
- Smoking history of at least 10 pack years;
- Aged over 40 years;
- Admitted to the respiratory or general medicine wards at the Alfred Hospital (Melbourne, Australia) for an ECOPD.

**Exclusion criteria:**

- Comorbidities which might prevent them from safely undertaking a home-based exercise program (musculoskeletal or neurological condition);
- Attended a pulmonary rehabilitation program in the previous 12 months;
- Inability to provide informed consent (cognitive impairment or not English speaker).

**Recruitment:**

Hospital inpatient lists were screened daily to identify potentially eligible participants. Eligibility was then confirmed with the ward physiotherapist in charge of the patient (if possible) and during a recruitment interview with the participant. If both eligible and agreeable, participants signed the consent form and an appointment for the baseline assessment was made to occur post discharge. In situations where it was not possible to schedule a baseline assessment date, because discharge date was not yet determined, the researcher monitored daily for discharge status and then communicated with the participant to book the assessment.

**Outcomes:**

The outcomes related to feasibility were eligibility and consent for the trial, attendance and completion of pulmonary rehabilitation. This was to understand if the intervention was useful and acceptable to people in the target population (49).

- *Eligibility*: measured by the number of patients who met the inclusion criteria;



- *Consent*: measured by the number of eligible participants who consented to participate in the study;
- *Uptake*: measured by the number of participants that commenced the intervention;
- *Attendance*: measured by the number of weeks attended in the intervention;
- *Completion*: measured by the number of participants that achieved at least 70% of the program (6 sessions);
- *Acceptability*: patient reported-satisfaction was measured by semi-structured interview at the end of the program.

The clinical outcomes measured were:

- *Functional exercise capacity*: measured by 6-minute walk distance (6MWD): a valid measure of exercise capacity in COPD and is responsive to pulmonary rehabilitation (50). The test was performed twice and the greatest distance recorded.
- *Dyspnoea*: measured by *Modified Medical Research Council Scale*, that measures functional breathlessness on a scale with scoring from zero to four (51);
- *Quality of life*: measured by *Chronic Respiratory Disease Questionnaire*, which is valid in people with COPD and responsive to pulmonary rehabilitation (52). The questionnaire has 20 questions and assesses dyspnoea, fatigue, emotional function and mastery using a 7-point Likert scale;
- *Self efficacy*: measured by *Pulmonary rehabilitation adapted index of self-efficacy*. The questionnaire has 15 statements about general and pulmonary rehabilitation-specific self-efficacy and is reproducible and sensitive to change following pulmonary rehabilitation in individuals with COPD (53);

- *Anxiety and depression*: measured by *Hospital Anxiety and Depression Scale*, a questionnaire that consists of a series of 14 statements, with responses based on a 4-point Likert scale (54).

### **Data Collection:**

Participants returned to the hospital for baseline assessment which was performed in the week after hospital discharge. Baseline demographics of age, gender, body mass index and lung function (spirometry) were collected from medical chart. Clinical measures were recorded at baseline and immediately following the intervention period (8 weeks). A researcher not involved in delivery of the intervention assessed the participants pre and post the intervention period. After completion of the program recruited participants undertook a semi-structured interview, to describe their experiences of undertaking home-based pulmonary rehabilitation following hospitalisation. The interviews were digitally recorded and transcribed verbatim.

### **Intervention:**

Participants received an 8-week home-based pulmonary rehabilitation program (31) commenced within 1 to 3 weeks after hospital discharge. The program consisted of one home visit by a physiotherapist to ensure safety and understanding of the exercises, followed by 7 weekly telephone calls with a physiotherapist that were based in motivational interviewing (8, 26, 28). This model of pulmonary rehabilitation has previously been demonstrated to be effective for people with stable COPD (31). The home-based program included individual aerobic exercise training (walking), as well as

resistance training for the arms and legs using daily activities and equipment that is readily available in the home environment. Participants were encouraged to exercise for 30 minutes, 5 times per week and to document this in an exercise diary. The structured weekly phone calls were delivered by a physiotherapist trained in motivational interviewing who reviewed the home diaries, the exercise progression and delivered self-management training based on Lung Foundation Australia guidelines. During the calls participants were also provided with a menu of topics covering aspects of self-management (26) and were encouraged to choose one topic for discussion and goal setting each week. Participants also received the “Living well with COPD” book by Lung Foundation Australia.

#### **Data analysis:**

Data analysis was conducted using SPSS V.25.0 (IBM, New York). Descriptive statistics (mean and standard deviation (SD) and number n (%)) were used to describe the sample and clinical outcomes. Paired t-tests were used to compare within groups and between groups outcome results.

#### **PHASE 2 – QUALITATIVE STUDY**

Data from Phase I revealed that a substantial number of patients did not take up the offer of home-based pulmonary rehabilitation. Anecdotally there appeared to be some consistent reasons for this, such as the burden of attending the hospital for an assessment prior to commencement of the program. However, the perspectives of patients regarding uptake of an offer of home-based pulmonary rehabilitation was not collected in a systematic manner. As clinicians have close contact with patients during their hospital stay it was deemed that interviewing these professionals may further enhance

understanding of barriers and facilitators to accepting an offer of home-based pulmonary rehabilitation shortly after an exacerbation of COPD. Understanding these barriers and facilitators would allow for changes to the study protocol that would make home-based pulmonary rehabilitation accessible for the largest number of patients. The aim of Phase II was to document the perspectives of both patients and clinicians regarding potential reasons for declining home-based pulmonary rehabilitation following an exacerbation, and how the intervention could be optimised.

### **Participants:**

(i) *Clinicians*: Inclusion criteria were being a health care practitioner current working at The Alfred Hospital within the pulmonary rehabilitation program, general medicine ward or respiratory ward.

(ii) *Hospitalized Patients*: Inclusion criteria were admission to Alfred Health in Melbourne with a primary diagnosis of an exacerbation of COPD, current or former smoker of at least 10 pack years and aged 40 years or over. Inclusion criteria were the same as Phase I in an effort to replicate the same population. It was not possible to re-interview participants associated with Phase I due in accordance with ethics committee standards.

### **Data Collection:**

One author (BW, PhD student, female) conducted all interviews. The interviews were audio-recorded and later transcribed verbatim for analysis. The qualitative interviews were performed over the phone or face-to-face in two distinct group of people: (i) Clinicians and (ii) Hospitalized Patients.

(i) *Clinicians*: The clinicians were invited to participate in this sub-study via email.

Those who consented to participate were asked a series of open ended questions about their perspectives regarding home-based pulmonary rehabilitation, timing of recruitment, and strategies for recruitment (supplemental material).

(ii) *Hospitalized Patients*: The recruitment followed the same steps as the main study and patients who agreed to participate in the qualitative sub-study were interviewed by a researcher during the inpatient period. Participants were asked about their thoughts on possible constraints in taking part in a home-based pulmonary rehabilitation program after an exacerbation and suggestions for how to improve such a program (supplemental material).

### **Data analysis:**

Content analysis was used to identify the most consistent themes during the interviews.

The transcribed interviews went through a four-step process that included: a) immersing oneself in data, b) selecting meaningful units, c) condensing and labelling of data, and d) clustering and formulation of themes (55). Data from clinician and participant interviews were analysed separately as perceptions were likely to differ between groups.

### **PHASE III – RE-PILOT THE REVISED PROTOCOL**

Overall, data from Phase II identified the following barriers to home-based pulmonary rehabilitation: issues of getting to the outpatient clinic for assessment; confidence in exercising after exacerbation of COPD; lack of information regarding pulmonary rehabilitation benefits and program structure. With that information in hand the protocol

from Phase I was redesigned to overcome these barriers. The main changes to the protocol were: (i) the time and location of the first assessment (discharge day, in the ward); (ii) improving information to patients about home-based pulmonary rehabilitation benefits and structure (video testimonials); and (iii) adding a handout of information for clinicians informing them about the research and encouraging them to discuss pulmonary rehabilitation options with their patients.

### **Participants:**

Phase III adopted the same eligibility criteria as from Phase I, with the exception that Phase III did not exclude participants based on their previous participation in pulmonary rehabilitation programs. Participants were not included if they were currently enrolled in a pulmonary rehabilitation program.

### **Recruitment:**

Recruitment followed the same steps from Phase I, however when a eligible participant were screened, the physiotherapist in charge of the case would receive a hand-out with information regarding pulmonary rehabilitation benefits and explanation about the early home-based trial program. The clinicians were also encouraged to open the discussion about early pulmonary rehabilitation as part of the patient's discharge plan. Before signing the consent form, all eligible participants were offered to watch a short video of testimonials from people who have previously undertaken the home-based pulmonary rehabilitation program. If the eligible participant agreed to participate they would sign the consent form and the first assessment was conducted on site before discharge.

**Outcomes:**

Phase III maintained the same outcomes related to feasibility (50) and clinical measures as Phase I, and followed the same standards for assessment. One test was added to the clinical outcomes aiming to facilitate functional capacity assessment in the new reality:

- *One Minute sit-to-stand test*: is a valid, reliable and responsive test to assess exercise capacity in people with COPD (56). Using a standard armless chair, participants were instructed to stand up and sit down as many times as possible during one minute (56).

**Data Collection:**

The first assessment was performed on the day of discharge (or the day prior). Baseline demographics of age, gender, body mass index and lung function (spirometry) were collected from medical chart and clinical measures were recorded at baseline (before discharge) and immediately following the intervention period (8 weeks). A researcher not involved in the intervention assessed the participants pre and post the intervention period.

**Intervention:**

There were no changes in the delivered intervention compared to Phase 1 of the study.

**Data analysis:**

Data analysis was conducted using SPSS V.25.0 (IBM, New York). Descriptive statistics (mean and standard deviation (SD) and number n (%)) were used to describe the sample

and clinical outcomes. Paired t-tests were used to compare within groups and between groups outcome results.



## 5.4 Manuscript

**Early home-based pulmonary rehabilitation following acute exacerbation of COPD:**

**A feasibility study using an action research approach.**

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Australia

## ABSTRACT

**Objective:** Pulmonary rehabilitation (PR) improves function, reduces symptoms and decreases healthcare usage in people with chronic obstructive pulmonary disease (COPD) following an exacerbation (ECOPD). However, rehabilitation uptake rates are low. This study aimed to address barriers to uptake and completion of PR following ECOPD using an action research approach. **Methods and Results:** Phase I tested a home-based PR program started early after ECOPD. From 97 screened patients, 26 were eligible and 10 (38%) started home-based PR. Eight participants undertook  $\geq 70\%$  of PR sessions, achieving clinically meaningful improvement in 6minute walk distance (mean (SD) change 76(60)m) and chronic respiratory disease questionnaire (CRQ) total score (15(21) units). Phase II identified potential barriers to uptake of home-based PR including access issues, confidence to exercise, and lack of information about PR benefits. Phase III involved re-testing the program with changes to recruitment and assessment strategies. From 77 screened patients, 23 were eligible and five (22%) started the program. **Discussion:** Home-based PR improved clinical outcomes, but program eligibility and uptake remain challenging. Efforts should be made to ensure PR program eligibility criteria are broad enough to accommodate patient needs, and new ways of engaging patients are needed to improve PR uptake after ECOPD.

Key words: Home-based pulmonary Rehabilitation; Exacerbation, COPD, feasibility

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease that is associated with reduced functional capacity, poor health-related quality of life and high mortality<sup>1</sup>. Exacerbations of COPD (ECOPD) contribute to disease progression and increasing symptoms<sup>2</sup>. ECOPD are commonly defined as a worsening of baseline symptoms<sup>1</sup> and are one of the leading causes of hospital admission and death in people with COPD<sup>3</sup>. This highlights the importance of identifying and providing interventions that reduce the negative consequences of exacerbations<sup>3,4</sup>.

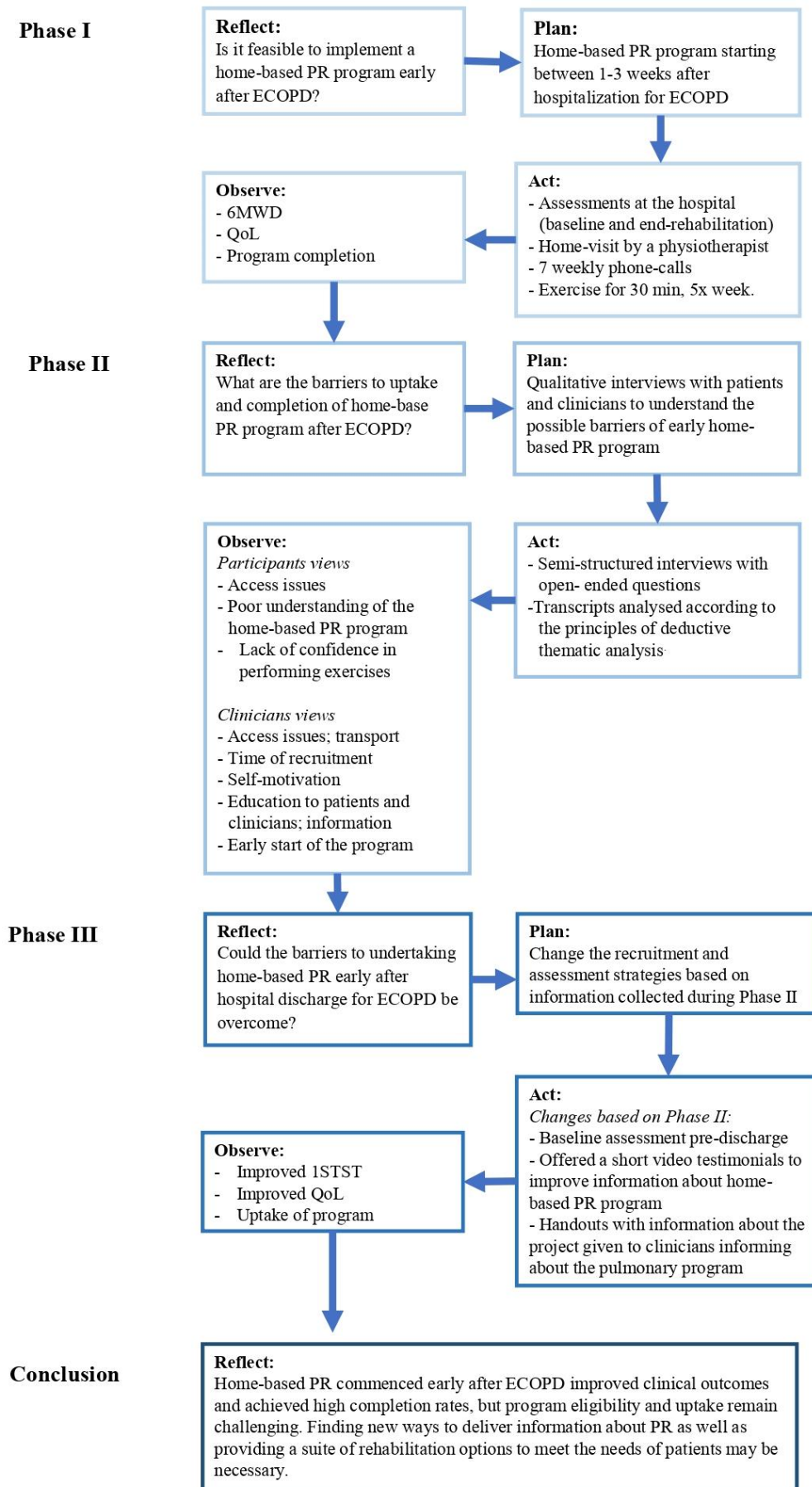
Robust evidence supports pulmonary rehabilitation leading to improved exercise capacity and quality of life, and reduced symptoms and health care utilisation in people with stable COPD<sup>5</sup>. Additionally, a systematic review reported that PR started early after an ECOPD could decrease hospital admissions and mortality<sup>6</sup>.

However participation rates for PR programs after ECOPD are exceedingly low<sup>7</sup>. In the United Kingdom, less than 10% of all people discharged from hospital following ECOPD completed an outpatient PR program<sup>8</sup>. Moreover, a multicentre study analysing PR participation in the US indicates less than 3% of people hospitalised with ECOPD received PR in the year following exacerbation, with fewer than 2% receiving PR within 6 months after hospitalisation<sup>7</sup>. Even fewer people (0.3%) commenced PR within the first month after hospital discharge<sup>7</sup>. Alternative PR models have been proposed to enhance program uptake in people with stable COPD<sup>9</sup>. The HomeBase model of PR is one such alternative, demonstrated to be safe and to deliver similar benefits to outpatient, centre-based, PR in people with stable COPD<sup>9</sup>. A nested qualitative study reported that participants felt well supported and the HomeBase program could fit in with their daily lives<sup>10</sup>. However, whether the same HomeBase model of PR, delivered early following hospitalisation for ECOPD is feasible and acceptable is unknown. The present study

employed an action research design<sup>11</sup> to enable continuous learning regarding feasibility of HomeBase PR for people following ECOPD.

## **METHODS**

The study comprised three phases (Figure 1): i) pilot study testing feasibility of the HomeBase PR program early following ECOPD; ii) qualitative study to understand issues of feasibility from Phase I to support changes to the study protocol under investigation; and iii) re-pilot study for feasibility and acceptance of the modified protocol. The study was approved by the Human Research Ethics Committees of Alfred Health (475/15), and written informed consent was obtained from all participants.



**Figure 1.** Flow-chart of the action research design

## **PHASE I – FEASIBILITY STUDY**

### *Participants:*

Individuals with a confirmed diagnosis of COPD, smoking history of at least 10 pack years and aged over 40 years who were admitted to the respiratory or general medicine wards at the Alfred Hospital (Melbourne, Australia) for an ECOPD were eligible to be included. Participants were excluded if they had comorbidities which might prevent them from safely undertaking a home-based exercise program (e.g. musculoskeletal or neurological condition), had attended a PR program in the previous 12 months, or could not consent on the study (cognitive impairment or non-English speaker).

### *Intervention:*

Eligible participants were approached by a researcher not involved in their daily inpatient management. Individuals who consented to participate had a baseline assessment booked for the week after discharge in the physiotherapy outpatient clinic (Alfred Hospital).

Participants undertook an early (commenced within 3 weeks after discharge) home-based program. The home-based PR program consisted of one home visit by a physiotherapist, to prescribe exercise training and ensure safety and understanding of the program.

Aerobic exercise was prescribed at a speed equivalent to 70-80% of baseline six-minute walked distance (6MWD). Where a 6MWT was unable to be performed exercise training was prescribed on the basis of symptoms (BORG 3-4). Resistance training used free weights (with equipment accessible in the home environment) and functional activities (e.g. sit-to-stand from a dining chair, step ups on home stairs or on the neighborhood, and water bottles for upper limb weights). The initial home visit was followed by seven weekly phone calls based in motivational interviewing<sup>9</sup>. Participants were encouraged to undertake exercise training (30 minutes aerobic training plus resistance training) 5 times per week and to document this in an exercise diary. The structured weekly phone calls



were delivered by a physiotherapist trained in motivational interviewing who reviewed the home diaries, exercise progression and delivered self-management training. During the calls participants were also provided with a menu of topics covering aspects of self-management<sup>12</sup> and were encouraged to choose one topic for discussion and goal setting each week.

*Outcomes:*

Baseline demographics of age, gender, body mass index and lung function (spirometry) were collected from participant's medical records. Feasibility outcomes for program implementation were eligibility, uptake and completion<sup>13</sup> (Table 1). Key clinical outcomes of interest were functional exercise capacity<sup>14</sup>, dyspnoea<sup>15</sup>, quality of life<sup>16</sup>, self efficacy<sup>17</sup>, and anxiety and depression<sup>18</sup> (Table 1). A researcher not involved in delivering the intervention assessed the participants pre- and post- the intervention period. Completion rates were collated at the end of the intervention period, with an a priori definition of completion as undertaking a minimum of 70% of planned PR sessions<sup>19</sup>.

**Table 1.** Phase I and III outcomes and instruments.

Feasibility measures		
	Measurement description	Results interpretation
Eligibility	- Number of patients who met the inclusion criteria	Whether people in the target population would use the intervention <sup>13</sup> .
Consent	- Number who consent	
	- Number who commence the rehabilitation program	
Attendance	- Number of weeks attended	
Completion	- Number who complete at least 70% of the program	Understand how this intervention would fit with daily-life activities <sup>13</sup> .
Satisfaction	- Patient reported-satisfaction (through semi-structured interview at the end of the program)	
Clinical Outcomes:		
	Measurement description	Results interpretation
Functional exercise capacity	<i>6-minute walk distance (6MWD)</i> : valid measure of exercise capacity in COPD and is responsive to PR <sup>14</sup> . Test was performed twice and the greater distance recorded.	Greater distance walked represent better functional capacity. MCID = 25 – 30 metres <sup>20</sup> .
	For phase III only - One Minute sit-to-stand test: valid, reliable and responsive test to assess exercise capacity in people with COPD <sup>21</sup> . Using a standard armless chair, participants were instructed to stand up and sit down as many times as possible during one minute <sup>21</sup> .	Higher number of repetitions represent better functional capacity. MCID = three repetitions <sup>21</sup> .
Dyspnoea	<i>Modified Medical research Council Scale</i> : measures functional breathlessness on a scale with scoring from zero to four <sup>15</sup> .	0 = breathlessness does not interfere in activities 4= indicates important impairment due to breathlessness. MCID = change of 1 unit <sup>22</sup> .
Anxiety and depression	<i>Hospital Anxiety and Depression Scale</i> : it consists of a series of 14 statements, with responses based on a 4-point Likert scale <sup>18</sup> .	Higher score is indicative of greater anxiety or depression. MCID = 1.5 units <sup>23</sup> .
Quality of life	<i>Chronic Respiratory Disease Questionnaire</i> : valid and responsive tool in PR <sup>16</sup> . The questionnaire has 20 questions and assesses dyspnoea, fatigue, emotional function and mastery using a 7-point Likert scale.	Higher score indicating better HRQOL. CRQ total score MCID = 10 points <sup>24</sup> .

Self efficacy	<i>Pulmonary adapted index of Self-efficacy</i> : the questionnaire has 15 statements about general and pulmonary rehabilitation-specific self-efficacy questions and is reproducible and sensitive to change following PR in individuals with COPD <sup>17</sup> .	Higher score indicating greater levels of self efficacy. MCID = change from 0.5 to 1.5 units <sup>25</sup> .
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Table legend: MCID: Minimal clinically important difference

### *Assessments:*

Clinical measures were recorded in the week after discharge (baseline), and following completion of the 8-week intervention period at the outpatient clinic at The Alfred Hospital. Following program completion, participants undertook a semi-structured interview to describe their experiences of home-based PR participation.

The outcomes were analysed using descriptive statistics, qualitative analysis, and compilation of basic data related to recruitment. Paired t-tests were used to compare pre and post measurements.

### *Results:*

During six months of recruitment, from 97 screened patients, 26 met the inclusion criteria (27%). Reasons for participant exclusion are detailed in Table 2. Of the 26 eligible participants, 15 (58%) consented to participate and 10 (38%) undertook the first assessment and started the program (Table 2). Reasons for not commencing the program were referral to palliative care (n=1), feeling unwell (n=1), new diagnosis of cancer (n=1), unable to contact (n=1) and failed to attend appointment (n=1).

**Table 2.** Feasibility outcomes from Phase I and Phase III

	<b>Phase I</b>	<b>Phase III</b>
<b>Screened</b>	n=97	n=77
<b>Not eligible</b>	n=71 <ul style="list-style-type: none"> <li>• PR within last 12 months n=26</li> <li>• &lt;10 pack year smoking history n=8</li> <li>• Cognitive issues n=18</li> <li>• Social issues n=6</li> <li>• Non-english speaking background n=4</li> <li>• Eligibility unable to be established n=9</li> </ul>	n=58 <ul style="list-style-type: none"> <li>• Currently enrolled in PR n=12</li> <li>• &lt;10 pack year smoking history n=4</li> <li>• Cognitive issues n=9</li> <li>• Social issues n=8</li> <li>• Non-english speaking background n=2</li> <li>• Lived out of area n=5</li> <li>• Not suitable for home-based exercise n=10</li> <li>• Other comorbidities precluding exercise n=4</li> <li>• Eligibility unable to be established n=4</li> </ul>
<b>Eligible</b>	n=26	n=19
<b>Did not consent</b>	n=11 <ul style="list-style-type: none"> <li>• Did not wish to participate in PR n=7</li> <li>• Preferred centre-based PR n=1</li> <li>• Didn't want health professional visiting house n=1</li> <li>• Unable to attend for assessment n=2</li> </ul>	n=9 <ul style="list-style-type: none"> <li>• Did not wish to participate in PR n=3</li> <li>• Preferred centre-based PR n=4</li> <li>• Already doing other home exercise program n=2</li> </ul>
<b>Consented</b>	n=15	n=10
<b>Commenced program</b>	n=10 <p>Reasons for not commencing program (n=5):</p> <ul style="list-style-type: none"> <li>• Referred to palliative care (1)</li> <li>• Unwell (1)</li> <li>• Unable to contact (1)</li> <li>• New diagnosis of cancer (1)</li> <li>• Failed to attend appointment (1)</li> </ul>	n=5 <p>Reasons for not commencing program (n=5):</p> <ul style="list-style-type: none"> <li>• Declined to participate due to schedule n=2</li> <li>• Unable to contact n=3</li> </ul>
<b>PR Completers</b>	n=8 <p>Reasons for non-completion:</p> <ul style="list-style-type: none"> <li>• Developed another health condition n=1</li> <li>• Started other home-based physiotherapy program n=1</li> </ul>	n=4 <p>Reasons for non-completion:</p> <ul style="list-style-type: none"> <li>• Working fulltime, not enough time for exercise n=1</li> </ul>
<b>Undertook final assessment</b>	n=10 (n=8 for 6MWT)	n=5
<b>Video testimonials</b>		Offered: n=17 (89% of those eligible) Watched video n=11 <ul style="list-style-type: none"> <li>• Consented n=9</li> </ul> Declined video n=6 Not offered video n=2 <ul style="list-style-type: none"> <li>• Already consented n=1</li> <li>• Already refused n=1</li> <li>• Discharged prior to approach n=4</li> </ul>
<b>Clinician information handout</b>		Provided n=10 (53% of those eligible) Not provided n=9 <ul style="list-style-type: none"> <li>• Not able to contact clinician n=5</li> <li>• Physiotherapist already aware of patient eligibility n=4</li> </ul>

Eight participants achieved >70% of the program ( $\geq 6$  PR sessions); while two participants only completed 2 or 3 sessions of PR due to medical issues ( $n=1$ ) and starting an alternative home-based physiotherapy program ( $n=1$ ). All participants completed post-intervention questionnaires, and  $n=8$  attended the centre for post-rehabilitation physical assessment. At the conclusion of the PR program, participants demonstrated clinically important improvements in exercise capacity (mean (SD) change 6MWD 76 (60)m), and quality of life (CRQ total score 15(21)units) (Table 3).

Qualitative interviews with participants ( $n=9$ ) after the program indicated they were satisfied with the structure and content of the home-based PR program (Box 1).

**Table 3.** Participant characteristics and clinical outcomes from Phases I and III.

	Phase I (n=10)		Phase III (n=5)	
	Baseline	Post-intervention	Baseline	Post-rehabilitation
<b>Gender male/female</b>	6/4		2/3	
<b>Age, years</b>	75 (8)		68 (15)	
<b>FEV<sub>1</sub>, % predicted</b>	51 (31) (n=7)		54 (17) (n=4)	
<b>FEV<sub>1</sub>, L</b>	1.2 (0.7) (n=7)		1.2 (0.1) (n=4)	
<b>Hospital length of stay, days</b>	10 (7)		9 (13)	
<b>Current smokers, n</b>	2		0	
<b>Smoking history, pack years</b>	44 (25)		44 (10 to 160)	
<b>6MWD, m</b>	309 (131) (n=8)	384 (149) (n=8) <sup>§*</sup>	-	255 (203) (n=3)
<b>1STST, number of repetitions</b>	-	-	13 (8)	9 (11) (n=3)
<b>mMRC, n</b>				
<b>0</b>	2	1	0	0
<b>1</b>	1	4	1	2
<b>2</b>	3	3	2	1
<b>3</b>	3	1	0	2
<b>4</b>	1	1	2	0
<b>HADS Depression</b>	5 (4)	4 (3)	6 (3)	8 (5)
<b>Case</b>	0	0	0	1
<b>No case</b>	10	10	5	4
<b>HADS Anxiety</b>	6 (3)	4 (3) <sup>§</sup>	8 (4)	6 (4)
<b>Case</b>	1	0	1	1
<b>No case</b>	9	10	4	4
<b>CRQ Total</b>	71 (23)	86 (19) <sup>§</sup>	58(36)	84 (29) <sup>§</sup>
<b>PRAISE</b>	48 (7)	50 (5) <sup>§</sup>	47 (4)	51 (4) <sup>§</sup>

Table legend: Data are mean (SD) except where otherwise indicated. Data for number of hospital length of stay and smoking history are median (IQR). \*p<0.05; §Mean improvements exceed MCID.

n, number of participants; FEV1: forced expiratory volume in one second; 6MWD: sixminute walk distance; m, metres; 1STST, One minute sit-to-stand test; mMRC, Modified Medical Research Council Questionnaire; HADS, Hospital Anxiety and Depression Scale; CRQ, Chronic Respiratory Questionnaire; PRAISE, Pulmonary Rehabilitation Adapted Index of Self-Efficacy.

#### Box 1 - Themes and subthemes identified during end rehabilitation interviews.

Motivation is a key to the program success

- Self-motivation is important to complete the program
- Phone-calls helped with motivation
- Increased confidence with the program
- The exercise diaries help to motivate and keep track of progress

Program was beneficial

- Could see improvement during the program
- Learned how to deal with disease and exercises
- Would recommend home-based pulmonary rehabilitation to people with COPD

Plans for the future

- Continue exercising after program ends
- Learned how to maintain a routine of exercises and that will be beneficial

Overcoming centre-based barriers

- Exercises are not scheduled, can be done during work and while travelling
- Preference for doing exercises alone
- Does not need to use public transportation

#### *Reflection:*

Data from Phase I revealed that 73% of patients were ineligible and only 38% of potential participants commenced home-based PR. The reasons potential participants refused the offer of an early home-based PR program were similar to those previously reported, including not wanting to participate in a clinical trial; being unable to attend the hospital



for assessment; not wanting a healthcare professional to visit the house; and preferring to attend centre-based PR. However, Phase I had not been designed to collect patient or clinician perspectives as to possible barriers to uptake of early home-based PR program. Therefore, we concluded that our approach could be improved if it were informed by patient and clinician perspectives.

## **PHASE II – QUALITATIVE STUDY**

Phase II aimed to document the perspectives of both patients and clinicians regarding the reasons why people decline home-based PR following an ECOPD, with the view to identifying how barriers to undertaking the program could be overcome.

### *Participants:*

(i) *Clinicians:* Clinicians who were currently working in pulmonary rehabilitation, or on the general medical or respiratory wards at the Alfred Hospital were invited via email to participate.

(ii) *Hospitalised Patients:* Individuals with a confirmed diagnosis of COPD, smoking history of at least 10 pack years and aged over 40 years who were admitted to the respiratory or general medicine wards at the Alfred Hospital (Melbourne, Australia) for an ECOPD were recruited. No patient participants in Phase II had been participants in Phase I.

### *Intervention:*

Clinicians and patients who agreed to participate in Phase II undertook audio-recorded, semi-structured interviews (Supplement A). Interviews were undertaken over the phone or face-to-face, and transcribed verbatim for analysis. Clinicians were asked a series of open ended questions about their perspectives of home-based pulmonary rehabilitation,

timing of recruitment, and strategies for recruitment. Patients were asked their thoughts about possible constraints to taking part in a home-based pulmonary rehabilitation program and suggestions for how to improve a program.

*Analysis of qualitative data:*

The transcribed interviews were manually coded line-by-line and analysed according to the principles of deductive thematic analysis<sup>26</sup>. The data analysis was a four-step process that incorporated: a) immersing oneself in data, b) selecting meaningful units, c) condensing and labelling of data (coding), and d) clustering and formulation of themes<sup>26</sup>. All de-identified transcripts of the interviews were analysed by two researchers independently; both of whom had experience of analyzing qualitative interviews and conducting PR (one with more than 10 years of experience, the other with 2 years). The researchers then compared major themes and any disagreements were solved by discussion. Data from clinician and participant interviews were analysed separately.

*Results:*

Twelve clinicians and 14 hospitalised patients participated in Phase II. (Table 4).

*(i) Clinicians:* Most clinicians felt that limited access to outpatient clinic for possible assessments, and a lack of information about pulmonary rehabilitation and its benefits were potential barriers for patients to engage in home-based pulmonary rehabilitation programs. The interviewed clinicians suggested it would be preferable to approach patients close to discharge when the patients are planning their return to daily life activities, meaning pulmonary rehabilitation options could be presented as a part of the discharge plan. Clinicians interviewed also highlighted the need for them to have more information regarding ongoing research projects so they could recommend to patients the most suitable treatments available for each case.

(ii) *Hospitalised Patients*: Patients felt that potential barriers to uptake of home-based pulmonary rehabilitation early after hospital discharge included access to outpatient clinic for assessments, and issues with and confidence in performing exercises. However, patient responses were more diverse compared to clinicians and indicated that most patients were not well informed about benefits of pulmonary rehabilitation, nor what to expect from participating. This lack of knowledge impacted on their ability to suggest substantial protocol changes.

**Table 4.** Results from Phase II- Qualitative Interviews with patients and clinicians

<i>Group</i>	<i>Theme</i>	<i>Quote</i>	<i>Suggestion for new protocol</i>
<b><i>Patients</i></b>	Access issues (n=4)	P01 "Getting into the hospital requires travel, a bit of walking in the carpark. To get to where the pulmonary rehabilitation actually is takes a long time" P13 "If they (patients) can't get to a main pulmonary rehabilitation group then the home based seems to be the better option for them"	Reduce travel to the hospital: perform the baseline assessment on discharge day or at the same day as an outpatient appointment
	Poor understanding of home-based program (n=4)	P05: If someone is saying that "I'm too sick", then you should be able to tell them that they need it to get better." P01 "I think if that is explain to them in hospital you might get a few more people to do it."	Education and modelling: show video testimonials from patients who completed home-based pulmonary rehabilitation program.
	Lack of confidence in performing exercises (n=5)	P10 "But there are times that just walking at the supermarket that can also be labouring if you are not feeling 100% you might get easier to throw the towel" P18 "If you are at home, you don't know how much you can do, you might overdo or underdo."	Education during inpatient phase
<b><i>Clinicians</i></b>	Access issues (n=10)	C01 "Any community access for someone who is relative housebound is obviously challenging" C02 "If they (patients) got lots of issues with transport, they live far away from the hospital, they might be working as well. These people should definitely be offered home-based"	Reduce travel to the hospital: perform the baseline assessment on discharge day or at the same day as an outpatient appointment
	Time for invite to participate (n=9)	C02 "I think it's important to almost plant that seed of "you need to start thinking about attending PR" pretty earlier in their admission and then almost reinforce that during and at the end" C08 "Towards the end. Some of them (patients) might be a bit too sick in the beginning but I think towards the end of the admission is probably the best time"	Eligible participant would be approached toward the end of hospital admission
	Self-motivation (n=5)	C04 "It would depend on the patient. So maybe some patients would be reluctant to do home-based if they thought that they were going to have maybe motivational issues or commitment issues about completing the program" C10 "Some people feel that they won't be motivated enough to do it at home"	Goal oriented pulmonary rehab (no change from last program)

Education to patients (n=9)	<p><i>C05 “Educating them about the programs are going to work and really trying to reassure them that it's actually going to be really beneficial to do pulmonary rehabilitation”</i></p> <p><i>C07 “I think that I kind of already talked about, maybe having that information early in admission and having something to look over, a handout”</i></p>	Show video testimonials from patients who have completed a pulmonary rehabilitation program.
Education to clinicians (n=3)	<p><i>C05 “Maybe run an education session for them (ward physiotherapists) about what the project is and why is so important, so that they can educate the patients with all of the options (of pulmonary rehabilitation)”</i></p> <p><i>C10 “make staff aware that there is this home-based option there, and then of course this can increase the home-bases uptake”</i></p>	Handouts detailing eligibility for pulmonary rehabilitation and home-based programs
Early pulmonary rehabilitation (n=8)	<p><i>C05 “But after 2 weeks or 3 weeks they are generally ready, they’ve got over their illness physically and mentally and they are ready to get into exercise”</i></p> <p><i>C06 “Two weeks, 2-3 weeks period after an exacerbation is a good time to try to grab them (patients, or anytime just getting them involved would be good”</i></p>	Start within 1-3 weeks after discharge (no change from last program)

### *Reflection:*

Phase II identified potential barriers including access to assessments issues, confidence in exercising after ECOPD, lack of information of pulmonary rehabilitation benefits and structure. With that information, the protocol from Phase I was redesigned in an effort overcome these barriers. Because Phase I participants who undertook home-based PR were satisfied with its structure and content, the changes to the protocol for Phase III focused on strategies to improve program uptake. Specifically:

- (i) Time and location of the first assessment: Participants were recruited on the discharge day or the day before, and the first assessments were done at the time of the consent, in order to remove the requirement to travel back to the hospital for assessment. The One Minute sit-to-stand test (1STST) was added to the assessment, as it is a valid, reliable and responsive tool to assess exercise capacity in people with COPD that requires minimal space to be performed<sup>21</sup> and may be more feasible post ECOPD (Table 1).
- (ii) Improving information to patients about home-based pulmonary rehabilitation benefits and structure: During recruitment, eligible participants were offered to watch short video testimonials from patients who had previously undertaken the home-based program; and,
- (iii) Clinician information: When a potential participant was identified, a handout was given to the clinician to notify them of the patient's eligibility and encouraging the clinician to open a discussion regarding pulmonary rehabilitation options.

### **PHASE III – RE-PILOT THE REVISED PROTOCOL**

#### *Participants:*

Phase III adopted the same eligibility criteria from Phase I, with the exception that Phase III did not exclude participants based on their previous participation in PR programs. Participants were not included if they were currently enrolled in a PR program.

*Intervention:*

There were no changes in the delivered intervention compared to Phase I.

*Outcomes:*

Phase III maintained the same outcomes related to feasibility<sup>13</sup>. In Phase III the one-minute sit-to-stand test was added to the measures from Phase I, all other measures remained unchanged and followed the same standards for assessment.

*Assessments:*

After participants consented, clinical measures were recorded at baseline (prior to discharge from hospital) and immediately following completion of the 8-week intervention period. The outcomes of Phase III were measured with descriptive statistics regarding feasibility and clinical outcomes, and qualitative analysis.

*Results:*

During seven months of recruitment, from 77 screened patients, 22 were eligible to the study (29%). Reasons for participant exclusion are detailed in Table 2. Of the 22 eligible participants, 10 (45%) consented to participate and 5 (23%) undertook the first assessment and started the program (Table 2). Reasons for not commencing the program were having a busy schedule (n=2) and being unable to contact (n=3).

In terms of recruitment strategies, information flyers were handed to clinicians on 10 occasions. Video testimonials were offered to 17 eligible participants, with n=7 choosing to watch the full video (4 minutes) and n=4 viewing part of it (Table 2). From the people

who watched the video testimonials nine (82%) consented to participate in the trial. All four PR completers in Phase III had viewed the video.

Four participants achieved >70% of the program ( $\geq 6$  PR sessions); while one participant only completed one session of PR due to working fulltime and having limited time to exercise (n=1). None of the participants who started HomeBase pulmonary rehabilitation performed 6MWT at the baseline assessment as four were in isolation on the ward and one did not want to leave the room for the assessment. There was a clinically meaningful improvement in quality of life after home-based PR in Phase III (Table 3). All participants that started the program were asked to perform the final assessments however, two participants could not return for assessments due to personal reasons and only responded to questionnaires; exercise capacity was not collected on these occasions.

## **DISCUSSION**

This feasibility study demonstrates the challenges in engaging patients in a pulmonary rehabilitation program early after hospitalisation. Although home-based pulmonary rehabilitation was well accepted by the participants who consented and engaged in the program, eligibility and uptake remained low. The present study demonstrated an overall uptake rate of 31% across phases I and III. Despite concerted efforts to overcome possible barriers to home-based PR, uptake rates did not improve between Phase I and Phase III. Given the potential for pulmonary rehabilitation to reduce hospital admissions<sup>6</sup>, the low eligibility for pulmonary rehabilitation following ECOPD represents an unrealised opportunity to enhance patient and health system outcomes. Although we used typical exclusion criteria for home-based rehabilitation programs (e.g. balance deficits, cerebral or lower limb palsies, musculoskeletal impairment or cardiac conditions that would



prevent independent exercise training), the large number of excluded patients suggests that these criteria may limit participation in home-based PR.

In this study we utilised a home-based PR program in an attempt to address well documented barriers to centre-based PR such as travel to the centre and competing demands on time<sup>27</sup>. As has been seen in people with stable COPD<sup>9</sup>, following hospitalisation for an ECOPD a home-based model of PR was acceptable to participants, had good retention in those who chose to commence the program, and produced clinically meaningful improvements in outcomes. Although the program was well received by those who undertook it, uptake in those who were eligible did not improve between Phase I and Phase III, and was less than that reported for centre-based post-exacerbation pulmonary rehabilitation<sup>28</sup>. As the period following ECOPD may be both physically and emotionally taxing for people with COPD, this could impact on willingness to accept an offer of rehabilitation. In previous studies of centre-based post-exacerbation pulmonary rehabilitation, uptake rates have ranged from 20-60%<sup>8, 29-31</sup>, demonstrating the difficulty in engaging patients in any pulmonary rehabilitation model at this time.

Despite a modest uptake rate for home-based PR in this trial, of those who commenced the program 80% completed at least 70% of the prescribed PR sessions (6 weeks). This completion rate is substantially higher than that seen in people with stable COPD attending centre-based PR<sup>28</sup>, however was not as great as that achieved by people with stable COPD undertaking home-based PR (91%)<sup>9</sup>. Completing PR is crucial to achieving benefit, with people who complete PR being 56% less likely to be admitted to hospital in the following year than those who are unable to complete rehabilitation (HR 0.439,  $p=0.02$ )<sup>9</sup>. With recent data suggesting fewer than 3% of individuals complete PR within 12 months of a hospital admission for ECOPD<sup>7</sup>, in addition to overcoming practical

obstacles to PR attendance, novel strategies are required to encourage patient engagement in the rehabilitation at this time.

During qualitative interviews in Phase II clinicians and patients indicated more information about the home-based PR program and its anticipated benefits would be useful. Limited patient and healthcare practitioner knowledge of pulmonary rehabilitation and its expected outcomes can act as a barrier to PR uptake and completion<sup>32</sup>. To help overcome this potential barrier, video testimonials from people who have previously completed home-based PR were employed in Phase III. Providing health education using narrative communication in a video format is demonstrated to be more engaging and provides social role models, as compared to brochures or statistics<sup>33</sup>. Of the five participants who commenced home-based PR in Phase III all had viewed the video testimonials. While this appears positive, given the small numbers the true effect of the use of video testimonials in this group of people experiencing an ECOPD is unclear. Other efforts to engage people with pulmonary rehabilitation during hospitalisation, including giving a ‘taster’ pulmonary rehabilitation session have been similarly lacklustre<sup>34</sup>. Given the period post hospitalisation is a difficult time to engage patients in rehabilitation, finding ways to engage patients with the rehabilitation process remains a challenge for clinicians and researchers alike.

Compounding modest uptake rates for home-based PR in this study, only 28% of all people admitted to hospital for ECOPD during the recruitment period were eligible for inclusion. This eligibility rate is lower than in other studies of post-exacerbation rehabilitation (29-60%)<sup>29-31, 35</sup> and for home-based PR in stable COPD (56%)<sup>9</sup>. In the present study all individuals admitted to the hospital for ECOPD were screened for eligibility. Of people who did not meet inclusion criteria, nearly a quarter (24%) had a comorbid condition that impacted safety and ability to enrol in a home-based program.

Multiple co-morbid conditions are common in people with COPD, with nearly all patients having at least one co-morbid condition and more than 50% having four or more comorbid conditions<sup>36</sup>. The presence of comorbidities in COPD is associated with increased likelihood of exacerbation and of hospitalisation<sup>36</sup>, confirming it is the most unwell and complex of patients with COPD who are the focus of post-exacerbation rehabilitation. Although the presence of co-morbidities may explain a proportion of non-eligible patients, it also highlights that a home-based PR program while overcoming common barriers to program attendance may not be appropriate for everyone. Future studies might focus on new interventions suitable for complex patients with multi-morbidity.

## **CONCLUSIONS**

A home-based PR program commenced early after ECOPD achieved improvements in clinical outcomes and high completion rates, however program uptake remains challenging. Given the period of hospitalisation is a difficult time to engage patients in rehabilitation, it may be necessary to find new ways to deliver information about PR, as well as providing a suite of rehabilitation options to meet the needs of patients may be necessary. Future studies might focus on new interventions suitable for complex patients with multi-morbidity after exacerbations of COPD.

## **Conflict of interest**

The Authors declare that there is no conflict of interest.

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## 5.5 Supplemental Material

### **Supplement A – Semi structured interviews**

Patients and Clinicians answered a series of open questions that were audio-recorded for later transcription. The researcher conducting the interviews had a question guide with the topics that should be present on the interview and the questions were incorporated in a conversation leaving the researched free to follow-up the questions enabling the researcher to gather the most complete answer from the participant. The guide for each interview is presented above:

#### Clinicians Interview Guide:

- 1- To begin, can you tell me your thoughts about home-based PR for people with COPD?
- 2- In your opinion, what might be some of the barriers that prevent people from taking up an offer of home-based PR?
- 3- Can you tell me about any strategies that might make it easier for people with COPD to take up the offer of home-based pulmonary rehabilitation after they have had an exacerbation?
- 4- Can you please describe for me what kind of patients you think would benefit from home-based PR?
- 5- What are your thoughts on the optimal timing of pulmonary rehabilitation for people who have had an exacerbation of COPD?
- 6 - Do you have any other thoughts or suggestions about how we could make early PR easier for people who have just had an acute exacerbation of COPD?

#### Hospitalised Patients Interview Guide:

- 1- To begin, could you tell me about any experience you have had with a PR programme in the past?
- 2- Can you describe what you would expect would be happening in a PR program?
- 3a- Can you tell me about the impressions you had about the home-based PR program that I described to you?
- 3b- Talking specifically about exercises, can you tell me your thoughts about performing exercises?
- 4- Thinking about you daily life activities and shortness of breath, can you describe for me what you think it will be like for you when you are discharge from hospital?
- 5- Can you describe for me your thoughts about taking part in this specific home-based PR program after you have had a flare up of COPD?
- 6- Can you tell me, what do you think might make it easier for you, or someone in a similar situation as you, to undertake home based PR after you go home from hospital?
- 7- In the event you were to have another admission to hospital for a flare up of your COPD/lung condition, what would be your thoughts about participating in home-based PR at the time of discharge?
- 8- Do you have any other thoughts or suggestions that could help us to improve the home-based pulmonary rehabilitation program?

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# CHAPTER SIX

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*Conclusions and future directions*

## 6.1 Overview of the main findings of the thesis

The four studies that compose this thesis (Chapter Two to Five) described the impact of exacerbations on the health status of people with COPD and add further evidence regarding the benefits and structure of pulmonary rehabilitation following an exacerbation of COPD. The conceptual framework (Figure 3), present a visual image of how this thesis sits in the international literature in the field. The continuous lines that lead to bold forms that presents what is knowns from the literature, while the discontinuous line leads to the thesis questions based on the lack of literature. The thesis findings for each chapter are presented inside the rectangular forms.

Exacerbations of COPD are a common feature of the disease and Chapter Two explored the natural recovery process after an exacerbation of COPD. This narrative review showed that following an exacerbation of COPD, the recovery process can take up to 14 days, however, in some subgroups this recovery phase may be prolonged. People with COPD at potential risk of prolonged recovery are those who are older, have more severe lung disease, have lower body mass index and experience chronic dyspnoea. Symptoms associated with a common cold at the onset of exacerbation, evidence of viral infection and severe dyspnoea during the exacerbation, are also features associated with prolonged recovery.

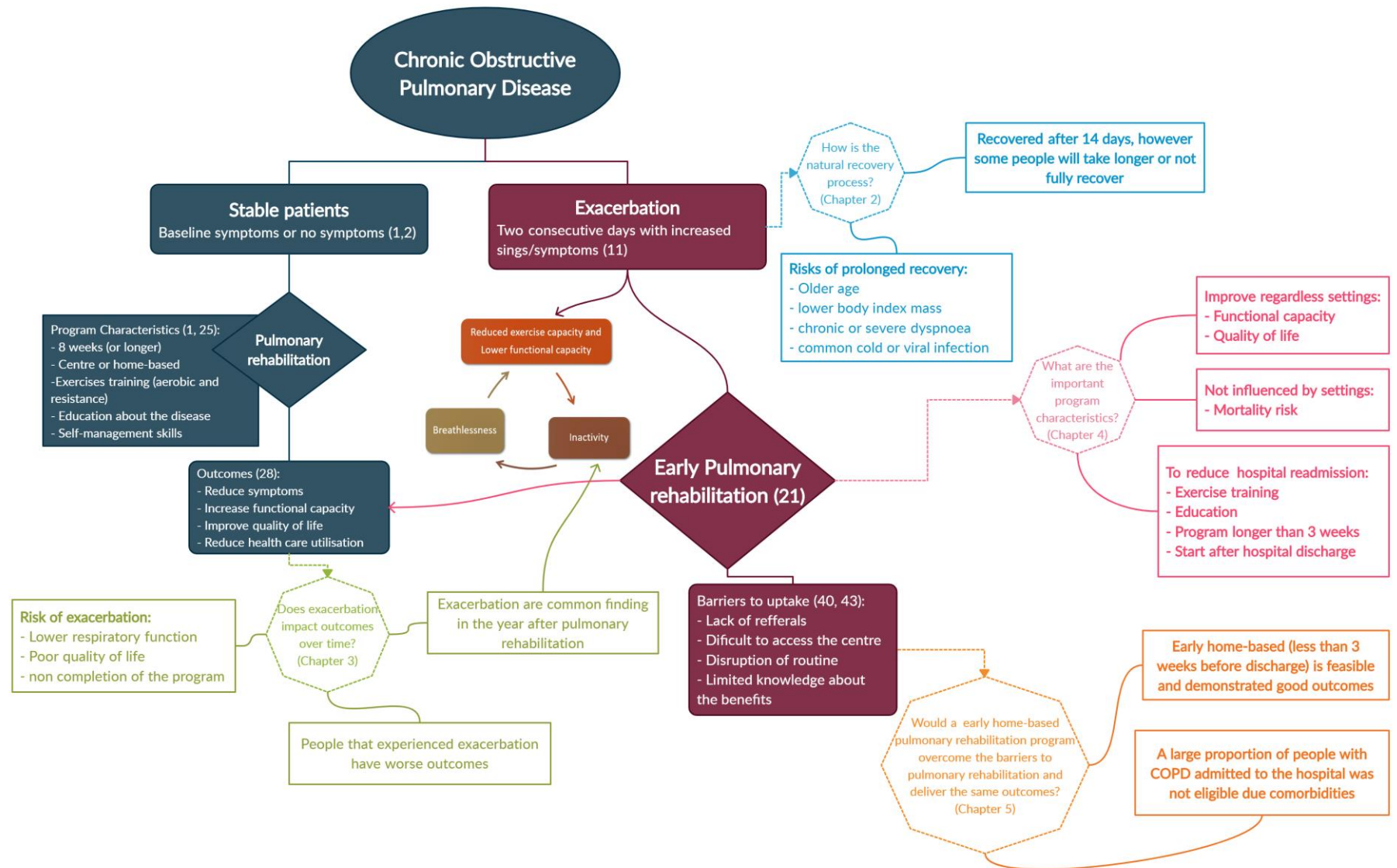
Chapter Three analysed the impact of having an exacerbation in the year after pulmonary rehabilitation. The findings revealed that more than one-third of participants had a severe exacerbation in the year following pulmonary rehabilitation. Severe exacerbations were more likely in those with worse lung function and poorer quality of life at programme

commencement. A severe exacerbation was also an independent predictor of worse 12-month outcomes for quality of life, functional capacity and symptoms. Participants who completed pulmonary rehabilitation (at least 70% of sessions) were less likely to have a severe exacerbation.

Chapter Four determined the impact of pulmonary rehabilitation programme characteristics such as exercise mode, programme location and supervision on clinical outcomes in people after an exacerbation of COPD. This systematic review found that hospital readmission can be reduced where pulmonary rehabilitation programmes included exercise training in association with education, and/or had longer duration (more than 3 weeks), and/or the programme started after discharge from hospital. However, functional capacity and quality of life improved regardless of the programme characteristics, which may be a function of natural recovery (Chapter Two). Contrastingly, mortality risk does not reduce irrespective of the programme's setting.

Chapter Five implemented and tested a home-based pulmonary rehabilitation programme starting early (less than three weeks) after discharge from hospital due to an exacerbation of COPD. The programme was feasible to deliver post discharge; with people with COPD demonstrating improved clinical outcomes at the end of rehabilitation. Despite the clinical benefits, uptake of early pulmonary rehabilitation after exacerbation was challenging. The study highlighted that a large proportion of the target population was not eligible for early home-based pulmonary rehabilitation due to the presence of other comorbidities.

Overall, the present thesis findings reinforce the negative impact of exacerbations on people with COPD. Additionally, it provides evidence of patients who might warrant a higher level of clinical concern in terms of their capacity to recover post exacerbation—namely those who are older, have lower body mass index and more severe lung disease—or who might be at risk of having more occasions of severe exacerbation after pulmonary rehabilitation—being those with lower initial lung function and poorer quality of life and who are unable to complete the rehabilitation programme. The thesis also identifies that early pulmonary rehabilitation programmes should be at least three weeks long, start after discharge and comprise exercise training in association with an educational component. Home-based pulmonary rehabilitation commenced early after hospital discharge for an exacerbation is feasible, and produces promising clinical outcomes, however future study protocols should focus on ways to incorporate individuals with associated comorbidities to potentially reach a larger proportion of the COPD population. The body of work presented follows the international trends of finding novel models of pulmonary rehabilitation in order to deliver better care to parcel of the COPD population that is usually not reached. Although that was not the main focus of the thesis, Chapter Three raise the discussion of the needs of maintenance programs after pulmonary rehabilitation programs once exacerbations were common in the year following rehabilitation and it influenced the outcomes.



**Figure 3.** Conceptual framework of the thesis

## 6.2 Implications for clinical practice

Exacerbations of COPD are common in the history of the disease and affect health status and lead to inactivity in people with COPD. Recovery from an exacerbation usually occurs two weeks after onset of symptoms, however, the research presented in this thesis alerts clinicians to those patients at risk of a poor recovery. Individuals who are older and have more severe disease and symptoms are less likely to recover post exacerbation. Enhanced post exacerbation monitoring, possibly including telephone contact, clinic visits, and support to attend pulmonary rehabilitation, may help to ameliorate the risk of poor post-exacerbation recovery in these patients. In addition, these patients may benefit from ongoing monitoring or exercise maintenance support after a programme of pulmonary rehabilitation.

Given that post-exacerbation recovery takes in the order of at least two weeks, commencing a programme of pulmonary rehabilitation within two weeks of symptom onset may limit the uptake and benefits of any such programme. However, where clinical services can ‘fast-track’ and support patient’s post-exacerbation commencement of pulmonary rehabilitation between two to four weeks after hospital discharge, clinical improvements and a reduced risk of hospital readmission would be expected outcomes. Furthermore, physical inactivity after an exacerbation can lead to negative consequences in the year post-exacerbation including reduced quadriceps strength, increased hospital readmission and higher mortality risk (57-59). A clinical focus on physical activity education and counselling, and encouragement and support for attendance at an early pulmonary rehabilitation programme may reduce the ongoing impact of physical inactivity post-exacerbation.



The early home-based pulmonary rehabilitation programme was shown to be feasible for people with COPD after exacerbation. It highlighted the importance of clinicians having an open discussion with patients about post-discharge rehabilitation options early during their hospitalisation, and the benefit of presenting alternative rehabilitation programme models, to help identify the best rehabilitation option to fulfil the patients' needs. In addition, where a clinical service is developing or delivering a pulmonary rehabilitation programme specifically targeting or including individuals post-exacerbation, the evidence presented in this thesis should encourage clinicians to ensure their programmes start after hospital discharge, are of more than three weeks duration and deliver exercise training in association with education.

Although undertaking pulmonary rehabilitation can reduce the need for future hospitalisation (22), people with COPD are still susceptible to experiencing severe exacerbations even after completing pulmonary rehabilitation. The work presented in Chapter Three reported a large proportion of people with COPD who have undertaken pulmonary rehabilitation still experience an exacerbation in the year following the programme, with exacerbations having a negative influence on clinical outcomes. Patients with lower respiratory function, poorer quality of life and who fail to complete the pulmonary rehabilitation programme are at higher risk of having a severe exacerbation. Identifying straightforward, easily implemented strategies by which clinicians can proactively monitor these patients may be important for reducing the impact of severe and repeated exacerbations. Strategies for such monitoring require further investigation (60), however might include maintenance exercise programmes with a home-visit component; enhanced telephone contact; or, referral to community exercise programmes (61).

Routinely referring all patients to a second centre-based pulmonary rehabilitation programme within 12 months may be a novel way to break the exacerbation cycle and to maintain clinical benefits. However, the practical implications of such a scheme including expense for the health system, availability of programmes and space within them, and clear patient related barriers to attending centre-based pulmonary rehabilitation may mean that those patients most vulnerable and at highest risk would still struggle to complete traditional outpatient pulmonary rehabilitation. This further highlights the need for clinical services to consider alternative models of pulmonary rehabilitation delivery. Such alternatives may include low-cost home-based programmes that have been demonstrated to be safe and effective. Implementing these alternative rehabilitation delivery models into practice – alongside existing centre-based rehabilitation services – would provide a suite of rehabilitation options that might help to provide benefit to a wider range of patients.

## 6.3 Implications for future research

To date, there is a lack of studies focused specifically on describing the natural recovery of physical function and wellbeing following exacerbation of COPD. Research of this nature, with a focus on functional and patient reported outcomes, could provide new evidence on the natural recovery process after the onset of exacerbation. Such a study should consider close monitoring of function, symptoms and physiological outcomes both during the hospital admission and after discharge, for at least one month in order to best track early and late recovery. Included assessments should focus on outcomes where literature is sparse, such as functional capacity, health status, quality of life, symptoms and strength. A cohort study could assess participants at time points that would provide an

overview of the recovery process (i.e. days zero, three, seven, 14, 21 and 30).

Assessments could be set in the hospital and/or at participants' house to ensure it would not be a burden to the participant and the time points are accurate. A recovery cohort study may identify additional risk predictors of prolonged recovery that would be amenable to a rehabilitation intervention.

The research presented in this thesis identified that people with COPD who do not complete at least 70% of a pulmonary rehabilitation programme have higher risk of an exacerbation episode in the following year. Therefore, pulmonary rehabilitation participation seems to have an important role in delaying the natural progression of COPD. However, retaining participants within a pulmonary rehabilitation programme is challenging, with reports of programme non-completion rates ranging from 10% to 58% (43, 44). An ongoing challenge for the rehabilitation community is identifying strategies that will reduce the dropout rate from pulmonary rehabilitation. Whether the use of technology, such as video-conferencing or interaction via a website or smartphone applications to support and stimulate exercise participation (62, 63) might improve pulmonary rehabilitation completion rates is still unknown. At present, pulmonary rehabilitation delivery is largely a one-size fits all model with the nature of its outpatient, centre-based delivery. If effective pulmonary rehabilitation delivery was available in multiple models at the majority of centres, this might allow patients to choose the model of rehabilitation that best suits their needs. Understanding whether patient choice of rehabilitation model leads to improved programme completion rates requires further investigation.

To be able to deliver post-exacerbation pulmonary rehabilitation in the home, to a greater number of individuals who might benefit, future studies should consider strategies to include more people with COPD with associated comorbidities, in whom uptake of traditional outpatient pulmonary rehabilitation might otherwise be a challenge (64). These strategies might include investigating the use of technology such as videoconferencing to provide real-time, remote monitoring of exercise training in a telerehabilitation environment, to potentially alleviate exercise safety concerns. A virtual ‘group’ telerehabilitation setting may also provide additional social support for the most unwell patients, who may otherwise have limited participation in group activities.

The systematic review included in the present thesis gave direction for clinical practice stating that early pulmonary rehabilitation programmes should deliver longer programmes, including education and starting after discharge. However, the included studies did not directly compare distinct programme characteristics, such as shorter vs longer programs, or supervision vs no supervision. Future studies should focus on comparing specific programme characteristics such as supervision during the exercises with unsupervised, programmes starting during hospital with outpatient programmes. In that way more robust evidence can be provided regarding the most important programme characteristics and the results would be important to clinical practice.

## 6.4 Thesis strengths and limitations

This thesis brings to light new evidence relating to the impact of exacerbations of COPD, and interventions that may be beneficial in this period. The current literature has been largely focussed on the speed of recovery from exacerbation. This thesis provides detailed

information on the natural recovery process after an exacerbation of COPD and how exacerbations of COPD affect clinical outcomes after pulmonary rehabilitation. The work presented in this thesis provides new evidence regarding risk factors for exacerbation relative to rehabilitation participation, as well as identifying key components of rehabilitation that appear beneficial in supporting recovery after an exacerbation. Also, a new strategy for delivering pulmonary rehabilitation early after exacerbation of COPD was tested for feasibility with important outcomes.

Despite the strengths of the work presented, this thesis structure possesses a few limitations. The inclusion of a narrative review regarding exacerbation recovery, instead of a systematic review, might have resulted in some information being omitted from the work - however, the literature on the topic was very small and there are not many controlled trials on the topic. The narrative review is an important body of work that combined epidemiological studies and identified sufficient data that enabled strong conclusions.

Chapter Three of this thesis comprises a secondary analysis of a larger randomised controlled trial. A prospective clinical trial specifically designed to answer the question of interest would provide a stronger research methodology. Nevertheless, the randomised control trial used as a basis for the secondary analysis had collected the necessary data in a robust manner, with a considerable sample size, to be able to confidently answer the question of interest.

Ideally, the feasibility study contained in Chapter Five would have taken the form of a randomised controlled trial. However, the use of an action research approach enabled a broad analysis of the feasibility of implementation and practicalities of using a home-based pulmonary rehabilitation intervention early after hospital discharge – which will be important for informing future, larger scale, randomised controlled trials.

## 6.5 Conclusion

The body of work presented in this thesis identifies that particular individuals with COPD, namely those who are older, and have more severe disease and symptoms, are more likely to have delayed recovery following a respiratory exacerbation. Being able to complete a programme of pulmonary rehabilitation reduces the risk of experiencing a severe exacerbation in the following year – raising the possibility that repeated dosing of pulmonary rehabilitation may help to reduce exacerbation frequency, and maintain clinical benefits of rehabilitation. Models of pulmonary rehabilitation delivered early after an exacerbation are most effective when started after hospital discharge, of at least three weeks duration, and encompass both exercises training and education. Home-based models of pulmonary rehabilitation, delivered early after hospital discharge, have the potential to enhance post-exacerbation recovery and reduce rehospitalisation. Future work needs to examine how models of early pulmonary rehabilitation can facilitate uptake and completion in a broader range of people with COPD, including those with comorbid conditions.

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# APENDICES

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## Appendix A – Ethics Approval Certificates

## Appendix A.1 – Chapter Three

**La Trobe University  
Faculty of Health Sciences  
MEMORANDUM**

**TO:** Dr Anne Holland,  
Christine McDonald, Ajay Mahal, School of Physiotherapy  
Catherine Hill,  
Annemarie Lee, Angela Burge

**SUBJECT:** *Reference:* **FHEC11/134**

*Student or  
Other Investigator:*

*Title:* **Benefits and costs of home-based pulmonary  
rehabilitation in chronic obstructive pulmonary  
disease**

**DATE:** 24 August, 2011

The Faculty Human Ethics Committee's (FHEC) reviewers have considered and approved the above project. You may now proceed.

Please note that the Informed Consent forms need to be retained for a minimum of 5 years. Please ensure that each participant retains a copy of the Informed Consent form. Researchers are also required to retain a copy of all Informed Consent forms separately from the data. The data must be retained for a period of 15 years.

Please note that any modification to the project must be submitted in writing to FHEC for approval. You are required to provide an annual report (where applicable) and/or a final report on completion of the project. A copy of the progress/final report can be downloaded from the following website:  
<http://www.latrobe.edu.au/rgso/forms-resources/forms/ethic-prog-final.rtf>

Please return the completed form to The Secretary, FHEC, Faculty of Health Sciences Office, La Trobe University, Victoria 3086.

**If you have a student/s involved in this project, a copy of this memorandum is enclosed for you to forward to the student(s) concerned.**



**Dr Ellie Fossey**  
Chair  
Faculty Human Ethics Committee  
Faculty of Health Sciences



## ETHICS COMMITTEE CERTIFICATE OF APPROVAL

*This is to certify that*

**Project No:** 261/11

**Project Title:** Benefits and costs of home-based pulmonary rehabilitation for people with chronic obstructive pulmonary disease

**Principal Researcher:** A/Professor Anne Holland

**Participant Information and Consent Form version 2 dated:** 18-Jul-2011

*was considered by the Ethics Committee on 28-Jul-2011 and APPROVED on 28-Jul-2011*

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It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

**The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of**

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

**Additionally, the Principal Researcher is required to submit**

- A Progress Report on the anniversary of approval and on completion of the project (*forms to be provided*);

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

### SPECIAL CONDITIONS

*None*

SIGNED:   
Chair, Ethics Committee (or delegate)

**R. FREW**  
**SECRETARY**  
**ETHICS COMMITTEE**

*Please quote Project No and Title in all correspondence*

**Human Research Ethics Committee**  
Research Ethics Unit  
Henry Buck Building  
Austin Hospital

**Austin Hospital**

145 Studley Road  
PO Box 5555 Heidelberg  
Victoria Australia 3084  
Telephone 03 9496 5000  
Facsimile 03 9458 4779  
www.austin.org.au

**TO:** **A/Prof Anne Holland**  
**Alfred Health Clinical School, LaTrobe University**  
**Level 4, The Alfred Centre, Commercial Rd Melbourne VIC**  
**3004**

**PROJECT:** Benefits and costs of home-based pulmonary rehabilitation in  
chronic obstructive pulmonary disease

**PROTOCOL NO:**

**PROJECT NO:** H2011/04364

**FROM:** **Ms Jill Davis, Research Ethics Unit Manager**

**DATE:** 22 September 2011

**RE:** **Protocol Version 2 dated 20 June 2011**  
**Participant Information and Consent Form Version 2 dated**  
**20 July 2011**  
**Advertisement**  
**Modified Medical Research Council Dyspnoea Scale**  
**Chronic Respiratory Questionnaire (Self Reported) Follow**  
**Up**  
**Your Health and Well-Being Survey**  
**Home Exercise Diary**

**Approval Period: 22 September 2011 to 22 September 2014**

Agenda Item:

Further to my letter dated 25 August 2011 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the Human Research Ethics Committee at their meeting on 18 August 2011 is satisfactory. This project now has full ethical approval for a period of three years from the date of this letter.

Before the study can commence you must ensure that you have:

- For trials involving radiation it is your responsibility to ensure the research is added to the Austin Health Management Licence issued by Department of Human Services – Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The HREC must be notified when the research has been added to the licence.
- It is a requirement that a progress report is submitted to the Committee annually, or more frequently as directed. Please note a final report must be

submitted for all studies. Should you plan for your study to go beyond the 3-year ethics approval, please request in writing an extension of ethics approval prior to its lapsing. If your study will not commence within 12 months, a request must be forwarded to the HREC justifying the delay beyond 12 months. Should such a request not be received, ethics approval will lapse and a resubmission to the HREC will then be necessary.

- After commencement of your study, should the trial be discontinued prematurely you must notify the HREC of this, citing the reason.
- Any changes to the original application will require a submission of a protocol amendment for consideration as this approval only relates to the original application as detailed above.
- Please notify the HREC of any changes to research personnel. All new investigators must be approved prior to performing any study related activities.
- It is now your responsibility to ensure that all people (i.e. all investigators, sponsor and other relevant departments in the hospital) associated with this particular study are made aware of what has been approved.

The Committee wishes to be informed as soon as practicable of any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers. The HREC has adopted the NHMRC Australian Health Ethics Committee (AHEC) Position Statement 'Monitoring and reporting of safety for clinical trials involving therapeutic products' May 2009

**Please ensure you frequently refer to the Research Ethics Unit website <http://www.austin.org.au/Page.aspx?ID=415> for all up to date information about research and ethical requirements.**

#### DETAILS OF ETHICS COMMITTEE:

It is the policy of the Committee not to release personal details of its members. However I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairperson  
Ethicist  
Lawyer  
Lay Man  
Lay Woman  
Person fulfilling a Pastoral Care Role  
Person with Counselling Experience  
Person with Research Experience

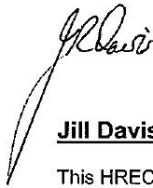
#### **Additional members include:**

- Chairs of all sub committees, or nominees
- Other persons as considered appropriate for the type/s of research usually being considered

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the National Statement on Ethical Conduct in Human Research (NHMRC The National Statement) and the Note for Guidance on Good Clinical Research Practice (CPMP/ICH/135/95) annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Records Act 2001.

PLEASE NOTE: The Committee requests that the Research Ethics Unit [ethics@austin.org.au](mailto:ethics@austin.org.au) is informed of the actual starting date of the study as soon as the study commences. A written notice (e-mail, fax or letter) is considered the appropriate format for notification.



**Jill Davis**

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice. The process this HREC uses to review multi-centre research proposals has been certified by the NHMRC.

## Appendix A.1 – Chapter Five



### University Human Ethics Committee

#### RESEARCH OFFICE

#### MEMORANDUM

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**To:** Professor Anne Holland, School of Allied Health, College of SHE

**From:** Senior Human Ethics Officer, Ethics and Integrity

**Subject:** UHEC acceptance of The Alfred HREC approved project - 475/15

**Title:** Early Home-based Rehabilitation Intervention for COPD Acute exacerbations (EHRICA): a feasibility study

**Date:** 13 April 2016

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Thank you for submitting the above protocol to the University Human Ethics Committee (UHEC). Your material was forwarded to the UHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Alfred HREC**, the UHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by **The Alfred HREC**.

**Limit of Approval.** La Trobe UHEC endorsement is limited strictly to the research protocol as approved by **The Alfred HREC**.

**Variation to Project.** As a consequence of the previous condition, any subsequent modifications approved by **The Alfred HREC** for the project should be notified formally to the UHEC.

**Annual Progress Reports.** Copies of all progress reports submitted to **The Alfred HREC** must be forwarded to the UHEC. Failure to submit a progress report will mean that endorsement for your involvement this project will be rescinded. An audit related to your involvement in the study may be conducted by the UHEC at any time.

**Final Report.** A copy of the final report is to be forwarded to the UHEC within one month of it being submitted to **The Alfred HREC**.

If you have any queries on the information above please e-mail: [humanethics@latrobe.edu.au](mailto:humanethics@latrobe.edu.au) or



contact me by phone.

On behalf of the La Trobe University Human Ethics Committee, best wishes with your research!

Kind regards,

Sara Paradowski  
Senior Human Ethics Officer  
Executive Officer – University Human Ethics Committee  
Ethics and Integrity / Research Office  
La Trobe University Bundoora, Victoria 3086  
P: (03) 9479 – 1443 / F: (03) 9479 - 1464  
<http://www.latrobe.edu.au/researchers/ethics/human-ethics>



## Ethics Committee

### Certificate of Approval of Amendments

This is to certify that amendments to

Project: **475/15 Early Home-based Rehabilitation Intervention for COPD Acute exacerbations (EHRICA): a feasibility study**

Principal Researcher: **Professor Anne Holland**

Amendment:

**Addition of clinician and patient interviews**

Attachments:

Protocol version **2** dated **31-Jan-2017**

PICF (clinician interview) version **2** dated **12-Nov-2016**

PICF (patient interview) version **2** dated **31-Jan-2016**

Invitation letter (clinician interview) version **1** dated **25-Nov-2016**

Interview guide (clinicians) version **1** dated **5-Dec-2016**

Interview guide (patients) version **3** dated **31-Jan-2017**

have been approved in accordance with your amendment application dated **30-Nov-2016** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

**Professor John J. McNeil**  
**Chair, Ethics Committee**

**Date: 6-Feb-2017**

*All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).*

*The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).*



## Ethics Committee

### Certificate of Approval of Amendments

This is to certify that amendments to

Project: **475/15 Early Home-based Rehabilitation Intervention for COPD Acute exacerbations (EHRICA): a feasibility study**

Principal Researcher: **Professor Anne Holland and Dr Cristino Oliveira**

Amendment: **Re-pilot the study intervention with 10 new participants to test changes to protocol based on the qualitative interviews undertaken in Phase 2**

Key changes to the intervention protocol following phase 2 are:

- To improve information to clinicians about the HomeBased pulmonary rehabilitation study protocol and ask for their assistance in opening a dialogue with eligible participants regarding pulmonary rehabilitation in general (amendment protocol under 5.4 Clinicians Handouts);
- Use video testimonials collected from previous pulmonary rehabilitation participants to better inform eligible participants about HomeBased PR (amendment protocol under 5.5 Video testimonials);
- Baseline assessments will be performed prior to discharge from hospital (amendment protocol under 5.6 Data collection);
- Add an additional assessment the One-minute sit-to-stand test (1STST) to baseline and end rehabilitation assessments (amendment protocol under 5.9 Clinical assessments)

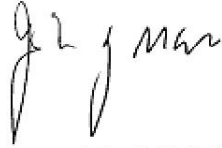
Amendment Protocol dated: **14-Feb-2018**

Participant Information & Consent Form **Version 4** dated: **22-Feb-2018**

Clinician Hand-out **Version 1** dated: **28-Feb-2018**

have been approved in accordance with your amendment application dated **14-Feb-2018** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.



**Professor John J. McNeil**  
**Chair, Ethics Committee**

**Date: 1-Mar-2018**

*All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).*

*The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).*

## Appendix B – Participants' Information Sheets

Phase I



**Participant Information and Consent Form  
Alfred Hospital**

Full Project Title: **Early Home-based Rehabilitation Intervention for COPD  
Acute exacerbations (EHRICA): a feasibility study**

Principal Researcher: Professor Anne Holland

Associate Researchers: Professor Belinda Miller

Dr Cristino Oliveira

Dr Narelle Cox

Ms Bruna Wageck

Ms Janet Bondarenko

Ms Monique Corbett

**1. Introduction**

You are invited to take part in this research project. We have contacted you because your respiratory doctor, nurse or physiotherapist indicated that you might be interested in taking part. We have approached you because you have been admitted at the Alfred Hospital and diagnosed with an acute exacerbation of chronic obstructive pulmonary disease (COPD). We believe that your participation could assist us to find out whether pulmonary rehabilitation programs that take place at home following hospital discharge are feasible and effective.

Patients with COPD do not currently receive rehabilitation in the early phase after hospitalisation due to an acute exacerbation. The research project aims to discover whether an 8-week home-based pulmonary rehabilitation program following hospitalisation is feasible and improves symptoms, wellbeing and exercise capacity.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
  - consent to take part in the research project;
  - consent to be involved in the procedures described;
  - consent to the use of your personal and health information as described.
- You will be given a copy of this Participant Information and Consent Form to keep.

## **2. What is the purpose of this research project?**

The aim of this project is to discover whether a pulmonary rehabilitation program performed at home, following hospitalisation due to acute exacerbations of COPD, is feasible.

Pulmonary rehabilitation is an effective treatment for COPD which reduces symptoms, improves quality of life and increases exercise capacity. However, less than 10% of all people discharged from hospital following an acute exacerbation completed an outpatient hospital-based pulmonary program; rates of referral, uptake, adherence and completion were exceedingly low. Whilst the low rate of referral by health professionals is not well understood, patient-related barriers are well documented and include feeling too breathless to travel, fear of the hospital environment and physical limitations due to other diseases associated with the lung condition.

Previous studies have shown that home-based pulmonary rehabilitation improves symptoms and exercise capacity to a similar extent as hospital-based pulmonary rehabilitation in those with a stable clinical condition of COPD. However, the feasibility and benefits of the home-based program delivered early following hospital discharge while recovering from an acute exacerbation have not been yet documented.

A total of 10 people will participate in this project. People will be recruited from Alfred Hospital. Those people who choose to participate will take part in a home-based pulmonary rehabilitation program starting within one to three weeks following discharge from hospital.

This research has been funded by La Trobe University.

## **3. What does participation in this research project involve?**

Participation in this project will start within one to three weeks following hospital discharge and initiates with one home visit by a physiotherapist who will take approximately 1½ hour. This visit will involve commencing the exercise program, which will involve walking and light strength training for the upper and lower body, as well as education regarding use of the home diary and a pedometer. The pedometer will be used to help record and progress the distance walked, and participants will be asked to complete their exercise program 5 times each week. They will be asked to document their exercise sessions in a diary. The physiotherapist will then contact the participants once a week by telephone, at an agreed time during seven consecutive weeks. These telephone calls will be used to review the home diary, to progress the exercise program, and undertake self-management education and training. These phone calls will last a maximum of half an hour.

At the beginning of the study and at completion of the 8-week homebased pulmonary rehabilitation program we will assess your respiratory symptoms, wellbeing and exercise capacity. This will involve completing a walking test and completing four questionnaires. Each of these assessment occasions will take approximately 1½ hours and will be completed in the physiotherapy department at the Alfred Hospital.

You will be asked to do an interview where you are asked some questions regarding the positives and negatives of undertaking pulmonary rehabilitation at home. This interview will be conducted by one of the researchers and will take 20-30 minutes. The

interview will be audio-recorded, so that we can accurately recall your experiences. The interview will take place in your home or over the telephone, according to your preference. The transcript generated from the audio-recording will not contain any information that could identify you.

Your hospital medical records will be reviewed to collect information on your medical history, your lung function and visits or readmissions to the hospital during the study period. If you have not performed a pulmonary function test within 12 months of your final assessment (as part of your usual clinical care) you will have it assessed by one of our research personnel, the results of which will go into our research records and a report will be prepared to your doctor, upon request.

You will not be paid for your participation in this research.

#### **4. What are the possible benefits?**

You may receive those benefits which are usually experienced as a result of participation in a pulmonary rehabilitation program. These include reduced breathlessness, an improved sense of wellbeing and ability to exercise. We cannot guarantee or promise that you will receive any benefits from this project.

#### **5. What are the possible risks?**

Possible risks and discomforts include the discomfort of becoming breathless during the exercise tests and training sessions. You will be monitored by experienced staff during each exercise test to ensure that your oxygen levels and heart rate are satisfactory and that breathlessness is kept to an acceptable level.

You will have the first exercise session at home monitored by a physiotherapist, to ensure that the exercise program is safe and that you are not exercising too hard. The physiotherapist will show you how to monitor your exercise progression, to ensure that your breathlessness is kept to an acceptable level and that you are not exercising too hard. This will minimise the risk of becoming unwell. You may suspend or even end your participation in the project if distress occurs during the tests or exercise sessions. There may be additional unforeseen or unknown risks.

#### **6. Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at a later stage.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them when you withdraw from the research project.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or The Alfred Hospital.

#### **7. How will I be informed of the final results of this research project?**

When this project is finished you will be informed of the results by mail.



## **8. What will happen to information about me?**

Any information that is collected from you during the research project will be immediately stored using a code replacing your personal details so that you cannot be identified, and your will be privacy protected. This code will be kept in a locked cupboard in the La Trobe Clinical School at Alfred Health, which can be accessed only by the investigators. This approach enables researchers to re-identify your information if need be. Paper records will be stored against the code and kept in a locked filing cabinet at the La Trobe Clinical School at Alfred Health, with copies stored in the Physiotherapy Department at the Alfred Hospital. Electronic data will be stored on a computer against the patient code, and will be protected by password access. Study records will be kept for a period of 15 years from the end of the study. If you take part in an interview, these records include the digital sound recording that was made. After this time the information will be disposed of safely and securely through shredding of the documents and deletion of computer files.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored and will only be used for the purpose of this research project. It will only be disclosed with your permission, or in compliance with the law.

If you give us your permission by signing the Consent Form, we plan to publish the results of the trial in an international scientific journal, also the results will be used by the research Ms Bruna Wageck to obtain a PhD degree. In any publication, information will be provided in such a way that you cannot be identified. Only group data, not individual results, will be published.

Information about your participation in this research project may be recorded in your health records.

## **9. Can I access research information kept about me?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the principal investigator named at the end of this document if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for 15 years. The information will be disposed of safely and securely through shredding of the documents and deletion of computer files after 15 years has elapsed; access to information about you after this point will not be possible.

## **10. Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Alfred Health and La Trobe University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

## **11. Consent**

I have read, or have had this document read to me in a language that I understand, and I understand the purposes, procedures and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) .....

Signature

Date

Declaration by researcher\*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed) .....

Signature

Date

*Note: All parties signing the consent section must date their own signature.*

## **12. Who can I contact?**

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

### **For further information or appointments:**

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), please contact the principal investigator:

**Prof Anne Holland on (03) 9479 6744 or 0419379821.**

You may also contact the following persons:

Name: Professor Belinda Miller

Role: Respiratory Medicine physician, Alfred Health

Ph: (03) 9276 3770

### **For Complaints**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

Name: Ms Emily Bingle

Position: Research Governance Officer, Research and Ethics Unit, Alfred Health  
The Alfred Hospital, Commercial Rd, Melbourne 3004

Telephone: 03 9076 3619 Fax: 9076 8841

Email: [research@alfred.org.au](mailto:research@alfred.org.au)

You will need to tell Ms Bingle the following Alfred Health project number: 475/15

Further enquiries and/or complaints can also be addressed to:

The Secretary, Faculty Human Ethics Committee

Faculty of Health Sciences, La Trobe University, Victoria, 3086

Telephone: 03 9479 3582 Fax: 03 9479 5733

Email: [health@latrobe.edu.au](mailto:health@latrobe.edu.au)

**Participant Information and Consent Form**  
**Alfred Hospital**

Full Project Title: **Early Home-based Rehabilitation Intervention for COPD  
Acute exacerbations (EHRICA): a feasibility study**

Principal Researcher: Professor Anne Holland

Associate Researchers: Professor Belinda Miller

Dr Cristino Oliveira

Dr Narelle Cox

Ms Bruna Wageck

Ms Janet Bondarenko

Ms Monique Corbett

## **1. Introduction**

You are invited to take part in this research project. We have contacted you because you are aware of the COPD scenery and work with patients with COPD as inpatients and/or outpatients. We recently ran a feasibility study that offered the opportunity for patients with COPD to participate in an 8-week home-based PR programme early after discharge from an acute exacerbation. However, we found it difficult to recruit participants for the study. We believe that your participation could assist us to find out how to improve our early home-based pulmonary rehabilitation program to make it more suitable and attractive for patients on discharge from hospital after an exacerbation of their COPD.

Patients with COPD do not currently receive rehabilitation in the early phase after hospitalisation due to an acute exacerbation. The main research project aims to investigate whether an 8-week home-based pulmonary rehabilitation program following hospitalisation is feasible and improves symptoms, wellbeing and exercise capacity.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;

- consent to take part in the research project;
  - consent to be involved in the procedures described;
  - consent to the use of the information you provide .
- You will be given a copy of this Participant Information and Consent Form to keep.

## **2. What is the purpose of this research project?**

The aim of this project is to investigate how to make a pulmonary rehabilitation program performed at home, following hospitalisation due to acute exacerbations of COPD, feasible, comfortable and effective.

Pulmonary rehabilitation is an effective treatment for COPD that reduces symptoms, improves quality of life and increases exercise capacity. However, less than 10% of all people discharged from hospital following an acute exacerbation completed an outpatient hospital-based pulmonary program; rates of referral, uptake, adherence and completion were exceedingly low. Whilst the low rate of referral by health professionals is not well understood, patient-related barriers are well documented and include feeling too breathless to travel, fear of the hospital environment and physical limitations due to other diseases associated with the lung condition.

Previous studies have shown that home-based pulmonary rehabilitation improves symptoms and exercise capacity to a similar extent as hospital-based pulmonary rehabilitation in those with a stable clinical condition of COPD. However, the feasibility and benefits of the home-based program delivered early following hospital discharge while recovering from an acute exacerbation have not yet been documented.

We will contact by email clinicians at The Alfred Hospital that are engaged in COPD treatment and rehabilitation. Those people who consent to participate will receive a phone call to schedule a 30-minute interview with one of our researchers.

This research has been funded by La Trobe University.

## **3. What does participation in this research project involve?**

Participation in this project will involve a face-to-face or a phone interview with one of our researchers. The interview will take approximately 20-30 minutes and will be audio-recorded so it can be transcript for further analysis. Each participant will be interviewed once.

You will be asked for your thoughts regarding home-based pulmonary rehabilitation, timing of recruitment, possible barriers to participation and strategies for recruitment. The transcript generated from the audio-recording will not contain any information that could identify you.

You will not be paid for your participation in this research.

## **4. What are the possible benefits?**

You will help in the understanding of the needs and expectations of people with COPD after hospital discharge, and what would make it easier for them to take part in a home-based pulmonary rehabilitation. This information will help us to make home-based pulmonary rehabilitation more acceptable and attractive, so more people can benefit from pulmonary rehabilitation in the future. We cannot guarantee or promise that you will receive any other benefits from this project.

## **5. What are the possible risks?**

Possible risks and discomforts include the discomfort of being asked about your thoughts surrounding pulmonary rehabilitation and the relation with what you witness in your work. You may suspend or end your participation anytime during the interview

if you feel distressed or uncomfortable with any questions. There may be additional unforeseen or unknown risks.

**6. Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at a later stage.

If you decide to leave the project, the researchers would like to keep the information that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them when you withdraw from the research project.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or The Alfred Hospital.

**7. How will I be informed of the final results of this research project?**

When this project is finished you will be informed of the results by email.

**8. What will happen to information about me?**

Any information that is collected from you during the research project will be stored using a code replacing your personal details so that you cannot be identified, and your privacy will be protected. This code will be kept in a locked cupboard in the La Trobe Clinical School at Alfred Health, which can be accessed only by the investigators. This approach enables researchers to re-identify your information in case you decided to have access to it. The electronic data will be stored on a computer against the a code, and will be protected by password access. Study records will be kept for a period of 7 years from the end of the study. If you take part in an interview, these records include the digital sound recording that was made and the transcript of the interview. After this time the information will be disposed of safely and securely through shredding of the documents and deletion of computer files.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored and will only be used for the purpose of this research project. It will only be disclosed with your permission, or in compliance with the law.

If you give us your permission by signing the Consent Form, we plan to publish the results of the feasibility project in an international scientific journal. In any publication, information will be provided in such a way that you cannot be identified.

The results will be used by the student researcher Ms Bruna Wageck to obtain a PhD degree.

**9. Can I access research information kept about me?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact the principal investigator named at the end of this document if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for 7 years. The information will be disposed of safely and securely through shredding of the documents and deletion of computer files after 7 years has elapsed; access to information about you after this point will not be possible.

**10. Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Alfred Health and La Trobe University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

## **11. Consent**

I have read, or have had this document read to me in a language that I understand, and I understand the purposes, procedures and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) .....

Signature

Date

Declaration by researcher\*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed) .....

Signature

Date

*Note: All parties signing the consent section must date their own signature.*



## **12. Who can I contact?**

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

### **For further information or appointments:**

If you want any further information concerning this project, please contact the principal investigator:

**Prof Anne Holland on (03) 9479 6744 or 0419379821.**

You may also contact the following person:

Name: Ms Bruna Borges Wageck

Role: PhD student at La Trobe University

Ph: (03) 9479 6747 or 0450 420 290

### **For Complaints**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

Name: Complaints Officer, Research and Ethics Unit, Alfred Health  
The Alfred Hospital, Commercial Rd, Melbourne 3004

Telephone: 03 9076 3619 Fax: 9076 8841

Email: research@alfred.org.au

You will need to quote the following Alfred Health project number: 475/15

Further enquiries and/or complaints can also be addressed to:

The Secretary, Faculty Human Ethics Committee

Faculty of Health Sciences, La Trobe University, Victoria, 3086

Telephone: 03 9479 3582 Fax: 03 9479 5733

Email: health@latrobe.edu.au

**Participant Information and Consent Form**  
**Alfred Hospital**

Full Project Title: **Early Home-based Rehabilitation Intervention for COPD  
Acute exacerbations (EHRICA): a feasibility study**

Principal Researcher: Professor Anne Holland

Associate Researchers: Professor Belinda Miller

Dr Cristino Oliveira

Dr Narelle Cox

Ms Bruna Wageck

Ms Janet Bondarenko

Ms Monique Corbett

**1. Introduction**

You are invited to take part in this research project. We have contacted you because your respiratory doctor, nurse or physiotherapist indicated that you might be interested in taking part. We have approached you because you have been admitted at the Alfred Hospital and diagnosed with an acute exacerbation of chronic obstructive pulmonary disease (COPD). We believe that your participation could assist us to find out whether pulmonary rehabilitation programs that take place at home following hospital discharge are feasible and effective.

Patients with COPD do not currently receive rehabilitation in the early phase after hospitalisation due to an acute exacerbation. The research project aims to discover whether an 8-week home-based pulmonary rehabilitation program following hospitalisation is feasible and improves symptoms, wellbeing and exercise capacity.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;

- consent to be involved in the procedures described;
  - consent to the use of your personal and health information as described.
- You will be given a copy of this Participant Information and Consent Form to keep.

## **2. What is the purpose of this research project?**

The aim of this project is to discover whether a pulmonary rehabilitation program performed at home, following hospitalisation due to acute exacerbations of COPD, is feasible.

Pulmonary rehabilitation is an effective treatment for COPD which reduces symptoms, improves quality of life and increases exercise capacity. However, less than 10% of all people discharged from hospital following an acute exacerbation completed an outpatient hospital-based pulmonary program; rates of referral, uptake, adherence and completion were exceedingly low. Whilst the low rate of referral by health professionals is not well understood, patient-related barriers are well documented and include feeling too breathless to travel, fear of the hospital environment and physical limitations due to other diseases associated with the lung condition.

Previous studies have shown that home-based pulmonary rehabilitation improves symptoms and exercise capacity to a similar extent as hospital-based pulmonary rehabilitation in those with a stable clinical condition of COPD. However, the feasibility and benefits of the home-based program delivered early following hospital discharge while recovering from an acute exacerbation have not been yet documented.

A total of 10 people will participate in this project. People will be recruited from Alfred Hospital. Those people who choose to participate will take part in a home-based pulmonary rehabilitation program starting within one to three weeks following discharge from hospital.

This research has been funded by La Trobe University. The results of this research will be used by the researcher Ms Bruna Wageck to obtain a PhD degree.

## **3. What does participation in this research project involve?**

Participation in this project will start within one to three weeks following hospital discharge and initiates with one home visit by a physiotherapist who will take approximately 1½ hour. This visit will involve commencing the exercise program, which will involve walking and light strength training for the upper and lower body, as well as education regarding use of the home diary and a pedometer. The pedometer will be used to help record and progress the distance walked, and participants will be asked to complete their exercise program 5 times each week. They will be asked to document their exercise sessions in a diary. The physiotherapist will then contact the participants once a week by telephone, at an agreed time during seven consecutive weeks. These telephone calls will be used to review the home diary, to progress the exercise program, and undertake self-management education and training. These phone calls will last a maximum of half an hour.

At the beginning of the study and at completion of the 8-week homebased pulmonary rehabilitation program we will assess your respiratory symptoms, wellbeing and exercise capacity. This will involve completing a walking test, a test where you will stand up and sit down from a chair as often as you can in 1-minute, and completing four questionnaires. Each of these assessment occasions will take approximately 1½ hours and will be completed in the physiotherapy department at the Alfred Hospital. The first assessment will be performed prior to your discharge from the hospital.

Your hospital medical records will be reviewed to collect information on your medical history, your lung function and visits or readmissions to the hospital during the study

period. If you have not performed a pulmonary function test within 12 months of your final assessment (as part of your usual clinical care) you will have it assessed by one of our research personnel, the results of which will go into our research records and a report will be prepared to your doctor, upon request.

You will not be paid for your participation in this research.

#### **4. What are the possible benefits?**

You may receive those benefits which are usually experienced as a result of participation in a pulmonary rehabilitation program. These include reduced breathlessness, an improved sense of wellbeing and ability to exercise. We cannot guarantee or promise that you will receive any benefits from this project.

#### **5. What are the possible risks?**

Possible risks and discomforts include the discomfort of becoming breathless during the exercise tests and training sessions. You will be monitored by experienced staff during each exercise test to ensure that your oxygen levels and heart rate are satisfactory and that breathlessness is kept to an acceptable level.

You will have the first exercise session at home monitored by a physiotherapist, to ensure that the exercise program is safe and that you are not exercising too hard. The physiotherapist will show you how to monitor your exercise progression, to ensure that your breathlessness is kept to an acceptable level and that you are not exercising too hard. This will minimise the risk of becoming unwell. You may suspend or even end your participation in the project if distress occurs during the tests or exercise sessions. There may be additional unforeseen or unknown risks.

#### **6. Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at a later stage.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them when you withdraw from the research project.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or The Alfred Hospital.

#### **7. How will I be informed of the final results of this research project?**

When this project is finished you will be informed of the results by mail.

## **8. What will happen to information about me?**

Any information that is collected from you during the research project will be immediately stored using a code replacing your personal details so that you cannot be identified, and your will be privacy protected. This code will be kept in a locked cupboard in the La Trobe Clinical School at Alfred Health, which can be accessed only by the investigators. This approach enables researchers to re-identify your information if need be. Paper records will be stored against the code and kept in a locked filing cabinet at the La Trobe Clinical School at Alfred Health, with copies stored in the Physiotherapy Department at the Alfred Hospital. Electronic data will be stored on a computer against the patient code, and will be protected by password access. Study records will be kept for a period of 15 years from the end of the study. After this time the information will be disposed of safely and securely through shredding of the documents and deletion of computer files.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored and will only be used for the purpose of this research project. It will only be disclosed with your permission, or in compliance with the law.

If you give us your permission by signing the Consent Form, we plan to publish the results of the trial in an international scientific journal. In any publication, information will be provided in such a way that you cannot be identified. Only group data, not individual results, will be published.

Information about your participation in this research project may be recorded in your health records.

## **9. Can I access research information kept about me?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the principal investigator named at the end of this document if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for 15 years. The information will be disposed of safely and securely through shredding of the documents and deletion of computer files after 15 years has elapsed; access to information about you after this point will not be possible.

## **10. Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Alfred Health and La Trobe University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 11. Consent

I have read, or have had this document read to me in a language that I understand, and I understand the purposes, procedures and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) .....

Signature

Date

Declaration by researcher\*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed) .....

Signature

Date

*Note: All parties signing the consent section must date their own signature.*

## **12. Who can I contact?**

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

### **For further information or appointments:**

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), please contact the principal investigator:

**Prof Anne Holland on (03) 9479 6744 or 0419379821.**

You may also contact the following persons:

Name: Professor Belinda Miller

Role: Respiratory Medicine physician, Alfred Health

Ph: (03) 9276 3770

Name: Bruna Wageck

Role: PhD Student, La Trobe University.

Ph: 0450 420 290

### **For Complaints**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

Name: Ms Emily Bingle

Position: Research Governance Officer, Research and Ethics Unit, Alfred Health  
The Alfred Hospital, Commercial Rd, Melbourne 3004

Telephone: 03 9076 3619 Fax: 9076 8841

Email: research@alfred.org.au

You will need to tell Ms Bingle the following Alfred Health project number: 475/15

Further enquiries and/or complaints can also be addressed to:

The Secretary, Faculty Human Ethics Committee

Faculty of Health Sciences, La Trobe University, Victoria, 3086

Telephone: 03 9479 3582 Fax: 03 9479 5733

Email: health@latrobe.edu.au

## Appendix C – Thesis Amendment Report



Alicja N. Malicka, PhD

Director of Graduate Research

School of Allied Health, Human Services and Sport

College of Science, Health and Engineering

La Trobe University

Dear Dr Alicja N. Malicka

**Amendment report to the thesis entitled “Optimising the model of pulmonary rehabilitation following exacerbations of Chronic Obstructive Pulmonary Disease (COPD)”**

I am pleased to provide detailed responses to the Reviewer’s comments below. The thesis document was amended according to Reviewer’s suggestions.

**REVIEWER A**

i. Justification of classification

I have recommended that the thesis should be classified as passed and the candidate awarded the degree subject to the major amendments recommended in the examiners’ reports. The justification for this falls to the issues identified in the discussion, and given that the discussion is a key component of the overall intellectual piece, I deemed this to be a major amendment. However, I believe only minor adjustments will be required to address the issues raised.

ii. Recommendations for amendments

This is a substantial undertaking. Overall the work is presented with detail and clarity and the studies sit together in a logical sequence and develop as a research program. The prefaces were used to good effect to ensure flow and congruence. It is good to see that one of the papers has been published and all others submitted.

In regards to conceptual depth, I believe the work could have gone further, as discussed below. It may have been useful to employ an overarching conceptual framework that would have allowed the piece to be more connected to broader contexts. This may be discipline specific, but I believe this would have provided the candidate an anchor across the work for higher level discussion and connection to international movements within the discipline – and an opportunity for the candidate to demonstrate the depth of their knowledge in this way.

Thank you for this suggestion. The conceptual framework has been added in the discussion, in order to integrate the findings of this thesis with international literature and broader concepts of COPD management.

In regards to specific chapters,

#### Minor amendments

1- The introduction did well in outlining the body of work to be presented and in providing a detailed background. It would have been good to see more recognition and engagement with psychological influences on self-management – known to influence both exacerbation as well as PR engagement and outcomes. There were brief mentions of the connection with depression and of course HRQoL through the chapters, but I felt that further discussion and engagement was required as a conceptual background.

Additional information has been added to the introduction as follows:

*“Furthermore, the literature suggests that hospital admissions and readmission are significantly related to anxiety and depression factors (18).”*

*“Self-management strategies are important in order to promote behaviour change aiming to reduce anxiety and depression factors associated to COPD and ECOPD (18); and increase patient’s skill on how to manage their disease (26).”*

Further elaboration has been added to the Discussion after the results of the systematic review. In the systematic review education and self-management were analysed together and the review states that education is an important component to PR after exacerbation of COPD. Group education and self-management for analysis can be seen as limitation to the study, however the review results demonstrate the important role of education (and self-management) to PR after exacerbation.

2- The narrative review and secondary analysis were both well executed and presented, if again could have benefited from connection with a conceptual framework to elevate discussion.

I added a conceptual framework in the discussion session.

3- The systematic review was detailed and executed to a high level – well done – this was a substantial undertaking. One query, given the international recommendations for programs of around 8 week duration, it would have been useful to use this as a comparative cut off point. Grouping studies from 3 weeks to 12 weeks is very broad and one would wonder if the outcomes and results may have been masked by combining these. I guess what was lacking was a clear justification as to why these time points were chosen, particularly given the guidelines.

The optimal duration of pulmonary rehabilitation has not yet been defined. It is true that some guidelines suggest longer programs from around 8 weeks, however this is based on common practice rather than data from clinical trials. Exercise training studies frequently show benefits after 3 weeks of practice, so the authors decided that programs between 3-12 weeks would produce the expected outcomes and we followed the analysis as pre-determined on the review registration (PROSPERO). The rationale for selecting 3-12 weeks has been added to the methods section of the systematic review. The results shown that pulmonary rehabilitation is beneficial independent of program length to exercise capacity and quality of life and also, it revealed that programs of 3-12 weeks decreased hospital readmission. Thus, I acknowledge that it is a limitation to the study.

4- As a side note, when reporting small numbers – ie 30 studies – it would be useful, and somewhat conventional, to report the n= rather than or in addition to %.

Thank you, I added the “n=” in addition to the % in the text.

5- One last note on the systematic review – there was a need for a working definition of PR for this review – unless I missed this. This would have helped with clarity, for example, as to the justification that inpatient exercise of under three weeks duration, without an educational component, is still considered a PR program – given national and international guidelines around duration and selfmanagement focus.

We included studies that delivered exercises, not following PR guidelines. The idea was to include all studies that delivered exercises to ensure what components were important to achieve the benefits. I added a sentence to the eligibility criteria for more clarity.

Now it reads:

*“For this systematic review, we included both randomized and quasi-randomized controlled trials comparing early pulmonary rehabilitation (within 4 weeks after*

*discharge) to usual care or a control condition in patients with COPD who had recently been hospitalised for an exacerbation of COPD. To fulfill the review purpose we included all studies that delivered exercise after exacerbation of COPD, not only studies that followed pulmonary rehabilitation guidelines, to ensure we covered all components from pulmonary rehabilitation programs and were able to make comparisons (including education).”*

6- Following on from this theme, in Chapter 5, which was generally well undertaken and presented, it would have been ideal to have a clearer description of the educational/self-management component for the PR program – was this based on Lung Foundation Australia for example. This here, and the above definition in the systematic review, would have helped with transparency but also have demonstrated the candidate’s depth of understanding of the conceptual basis for PR.

The PR program was based on Lung Foundation Australia with phone calls using principles of motivational interviewing; and all participants received the living well with COPD book from Lung Foundation Australia. The book contains extended information about the disease and how to cope with it going through a vast number of topics related to quality of life. The topics from the books were also discussed during the motivational weekly phone calls. I added a sentence in the text to make it clear, now it reads:

*“The structured weekly phone calls were delivered by a physiotherapist trained in motivational interviewing who reviewed the home diaries, the exercise progression and delivered self-management training based on Lung Foundation Australia guidelines. During the calls participants were also provided with a menu of topics covering aspects of self-management (25) and were encouraged to choose one topic for discussion and goal setting each week. Participants also received the “Living well with COPD” book by Lung Foundation Australia.”*

7- Qualitative data analysis would also have benefited from further explanation – perhaps using a qual checklist would assist in directly discussing and addressing how concepts such as rigour, trustworthiness, transferability were handled. As well as justification for this particular qualitative approach for the study purpose – and definition of content analysis etc etc - I understand this is a small, supportive component within the feasibly study – but again this would allow the candidates to demonstrate their engagement and understanding of qualitative concepts.

I amend the “analysis of qualitative data” on the manuscript adding extra data about the coding and how the transcripts were handled. Now it reads:

*“The transcribed interviews were manually coded line-by-line and analysed according to the principles of deductive thematic analysis<sup>26</sup>. The data analysis was a four-step process that incorporated: a) immersing oneself in data, b) selecting meaningful units, c) condensing and labelling of data (coding), and d) clustering and formulation of themes<sup>26</sup>. All de-identified transcripts of the interviews were analysed by two researchers independently; both of whom had experience of analyzing qualitative interviews and conducting PR (one with more than 10 years of experience, the other with 2 years). The researchers then compared major themes and any disagreements were solved by discussion. Data from clinician and participant interviews were analysed separately.”*

Major amendments

8- The Discussion I did find somewhat problematic. Much of this reiterated previous chapters and there was a need for a much more overt connection between this body of work and international literature and broader concepts within the discipline. I think one cause for this was that the chapters were discussed separately in individual descriptive paragraphs throughout rather than integrated as a body of work – and that there was a distinct lack of literature.

I think the discussion is where a conceptual framework would really have helped the candidate to structure and place their work within the broader discipline and elevate the discussion above the descriptive and within a broader context.

I added a conceptual framework to the discussion chapter (depicted in Figure 3) and also amended the writing.

9- Limitations section was fine, however, rather than disparaging your very good narrative review, and that there were few studies – speak to the strengths and justification for why that particular approach was chosen to address the specific question being asked.

I added a sentence to justify the choice of a narrative review. Now it reads:

*“Despite the strengths of the work presented, this thesis structure possesses a few limitations. The inclusion of a narrative review regarding exacerbation recovery, instead of a systematic review, might have resulted in some information being omitted from the work - however, the literature on the topic was very small and there are not many controlled trials on the topic. The narrative review is an important body of work that combined epidemiological studies and identified sufficient data that enabled strong conclusions.”*

10- Conclusion again gave a descriptive summary of the work, but could speak to broader contexts and international trends.

The conclusion was amended to meet expectations.

Thankyou for the opportunity to examine this thesis. I hope the above comments are useful and will assist the candidate to demonstrate their knowledge – only minor adjustments would be required to address the issues raised. The candidate has achieved a substantial volume of work that will contribute to the discipline and to clinical practice, they should be highly commended for this.

## **REVIEWER B**

Justification of classification

The objective of this thesis was to optimise the model of pulmonary rehabilitation following exacerbations of COPD (ECOPD). The specific aims of each chapter were to:

- 1- Describe the natural recovery process following ECOPD for lung function, inflammatory markers, symptoms, physical activity and quality of life;
- 2- Examine the impact of ECOPD on clinical outcomes at 12 months after pulmonary rehabilitation and identify predictors of ECOPD in the year after pulmonary rehabilitation;
- 3- Determine the impact of the pulmonary rehabilitation program characteristics on clinical outcomes following an ECOPD;
- 4- Design and test a pulmonary rehabilitation protocol addressing barriers to uptake and completion of pulmonary rehabilitation following ECOPD.

In my opinion the thesis achieves its objective and satisfies the requirements for the thesis as outline in the Guidelines for Examiners. The thesis provides a comprehensive examination of the literature on patient recovery following ECOPD, the benefits of a pulmonary rehabilitation (PR) program and the characteristics of the program that may affect that recovery. The narrative and systematic reviews (Chapter 2 and 4, respectively) demonstrate the student's mastery and critical appraisal of a substantial body of knowledge related to ECOPD and PR and the findings of these reviews contributes original insights on the topic. The research described in Chapter 5 applies an action research model to assess whether home-based PR, initiated soon after hospital discharge for a severe ECOPD is feasible. The student has played a leading role in study design,



protocol development, literature searches and extraction, data collection, data analysis, as well as writing and review of manuscripts associated with the original research in the thesis. She has demonstrated that she can apply and interpret a wide variety of quantitative and as well as qualitative methodological techniques. The document is well written and the ideas are linked within and between chapters so that the thesis forms a cohesive body of knowledge. The original contributions to the literature (Chapter 2-5) have been published or submitted for publication. Below is a short description to support this assessment.

### Methodological Techniques

Majority of the thesis is devoted to examining the literature on AECOPD; its natural course of recovery, its effects on PR outcomes and the characteristics of PR programs that are associated with better results following AECOPD. Chapters 2 (narrative review) and 4 (systematic review with meta-analysis) provide comprehensive examination of the literature on the recovery following ECOPD and the characteristics of a pulmonary rehabilitation (PR) program that may affect that recovery. In Chapter 3, a secondary analysis of data from the HomeBase study, was performed to explore the impact of exacerbations on clinical outcomes (quality of life, aerobic capacity, dyspnea and physical activity) during the 12 months following PR. These investigations demonstrate that the student can perform comprehensive, focused literature searches and use advanced statistical analyses that included Kaplan Meier survival analysis, multiple linear regression, logistic regression, and meta-analysis with Forest plots to inform data interpretation. The student applied an action research model in research described in Chapter 5. The investigation examined whether it was feasible to implement a program, previously used to provide home-based PR to people with stable COPD, in people following severe ECOPD. The student was responsible developing the study concept,

protocol development, ethics application, data collection, data analysis, and writing and review of the manuscript. This investigation included qualitative research to explore patient and clinician views on barriers and facilitators that were used to modify the program prior to reassessment.

### Original Contributions

The thesis makes several original contributions to the current literature. The narrative review consolidated the literature to confirm that the typical timeframe for recovery from an ECOPD was approximately 2 weeks although recovery in many patients may not be complete by 3 months. It also highlighted that the definition of recovery varies depending on the parameter being examined. Patient-level factors that predict prolonged recovery are older age, severe lung disease, low BMI, and chronic dyspnea. Physical inactivity, skeletal muscle weakness, low exercise capacity, and reduced health-related quality of life and health status, factors that may be modified by PR, were also associated with prolonged recovery. Thus, these results can be used to direct interventions to limit prolonged recovery from ECOPD. Secondary analysis of the HomeBase trial extended our understanding of the effect of an ECOPD in the year following PR on PR outcomes at 12 months. Previous research had examined the exacerbations to six months following PR. A severe ECOPD predicted worse 12-month outcomes for the total, fatigue and emotional function domains of the CRQ, the mMRC, and the 6MWD. It also predicted lower moderate/vigorous physical activity, although the sample size was small. The insights offered by the systematic review of PR program characteristics provided welcome insights regarding the “active ingredients” of a PR program that decrease hospital readmission following PR. Despite a great deal of heterogeneity in the data, the findings provide clarity on program structure that was previously not available. Finally, the results of Chapter 5 examined early, home-based rehabilitation following an ECOPD

as a way of addressing concerns of limited uptake of PR in this patient population. Although overall, home-based PR may not be suitable for most patients, the study documents the barriers that must be overcome if it is to become a viable option in the future.

### Critical Analysis

The student has demonstrated appropriate and critical analysis of the information presented in the thesis. She has acknowledged the limitations of the findings in Chapter 4 due to the great heterogeneity of the data. Although the risk of bias was low for the criteria considered, several of the included studies suffered from low participant numbers and other weakness that affect the confidence in the review findings. Another concern regarding the findings in Chapter 4 is that the search strategy included studies that used exercise alone or exercise with education or self-management. However, the role of self-management was not considered in this review even though, generally, education alone is felt to have limited effects. Indeed, The American College of Chest Physicians and Canadian Thoracic Society guidelines on the prevention of acute exacerbation of COPD (2014) do not recommend education alone. Self-management is a topic of great interest in PR and its absence, or the absence of discussion of its importance, in this chapter seems to be an unfortunate oversight. Chapter 5 examines the feasibility of providing early, home-based PR following ECOPD. While I appreciate the need to present positive findings in a publication, I feel they were overstated in this chapter, which may give false director to some clinicians. The study reports that eligibility for home-based PR was very low and uptake in those eligible for the home-based program was low despite program modification based on comments from therapists and patients. The few patients who entered and complete PR showed significant improvement but this is not surprising as they were quite a select group and, as was the case in other reports in the thesis,

improvement was compared to status at exacerbation, not pre-exacerbation. Although not stated explicitly, early home PR may not be an appropriate intervention in this patient population. Or a radical re-design may be needed to increase patient numbers to achieve an acceptable cost-benefit ratio. The student rightly views the results of this thesis as an opportunity to focus PR interventions to improve outcomes for people following ECOPD. Chapter 2 notes that skeletal muscle weakness and low BMI are associated with poor recovery and the literature notes increased mortality associated with these factors. Most PR programs do not provide strength training that meets professional society guidelines, particularly in terms of prescribed load. In fact, it is unlikely that the home-based intervention reported in Chapter 5 did. The thesis and its publications could be an opportunity to highlight the need for strategies to institute and evaluate strength training, particularly for the lower extremities, for those recovering from ECOPD.

Literary presentation to the scholarly community

The original work from this thesis has been published or submitted for publication. Chapter 2 has been published in COPD Journal of Chronic Obstructive Pulmonary Disease, which has an impact factor of 2.503. Chapters 3, 4 and 5 have been submitted for publication in Respirology (Impact 4.756), Journal of Cardiopulmonary Rehabilitation and Prevention (Impact 1.568), and Chronic Respiratory Diseases (Impact 2.885), respectively. While these impact factors appear modest, the journals are well respected in the field of respiratory medicine and pulmonary rehabilitation, with Respirology being ranked in the top 15 journals in respiratory medicine.

## **Recommendations for amendments**

Minor changes

1- • Chapter 4, Abstract. States that exercise training alone was delivered in 43% of studies. Page 105/320 says that it was 40%. Similarly, page 105/320 says that 60% of programs were inpatient offerings but page 109/320 says that it was 57%. While these differences are small, they create confusion and should be reconciled.

Thank you for your comment, these typographical errors have been amended.

2- • Chapter 4, page 104/320. The number of studies for detailed analysis is not correct. 26,072-13,679 is not 162. The PRISMA diagram on Page 125/320 also contains errors.

The numbers were amended in the text and in the PRISMA diagram. Now it reads:

*“The electronic database searches identified a total of 14,162 citations after duplicates removed. From the total, 14,000 citations were excluded after screening titles and abstracts, leaving 162 studies for detailed evaluation.”*

3- • Chapter 4, page 114. Suggest that the commentary on mortality be in 1 vs 2 paragraphs.

That was amended, now commentary on mortality is presented in 1 paragraph.

4- • Chapter 5. Extended Methods/Phase I/Outcomes. Includes citations 50-57 that are not included in the reference list.

The reference list was amended.

5- • Chapter 5. Page 230/320. Please clarify the length of the program. It is listed a 8 weeks in one place and 9 in another.

The program length was 8 weeks, however the final assessments were booked for the week after the completion on the program. I understood how that could lead the reader to confusion. I changed the wording to “8 weeks”.

6- • Chapter 5, page 243/320. States that walking speed was prescribed as a percent of the 6MWT speed but aerobic capacity was based on a 1 minute sit-to-stand test. Please explain how the walking speed was determined using the sit-to-stand test.

When participants had not performed the 6MWT, walking speed were prescribed based on dyspnoea symptoms (3-4 Borg scale). I add a sentence to the text to clarify this matter, now it reads:

*“Aerobic exercise was prescribed at a speed equivalent to 70-80% of baseline six-minute walked distance (6MWD). Where a 6MWT was unable to be performed exercise training was prescribed on the basis of symptoms (BORG 3-4).”*

7- • Chapter 5. Table 3. The table should BMI. The table caption doesn't define the '\*' that accompanies the 6MWD in Phase I.

I amended the table legend, now it includes the definition to the '\*', it reads: *“\* $p < 0.05$ ”*

8- • Chapter 5, page 248/320, Table 2. States that people were excluded from Phase III if they had attended PR in the 12 prior to the current study. Page 234 and 258/320 say this wasn't an exclusion criterion. This discrepancy needs to be resolved.

Previous enrollment in PR for the last 12 months was not an exclusion criteria on Phase III, that number is from people who were ongoing pulmonary rehabilitation at the time of the recruitment. I amended the table, now it reads: *“• Currently enrolled in PR (=12)”*

9- • Chapter 5, page 258/320. Currently says that the outcome measures for Phase I and III were the same; however, the 1 minute sit-to-stand replaced the 6MWT. The information should be revised to accurately reflect the study protocol.

Due to the change in location for the baseline assessment, Phase III included addition of another exercise capacity test to ensure we had sufficient information for exercise prescription. The 1 minute sit-to-stand test was chosen because the test could be performed in the hospital wards. A sentence was added to explain these reasons, now it reads:

*“Phase III maintained the same outcomes related to feasibility<sup>13</sup>. In Phase III the one-minute sit-to-stand test was added to the measures from Phase I, all other measures remained unchanged and followed the same standards for assessment.”*

10- • Chapter 5, page 259/320. The statement ‘Given the potential for pulmonary rehabilitation to reduce hospital admissions<sup>6</sup>, the low eligibility for pulmonary rehabilitation following ECOPD represents an unrealised opportunity to enhance patient and health system outcomes’ requires clarification. The connection between low eligibility and patient and health systems outcomes is not readily apparent.

The highlighted sentence attempted to show a limitation to the home-based program. It is known that uptake of any modality of pulmonary rehabilitation is a challenge, however in this pilot study the eligibility to be recruited to home-based pulmonary rehabilitation was low. The small proportion of patients who were eligible suggests these criteria may limit participation in pulmonary rehabilitation. I add another sentence in other to discuss better the findings, I hope this helps brings clarity.

Now it reads: *“Given the potential for pulmonary rehabilitation to reduce hospital admissions<sup>6</sup>, the low eligibility for pulmonary rehabilitation following ECOPD represents an unrealised opportunity to enhance patient and health system outcomes. Although we used typical exclusion criteria for home-based rehabilitation programs (e.g. balance deficits, cerebral or lower limb palsies, musculoskeletal impairment or cardiac conditions*

*that would prevent independent exercise training), the large number of excluded patients suggests that these criteria may limit participation in home-based PR. “*

11- • Chapter 6, page 279/320. States that chapter 2 is a secondary analysis of the literature when it is actually chapter 3. This error should be corrected.

This sentence was corrected. Now it reads: *“Chapter Three of this thesis comprises a secondary analysis of a larger randomised controlled trial”*

12 - Typographical errors

- Page 27/320, para 2. Change ‘improve’ to ‘improves’
- Page 29/320, para 2, second sentence. The sentence is incomplete.
- Chapter 2, preface. Once defined, use the abbreviation ECOPD.
- Chapter 5, pg 233. Data analysis. First sentence. Change ‘were’ to ‘was’.
- Chapter 5, pg 245/320. Dyspnea. Change ‘indicate’ to ‘indicates’.

All typographical errors were corrected.

General points for consideration

13- • The author alternates the abbreviation for (acute) exacerbation of COPD between AECOPD and ECOPD. I understand that the terminology is likely a philosophical stance of the lab. However, if the publication associated with the content uses AECOPD then it would seem reasonable that the chapter preface does as well.

In this thesis I had chosen to be consistent with the newest terminology related to exacerbations of COPD. When the manuscript from Chapter 2 was published, it was still used the term “acute exacerbations of COPD”. However, new guidelines suggest the use of “exacerbation of COPD”. I understand that it may be inconsistency in the terminology



between manuscript and preface, however, to avoid confusion, I preferred to use the most up to date terminology in the thesis.

14- • Frequently the author uses the terms aerobic capacity and endurance interchangeably. It is important to note that capacity refers to the maximum performance and endurance is the ability to perform at a percentage of that capacity over a period of time.

Thank you for your comment. I reviewed the uses of both terms in the document and have amended where necessary.

Recommendation:

The thesis should be classified as passed and the candidate awarded the degree subject to the minor amendments recommended in the examiners' reports and the candidate given up to four weeks to effect the recommendations as well as correct any typographical errors being made and documented to the satisfaction of the principal supervisor and the School Director of Graduate Research or Head of School.