Exercise as an Alternative to Traditional Airway Clearance Techniques in Cystic Fibrosis

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Submitted by

Nathan Ward

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Department of Physiotherapy, Podiatry, and Prosthetics and Orthotics

School of Allied Health, Human Services and Sport

College of Science, Health and Engineering

La Trobe University

Victoria, Australia

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Dedication

This thesis is dedicated to my beautiful wife, Rebecca, and my amazing children, Hannah and Caleb. Rebecca, your patience, reassuring steadiness and all things, big and small, that you do for our family is greatly appreciated. Without you, this work would have not been possible. Hannah and Caleb, thank you for accepting when I said ‘I need to do some work’. I look forward to spending more time with you as you continue to develop into the amazing people that you are.

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Table of contents

Dedication ii

Acknowledgements iii

Table of contents v

List of abbreviations ix

List of tables x

Thesis summary xi

Statement of authorship xiii

Publications and presentations xvi

Grants and awards xx

CHAPTER 1: INTRODUCTION 1

1.1 Cystic fibrosis overview 2

1.1.1 Epidemiology 2

1.1.2 Diagnosis 3

1.1.3 Pathophysiology 4

1.1.4 Therapeutic management 5

1.2 Exercise as a therapeutic intervention in cystic fibrosis 8

1.3 Traditional airway clearance techniques in cystic fibrosis 9

1.3.1 Physiological rationale 9

1.3.2 Physiological mechanisms to improve mucociliary clearance 9

1.3.2.1 Improving ventilation 10

1.3.2.2 Expiratory flow 11

1.3.3 Airway clearance technique options 12

1.3.4 Evidence supporting the use of airway clearance techniques 14
1.3.4.1 Expectorated sputum 14
1.3.4.2 Direct measures of mucociliary clearance 15
1.3.4.3 Pulmonary function tests 15
1.3.5 Adherence with airway clearance techniques by people with cystic fibrosis 16
1.4 Exercise as an alternative to traditional airway clearance techniques in cystic fibrosis 18
1.4.1 Physiological rationale for the use of exercise as an airway clearance technique in cystic fibrosis 19
1.4.1.1 Nasal transepithelial potential difference and sodium conductance 19
1.4.1.2 Sputum solids content 20
1.4.1.3 Sputum rheology 21
1.4.1.4 Expiratory flow 22
1.4.1.5 Stimulation of cough 23
1.4.2 The effects of exercise on secretion clearance compared to rest 24
1.4.3 The effects of exercise on secretion clearance compared to traditional airway clearance techniques 24
1.4.4 Summary of exercise as an airway clearance technique 25
1.5 Study design considerations 26
1.5.1 Protocol 26
1.5.2 Selection of trial interventions 27
1.5.3 Outcome measures for clinical trials in cystic fibrosis 28
1.5.3.1 Mortality 28
1.5.3.2 Pulmonary function tests 29
1.5.3.3 Respiratory exacerbations 30
1.5.3.4 Expectorated sputum and mucociliary clearance 31
1.5.3.5 Exercise testing 32
1.5.3.6 Patient-reported outcomes 32

1.5.3.7 Summary of outcome measures in cystic fibrosis studies 34
1.5.4 Measuring adherence to exercise and traditional airway clearance techniques 34
1.6 Summary 37
Thesis aims and outline 39
CHAPTER 2: EXERCISE AS A THERAPEUTIC INTERVENTION IN CYSTIC FIBROSIS: A NARRATIVE LITERATURE REVIEW 42
Declaration of authorship – Chapter 2 43
CHAPTER 3: EXERCISE AS AN ALTERNATIVE TO TRADITIONAL AIRWAY CLEARANCE IN CYSTIC FIBROSIS: A SYSTEMATIC LITERATURE REVIEW 72
Declaration of authorship – Chapter 3 73
CHAPTER 4: EXERCISE AND AIRWAY CLEARANCE PRACTICES OF ADULTS WITH CYSTIC FIBROSIS: CURRENT AUSTRALIAN PRACTICE 99
Declaration of authorship – Chapter 4 100
CHAPTER 5: ASSESSMENT OF RESPIRATORY SYMPTOMS IN CYSTIC FIBROSIS 109
Declaration of authorship – Chapter 5 110
CHAPTER 6: AIRWAY CLEARANCE BY EXERCISING IN MILD CYSTIC FIBROSIS (ACE-CF): A FEASIBILITY STUDY 119
Declaration of authorship – Chapter 6 120
CHAPTER 7: DEVELOPMENT OF THE POSITIVE EXPIRATORY PRESSURE THERAPY RECORDER FOR ASSESSING ADHERENCE (PEPTRAC) 128
Declaration of authorship – Chapter 7 129
CHAPTER 8: CONCLUSIONS AND FUTURE DIRECTIONS 166

8.1. Summary of main findings 167

8.2. Implications for clinical practice 168

8.3. Implications for future research 171

8.3.1. Measurement of adherence 171

8.3.2. Optimisation of adherence 173

8.3.3. Specific recommendations for a multi-centred, medium to long term study investigating exercise as an alternative to traditional airway clearance techniques 174

8.4. Conclusions 180

APPENDICES 181

Appendix A.1 - Ethics approval certificates for Chapter 4 182

Appendix A.2 - Ethics approval certificates for Chapter 5 193

Appendix A.3 - Ethics approval certificates for Chapter 6 197

Appendix A.4 - Ethics approval certificates for Chapter 7 202

Appendix B.1 – Publishing agreement for Chapter 2 210

Appendix B.2 – Publishing agreement for Chapter 3 212

Appendix B.3 – Publishing agreement for Chapter 4 214

Appendix B.4 – Publishing agreement for Chapter 5 217

Appendix B.5 – Publishing agreement for Chapter 6 220

Appendix B.6 – Publishing agreement for Chapter 7 224

REFERENCES 228

List of abbreviations

ACT: airway clearance technique

CI: confidence interval

CF: cystic fibrosis

CFQ-R: Cystic Fibrosis Questionnaire Revised

CFTR: cystic fibrosis transmembrane conductance regulator

CT: computed tomography

EPP: equal pressure point

FET: forced expiratory technique

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

FEF_{25-75}: forced expiratory flow at 25-75% of forced vital capacity

HFCWO: high frequency chest wall oscillation

HRQOL: health-related quality of life

LCQ: Leicester Cough Questionnaire

MCC: mucociliary clearance

PD: postural drainage

PEFR: peak expiratory flow rate

PEP: positive expiratory pressure

PEPtrac: positive expiratory pressure therapy recorder for assessing adherence

PIFR: peak inspiratory flow rate

PFTs: pulmonary function tests

PRO: patient-reported outcome

ReS-CF: Respiratory Symptoms in Cystic Fibrosis tool

TPGLF: two phase gas liquid flow

VO_2peak: peak oxygen uptake

Wpeak: peak work

List of tables

Table 1.1 - Examples of ACTs available for people with CF. 13

Table 1.2 - Effects of exercise and traditional ACTs in CF on expiratory flow. 23

Table 8.1 - Summary of a proposed protocol of a multi-centred, medium to long term study investigating the use of exercise as an alternative to traditional ACTs. 179

Thesis summary

International practice guidelines recommend that people with cystic fibrosis (CF) regularly undertake both exercise and traditional airway clearance techniques (ACTs). However, some people with CF consider exercise to be an alternative to traditional ACTs. This thesis investigates the use of exercise as an alternative to traditional ACTs by people with CF by virtue of six studies:

1. A narrative literature review summarising the evidence for the use of exercise as a therapeutic intervention in CF.
2. A systematic literature review concluding that exercise is likely to be more effective than resting at improving airway clearance. Short term studies (n=9) comparing exercise to traditional ACTs for improving airway clearance have conflicting results and there is a paucity of longer term studies.
3. A survey of adults with CF across Australia (n=692) finding that 44% had used exercise as an alternative to traditional ACTs in the preceding three months, with these people tending to have milder respiratory disease.
4. A study of the psychometric properties of the Leicester Cough Questionnaire confirming that it is valid and reliable (n=59) and responsive (n=53) when completed by people with CF.
5. A feasibility study investigating exercise as an alternative to traditional ACTs in adults with mild respiratory CF disease, finding it was feasible to recruit participants to such a study (n=17 recruited of 57 screened, 30%). However, the target randomisation rate (80%) was not achieved due to inadequate adherence with the interventions during the run-in period.
6. A novel electronic recording device that was developed and a study (n=18 participants) finding it was able to objectively measure adherence (session attempts and within session quality) when airway clearance was performed using positive pressure ACT devices.

These studies provide the foundation for a large, multi-centred randomised clinical trial investigating exercise as an alternative to traditional ACTs.

Statement of authorship

This thesis includes work by the author that has been published or accepted for publication as described in the text. 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 acknowledgement 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.

Ethical approval was required for the work presented in this thesis by La Trobe University SHE College Human Ethics Sub-Committee (SHE CHESC acceptance of Royal Adelaide Hospital HREC approved project HREC/16/RAH/173), La Trobe University Human Ethics Committee (UHEC acceptance of RAH HREC approved project HREC/15/RAH/2, UHEC acceptance of RAH HREC approved project HREC/15/RAH/518, UHEC acceptance of RAH HREC approved project HREC/17/RAH/270), Royal Adelaide Hospital Human Research Ethics Committee (HREC/15/RAH/2, HREC/16/RAH/173, HREC/15/RAH/518, HREC/17/RAH/270), University of Adelaide Human Research Ethics Committee (32307 acceptance of RAH HREC approved project HREC/17/RAH/270), Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee (2016-110), Tasmanian Health and Medical Human Research Ethics Committee (H0015945), ACT Health Human Research Ethics Committee (ETH.1.17.009E).

Candidate's declaration

In the case of Chapters 2-7 of this thesis, the nature and extent of the candidate's contribution was as follows:

Thesis chapter	Publication title	Publication status	Extent of contribution
2	Exercise as a therapeutic intervention for people with cystic fibrosis.	Published	80%
3	Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review.	Epub ahead of print	70%
4	Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey.	Published	70%
5	The psychometric properties of the Leicester Cough Questionnaire and Respiratory Symptoms in CF tool in cystic fibrosis: a preliminary study.	Published	75%
6	Airway clearance by exercising in mild cystic fibrosis (ACE-CF): a feasibility study.	Published	70%
7	Development of a device to measure adherence and pressure characteristics of positive expiratory pressure therapies used by adults with cystic fibrosis.	Epub ahead of print	60%

Nathan Ward, 11 January 2021

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.

Name of supervisor	Signature
Anne Holland	

Publications and presentations

All manuscripts presented in this thesis were designed, conducted and written during the period of candidature for the specific purpose of obtaining the degree of Doctor of Philosophy. Each manuscript was prepared in accordance with the specific requirements of the relevant journal. The contribution of the student candidate, and each of the co-authors, for each study is included in the prefaces of Chapters 2-7.

Publications

- Ward N, Stiller K, Rowe H, Holland AE. The psychometric properties of the Leicester Cough Questionnaire and Respiratory Symptoms in CF tool in cystic fibrosis: a preliminary study. J Cyst Fibros 2017; 16: 425-432.
- Ward N, Stiller K, Rowe H, Morrow S, Morton J, Greville H, Holland AE. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): a feasibility study. Respir Med 2018; 142: 23-28.
- Ward N, Stiller K, Holland AE. Exercise as a therapeutic intervention for people with cystic fibrosis. Expert Rev Respir Med 2019; 13 (5): 449-458.
- Ward N, Stiller K, Holland AE and the Australian Cystic Fibrosis Exercise Survey Group. Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey. J Physiother 2019, 65: 43-50.
- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Development of a device to measure adherence and pressure characteristics of positive expiratory pressure therapies used by adults with cystic fibrosis. Physiother Theory Pract 2020, epub ahead of print. DOI:10.1080/09593985.2020.1858465.
- Ward N, Morrow S, Stiller K, Holland AE. Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review. Thorax 2020, epub ahead of print. DOI:10.1136/thoraxjnl-2020-215836.

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- Ward N. The Leicester Cough Questionnaire [summary]. J Physiother 2016; 62: 53.
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- Ward N, Stiller K, Rowe H, Holland AE. Assessment of cough in cystic fibrosis. TSANZSRS Annual Scientific Meeting, 1-6 April 2016, Perth, WA, Australia (poster). Published abstract: Respirology 2016, 21 (suppl 2): 168.
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- Ward N, Stiller K, Rowe H, Morrow S, Morton J, Greville H, Holland AE. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): clinical outcomes of a feasibility study. TSANZSRS Annual Scientific Meeting, 23-27 March 2018, Adelaide, SA, Australia (oral presentation and poster). Published abstract: Respirology 2018, 23 (suppl 1): 140.
- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Positive expiratory pressure therapy recorder for assessing compliance (PEPtrac): a new device for clinical practice. North American Cystic Fibrosis Conference, 18-21 October 2018, Denver, CO, US (poster). Published abstract: Ped Pulmonol 2018, 53 (suppl 2): 341.
- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. PEPtrac: development of a new device for measuring adherence with positive pressure airway clearance. Thoracic Society of Australia and New Zealand (SA/NT Branch) New Investigator Award, 15 November 2018, Adelaide, SA, Australia (oral presentation).

- Ward N, Stiller K, Bingham J, Bishop J, Button B, Chambers R, Chung C, Cobb R, Corda J, Dentice R, Green M, Hall K, Hauser J, Morrow S, Netluch R, Nichols A, Rowe H, Shaw A, Shortall D, Smith T, Wood J, Holland AE. Australian adults with cystic fibrosis commonly use exercise as an alternative to traditional airway clearance techniques: a national survey. TSANZSRS Annual Scientific Meeting, 29 March - 2 April 2019, Gold Coast, QLD, Australia (oral presentation and poster). Published abstract: Respirology 2019, 24 (suppl 1): 69.
- Ward N, Stiller K, Bingham J, Bishop J, Button B, Chambers R, Chung C, Cobb R, Corda J, Dentice R, Green M, Hall K, Hauser J, Morrow S, Netluch R, Nichols A, Rowe H, Shaw A, Shortall D, Smith T, Wood J, Holland AE. Airway clearance and exercise practices of adults with cystic fibrosis: current Australian practice. TSANZSRS Annual Scientific Meeting, 29 March - 2 April 2019, Gold Coast, QLD, Australia (oral presentation and poster). Published abstract: Respirology 2019, 24 (suppl 1): 69.
- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Oscillation properties of the Acapella DH® and Aerobika® during unsupervised airway clearance sessions in adults with cystic fibrosis. European Cystic Fibrosis Conference, 5-8 June 2019, Liverpool, UK (poster). Published abstract: J Cyst Fibros 2019, 18 (suppl 1): S163.
- Ward N. The role of exercise as a form of airway clearance in young people with cystic fibrosis. European Cystic Fibrosis Conference, 5-8 June 2019, Liverpool, UK (invited oral presentation).
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- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Pressure and oscillation properties generated by commonly used airway clearance devices in adults with cystic fibrosis during unsupervised use. 13th Australasian Cystic Fibrosis Conference, 4-6 August 2019, Perth, WA, Australia (eposter).

- Ward N, Ward B, Stiller K, Kenyon A, Holland AE. Expiratory duration and pressure properties of commonly used airway clearance devices when used unsupervised by adults with cystic fibrosis. North American Cystic Fibrosis Conference, 31 October – 2 November 2019, Nashville, TN, US (poster). Published abstract: Ped Pulmonol 2019, 54 (suppl 2): 382.
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- Thoracic Society of Australia and New Zealand Annual Scientific Meeting 2018 CF Special Interest Group best poster.
- North American Cystic Fibrosis Conference 2018 Junior Investigator Best Abstract in Clinical Research winner.
- 13th Australasian Cystic Fibrosis Conference 2019 Best Presentation Physiotherapy winner.

CHAPTER 1:

INTRODUCTION

Introduction

Cystic fibrosis (CF) is a life-limiting genetic condition and whilst affecting multiple organs, progressive respiratory disease and gastrointestinal dysfunction are the typical dominant phenotypic features. Progressive respiratory disease is the primary cause of death in most affected individuals.[1, 2] Treatments aimed at limiting the rate of progressive damage to the respiratory system have evolved, particularly over the last three decades, however these advances have resulted in an associated increase in treatment burden for affected individuals. Physiotherapy interventions, primarily in the form of airway clearance techniques (ACTs) and exercise, are a longstanding accepted component of the therapeutic regimen recommended to people with CF.[3, 4] Whilst performance of both ACTs and exercise is recommended, it has been suggested that exercise may act as a stand-alone form of airway clearance therapy.[5] This may be particularly relevant to people with mild CF disease who have well preserved lung function and a smaller volume of respiratory secretions. There are limited data however to support this approach. Further investigation of the efficacy of exercise as an alternative to traditional ACTs is warranted.

1.1 Cystic fibrosis overview

1.1.1 Epidemiology

Cystic fibrosis is often stated as being the most common autosomal recessive life-shortening condition affecting the Caucasian population, with an estimated 1 in 25 people being carriers of a CF genetic mutation, resulting in an incidence of 1 in 3000-3300.[6-8] When first described in 1938, CF was exclusively a disease of childhood, with a life expectancy of around six months.[9] Major advances in the understanding of the pathophysiology of CF and subsequent therapeutic developments has seen survival rates improve markedly, particularly over the last 30-40 years. Between 1979 and 2005, the mean age at death for people with CF living in Australia increased from 13.3 years (95% confidence interval [CI] 12.2-14.4) to 26.6 years (95% CI 25.6-27.7).[10] The most

recent report from the Australian CF Data Registry found that 53.2% of the population with CF were adults, an increase of 3.9% over only four years.[2] Due to modern therapeutic advances, around 18% of adults with CF now have a forced expiratory volume in one second (FEV_1) ≥ 90% predicted, with just under 30% of the adult CF population having an FEV_1 between 70-90% predicted.[10] This means there are more adults living with CF and more of these people have pulmonary function test (PFT) values that are normal or only mild-impaired.

1.1.2 Diagnosis

The diagnosis of CF historically occurred as a result of the presence of a combination of classical phenotypic symptoms, with an affected individual eventually undergoing a pilocarpine sweat test to confirm the diagnosis.[11] A sweat chloride (Cl^-) concentration >60mmol/L, combined with clinical features consistent with CF, confirmed the diagnosis.[12] In the late 1980s to early 1990s, newborn screening was introduced in Australia and has resulted in people being identified as possibly affected by CF within a few days of birth, even if asymptomatic.[13] The identification of the CF gene in 1989 led to the ability to directly test for relevant mutations.[9] Where a newborn screening result is positive, individuals undergo pilocarpine sweat testing and cystic fibrosis transmembrane conductance regulator (CFTR) genetic testing to confirm the diagnosis.[12] An individual is consider to have 'classical' CF when they have a sweat Cl^- concentration >60mmol/L and two CF-causing mutations are identified.[12] However, it must be noted that there is a cohort where the sweat test may be indeterminate (Cl^- = 30-60mmol/L). The presence of two CF-causing mutations may confirm the diagnosis in these cases however, in those individuals with only one identified CF-causing mutation, confirming the diagnosis is more challenging and has led to the use of terms such as atypical CF, non-classical CF, CFTR-related metabolic syndrome and CF screen positive inconclusive diagnosis (CFSPID), with the latter two now the preferred terminology.[12] These differences in terminology and certainty of a diagnosis need to be considered when designing CF

studies to ensure that appropriate individuals are recruited, particularly when targeting individuals with mild respiratory disease.

1.1.3 Pathophysiology

The clinical features of CF occur as a result of mutations in the CF gene leading to abnormal CFTR protein production. The CFTR protein is primarily responsible for the transport of Cl^- ions across the apical surface of epithelial cells.[8] It also has a role in the inhibition of epithelial sodium and calcium-activated chloride channels, regulates various intracellular processes and is involved in Cl^- and bicarbonate (HCO_3^-) exchange.[8]

It is currently accepted that it is the reduced Cl^- transport and increased sodium (Na^+) resorption, as a consequence of altered CFTR function, which leads to the hallmark phenotypic features of CF.[14-16] The classical CF phenotype is one of chronic respiratory disease (characterised by chronic cough, progressive bronchiectasis and colonisation with a range of bacterial pathogens), sinus disease (sinusitis and nasal polyps), pancreatic insufficiency, gastrointestinal malabsorption, malnutrition and azoospermia in males.[8, 9, 11, 17] Over 1,500 mutations in the CF gene have been described, however not all of these mutations will result in a typical CF phenotype.[15, 18, 19] Mutations in the CF gene are classified into six different categories based on the impact on CFTR, which ranges from no CFTR production through to relatively normal CFTR with an increased rate of degradation.[8, 15] Whilst genotype may predict some phenotypical characteristics (e.g. individuals who are F508del homozygous are likely pancreatic insufficient), there is no clear genotype-phenotype relationship with regards to the severity of respiratory disease.[19, 20]

Within the respiratory system, the reduced transport of Cl^- and HCO_3^- into the airway lumen, combined with the increased Na^+ resorption, results in water moving out of the airway lumen due to an osmotic gradient.[15, 21] As a consequence, there is a reduction in the water content of the airway surface liquid, a vital component of the innate airway

defence mechanism.[15, 21] The airway surface liquid, consisting of periciliary and mucus layers, is responsible for trapping dust and bacteria which are inhaled into the lungs, with the respiratory epithelial cilia continuously propelling the airway surface liquid (and suspended foreign material) towards the central airways where it can be expelled by coughing.[14, 21] Dehydration of both layers of the airway surface liquid in CF compromises the normal cilial movement and the mucociliary clearance (MCC) mechanism becomes impaired, leading to mucus retention, airway obstruction, colonisation with a variety of bacterial pathogens and a persistent host immune response.[14, 15]

It is now recognised that the respiratory sequelae of CF commence very early in life. Even in infants diagnosed by newborn screening, the majority of whom may not display any of the typical signs of CF, small airways disease may be present as evidenced by gas trapping on computed tomography (CT). A recent study of infants (median age 3.6 months) found 81% already had CT evidence of structural lung damage.[22] Whilst beginning in the small airways, eventually the recurrent cycle of mucus plugging, infection and inflammation results in progressive lung damage, spreading to the larger airways (as evidenced by bronchiectasis) and leading eventually to the development of respiratory failure, ultimately causing either death or the necessity for lung transplantation.[14, 15, 22, 23]

1.1.4 Therapeutic management

Historically, therapeutic interventions available to people with CF have targeted the secondary effects of the disease and focussed on three key areas: respiratory care to reduce mucus retention and obstruction and treat infections, addressing nutritional requirements, and education of the patient/family.[9, 24] Current guidelines recommend that once a diagnosis of CF is confirmed, individuals should commence the CF therapeutic regimen as soon as practicable irrespective of symptoms.[24] As new treatments have become available they have generally been added to the existing therapeutic regimen, meaning people with CF are now commonly prescribed a time-intensive, complex

regimen of daily treatment.[25, 26] This approach, combined with specialised multidisciplinary input, has seen the rate of survival improve markedly but also means that people with CF, some of who may be largely asymptomatic even as they move into adulthood, can spend nearly two hours each day performing their therapeutic regimen.[27]

International clinical practice guidelines recommend that people with CF undertake a daily regimen of ACTs and exercise in order to reduce the degree of mucus retention and airway obstruction.[3, 28, 29] The rationale, underlying physiology and evidence for these treatments are discussed in subsequent sections of this thesis, with exercise discussed more extensively in the published narrative review that forms Chapter 2. It needs to be acknowledged that both ACTs and exercise are time consuming, often need to be coordinated with the timing of inhaled medications and contribute significantly to the time burden associated with the CF therapeutic regimen, all of which may adversely affect treatment adherence and quality of life.[30, 31]

Whilst the therapies targeting the sequelae of disease arising from mutations in the CF gene have led to improvements in lifespan and health-related quality of life (HRQOL), the last five to 10 years has seen a dramatic shift in the treatment paradigm for CF. Gene therapy is still considered the potential panacea for CF even though success in achieving sustained gene expression has been limited.[32] However, with the development of high throughput molecular screening, various compounds have now been identified that directly modify the CFTR protein and are collectively known as disease modulators.[32] Ivacaftor was the first compound found to result in significant improvements in FEV_1, weight and HRQOL through potentiating CFTR.[33] However, whilst achieving a mean increase of 11% in FEV_1 compared to placebo, the initial Ivacaftor studies only targeted individuals with a specific mutation (G551D), accounting for only approximately 5% of the CF population.[33] Whilst the use of Ivacaftor has been expanded to include those with other residual function mutations, the majority of people with CF do not benefit from Ivacaftor monotherapy.[34] Subsequent research has identified additional compounds (e.g.

Lumacaftor and Tezacaftor) that can be administered with Ivacaftor to treat those homozygote for the most common mutation (F508del), however the changes in FEV_1 (mean relative treatment difference 4-7%) were less encouraging than those seen in the G551D Ivacaftor studies.[35, 36] Recent research has found that a combination of three compounds (Elexacaftor, Tezacaftor and Ivacaftor) has a clinically important effect (mean difference in FEV_1 = 10-14% over 4 weeks) in people who are F508del homozygote or heterozygote F508del with a minimal residual function mutation.[37, 38] Whilst these various modulator therapies are a relatively new development, evidence is emerging that they not only lead to an increase in PFTs in the short term but also a slowing of the rate of decline in PFTs over the medium term.[39] Modulator therapy is currently prescribed as an additional therapy to the existing therapeutic regimen. The effectiveness of these new medications at targeting the cause of the disease (i.e. defective CFTR protein) and not just managing the resultant effects (e.g. mucus retention) may mean some of the existing therapies may no longer be required. Therefore, a re-evaluation of the existing therapeutic regimen will be needed as the use of effective disease modulators becomes standard clinical care. For example, a recent survey of people with CF and clinicians regarding the potential withdrawal of therapies in the presence of effective modulator therapy found that the majority of people with CF were very interested (58% of respondents) or somewhat interested (30% of respondents) in undertaking studies where traditional ACTs are stopped, whilst clinicians were very interested in studies withdrawing inhaled hypertonic saline (65% of respondents) or Dornase alfa (63% of respondents).[40] Reconsideration of the role of exercise and traditional ACTs in the modern era of CF management should be an area of focus, given the high treatment burden associated with both of these interventions and potential change in pathophysiology resulting from modulator therapy.[40]

Despite the improvements in lifespan and HRQOL that have resulted from the advances in the range of therapies available to people with CF, maintaining adherence with the therapeutic regimen can be a challenge. Poor adherence with the prescribed therapeutic

regimen in CF is a well-recognised problem and most likely multifactorial in its origins.[41-43] Undoubtedly, the time-intensive nature of some interventions contributes to reduced adherence.[44] Adherence rates reported in the literature are highly variable, differing between therapies and also between studies for the same therapy.[42, 43] This variability in adherence rates is at least partially attributable to differing measurement methodologies.[42, 43, 45] Regardless, it is generally accepted that overall adherence with the prescribed therapeutic regimen in CF is low to moderate and that adherence with oral medications may be higher than with more time intensive therapies such as ACTs and exercise.[42, 43, 46-49] Numerous efforts, albeit with limited success, have been made to improve adherence with prescribed therapies in CF and methods to improve adherence remain an ongoing area of interest.[50] Reducing the treatment burden, by simplifying and rationalising regimens where possible, is one method that may help to improve adherence to the overall therapeutic regimen.[42]

1.2 Exercise as a therapeutic intervention in cystic fibrosis

Regular physical activity and exercise have been considered an important component of the therapeutic regimen in CF for many years.[4] A pivotal study in 1992, which found a link between peak oxygen consumption (VO_2peak) and survival in CF, independent of FEV_1, led to a rapid expansion in the research evaluating exercise as a therapeutic intervention in CF.[51] A recent study confirmed that in the modern era of CF management (but prior to the development of effective modulator therapy), this link between physical fitness and survival remains.[52] Chapter 2 of this thesis, a published narrative literature review, summarises the current literature regarding the use of exercise as a therapeutic intervention in CF. This review addresses the respiratory and non-respiratory benefits of exercise in CF, highlights the limitations in the current evidence-base and provides insights into potential developments over the next five years.

As will be discussed in Chapter 2 of this thesis, in addition to the overall health benefits of exercise in CF, exercise has also been proposed as a potential alternative or

substitute to traditional ACTs. However, a more in-depth review of the rationale and evidence supporting or refuting the use of exercise as an alternative to traditional ACTs is required for the purposes of this thesis and thus follows in the next section. When considering the potential for exercise to be an alternative to traditional ACTs, the following should be considered: 1) the underlying physiological principles by which MCC may be increased in CF, 2) what techniques are considered as traditional ACTs, 3) does exercise impact MCC and 4) if exercise impacts MCC, are the effects similar to those seen with traditional ACTs.

1.3 Traditional airway clearance techniques in cystic fibrosis

1.3.1 Physiological rationale

In CF, thickened respiratory secretions, which result from defective ion transport, overwhelm the normal MCC mechanism, are retained within the airways and lead to the formation of mucus plaques and airway obstruction.[15, 21, 53] Ongoing airway obstruction promotes the development of a chronic cycle of infection and inflammation, resulting in progressive damage to the airways (including the development of bronchiectasis), which in turn contributes to increased mucus retention, airway obstruction, infection and eventually progressive respiratory failure.[14] Therapies that improve MCC and reduce airway obstruction are considered cornerstones of CF management.[14, 15, 54] Along with a variety of medications which target mucus viscosity (e.g. Dornase alfa, hypertonic saline), performance of ACTs is routinely recommended to people with CF in order to improve MCC, reduce mucus plugging, improve symptoms and slow the progression of bronchiectasis.[3, 28, 55, 56]

1.3.2 Physiological mechanisms to improve mucociliary clearance

When attempting to improve MCC, there are two key physiological principles which need to be considered. Firstly, areas distal to mucus obstruction need to be ventilated and secondly, the rate of expiratory airflow must be increased sufficiently to promote cephalad secretion movement.[29, 57] The development of traditional ACTs has historically

been based on the use of either one or both of these principles in an attempt to reduce airway obstruction.

1.3.2.1 Improving ventilation

Obstruction of airways with mucus is a key finding in CF and contributes to the gas trapping observed early in the disease process.[22, 23] Removal of the mucus, for example by coughing or the use of techniques such as postural drainage (PD) or percussion and vibrations, will therefore improve ventilation and reduce the degree of gas trapping.[23] It is also proposed that ventilation of collapsed or under-recruited functional lung units may be increased by two physiological processes: interdependence and collateral ventilation. Interdependence is the process whereby a collapsed alveoli or segment may be recruited by forces exerted upon it when the volume of the adjacent alveoli or segment is increased.[29, 58] The process of interdependence, at least at a sublobar level, has been confirmed in animal (dog and pig) studies.[58, 59] End-inspiratory pauses between 2-5 seconds may further improve the ventilation of obstructed airways.[60] Collateral ventilation is the ventilation of lung units distal to an obstruction through the use of anatomical airways or channels not used during normal ventilation. The three recognised types of collateral channels are the Pores of Kohn, Canals of Lambert and Channels of Martin.[61, 62] While these channels are not routinely used in the healthy lung owing to a higher degree of resistance to air flow, it is possible to increase the ventilation through these collateral channels by increasing the airway pressure, with animal models suggesting the pressure required to initiate collateral ventilation is in the range of 17-28cmH_2O.[61, 63] Low (mean expiratory pressure = 12-15cmH_2O) and high (mean expiratory pressure = 20-35cmH_2O) pressure positive expiratory pressure (PEP) therapy was found, in a small study (n = 5) of adolescents and young adults with CF, to improve gas mixing and increase slow vital capacity, suggesting that these pressures may be sufficient in people with CF to recruit obstructed airways.[64] Whilst it is commonly accepted that PEP works by enhancing collateral ventilation, the exact mechanism by which obstructed airways may be recruited in people with CF when using PEP has not been definitively proven (i.e.

do these changes occur due to collateral ventilation, interdependence or a combination of both). Small airway resistance is increased in CF as a result of airway remodelling, even from a young age, and it is unknown if the collateral ventilation channels also experience a similar increase in resistance.[23] Therefore, the actual ability to utilise collateral ventilation in CF is unclear. Regardless of which physiological process is responsible, increasing the lung volume as part of an ACT, including PEP, may increase air flow through obstructed airways. Uncertainty also remains around the minimum treatment parameters required (e.g. change in inspiratory volume, expiratory duration per breath, expiratory pressure, overall treatment duration) to result in a clinically meaningful improvement in ventilation in the CF lung, particularly when considering the increased small airways resistance seen in this disease.[65] Whilst ventilation to obstructed regions in the CF lung may be increased through utilisation of interdependence and/or collateral ventilation, it needs to be recognised that these changes alone may not improve MCC.[66] It is likely that alternations in lung volumes need to be combined with an increase in expiratory flow rate in order to improve MCC in CF.

1.3.2.2 Expiratory flow

The second proposed principle to improve MCC is the manipulation of the expiratory flow rate in order to promote a cephalad movement of secretions. For changes in expiratory flow rate to improve MCC there must be a mechanism by which airflow acts upon the mucus. Two-phase gas-liquid flow (TPGLF) is the principle whereby a gas moving over a liquid imparts some of its energy to the liquid, resulting in the liquid moving in the same direction as the flow of gas.[67] Evidence from a laboratory study using simulated mucus suggests that for airflow to exert sufficient force to achieve secretion movement under the TPGLF principle, the airflow rate needs to be at least 30-60L/min.[68] This flow rate is higher than that typically achieved during relaxed expiration. Interestingly, in that study, mucus simulants with higher viscoelasticity (as is seen in CF) moved at lower air flow rates compared to the less viscous simulants.[68] There are currently no in vivo data on the minimum expiratory flows required in people with CF to cause cephalad secretion

movement and therefore the true clinical applicability of the in vitro data remains untested.

In addition to increasing the expiratory flow rate, to ensure a net movement of secretions occurs in a cephalad direction there should ideally be a bias in favour of the peak expiratory flow rate (PEFR) relative to the peak inspiratory flow rate (PIFR) of at least 10% (i.e. PEFR:PIFR ratio > 1.1).[68] Whilst in vitro data suggest both a minimum PEFR and PEFR:PIFR ratio are required to achieve secretion movement (as detailed later in Section 1.4.1.4), many commonly used ACTs do not meet either one or both of these criteria despite being shown to be of clinical benefit. It must be noted however, that forced expirations, known as huffing (discussed further in Section 1.3.3), do achieve both of these proposed targets and are now considered a routine component of most traditional ACT regimens.[29] Likewise, coughing also achieves the desired PEFR and PEFR:PIFR and is included as the final phase of most ACT regimens. Indeed, the question needs to be asked if huffing and coughing, based on their effects on airflow rate, are indeed the most important component of any ACT regimen.

1.3.3 Airway clearance technique options

There are a broad range of ACT options available to people with CF. Historically, the ACT most often recommended for people with CF consisted of PD, generally combined with percussion, vibrations and coughing.[4] It was recommended that this treatment be undertaken twice per day using several different PD positions during each treatment session, with each session lasting up to 30 minutes.[4] Whilst still used for infants in some CF centres, the requirement for a third party to perform the percussion and vibrations has led to the development over the last 30-40 years of a broad range of ACT options that are able to be performed independently (Table 1.1).[3, 28, 29, 69, 70] Some of these ACTs are based on the individual modifying their breathing pattern to manipulate their lung volumes and expiratory flow rates (i.e. non-device dependent) whilst other techniques

require the person to expire (+/- inspire) through a mechanical device (i.e. device dependent).

Table 1.1: Examples of ACTs available for people with CF.

	Examples
Non-device dependent	Active cycle of breathing technique
	Autogenic drainage
	Directed coughing
	Expiration with an open glottis in the lateral posture (L'Expiration Lente Totale Glotte Ouverte en decubitus Lateral - ELTGOL)
	Forced expiratory technique/huffing
	Percussion and vibrations
	Postural drainage/modified postural drainage
Device dependent	Positive expiratory pressure e.g. AstraPEP®, PariPEP®
	Oscillating positive expiratory pressure e.g. Flutter®, Acapella®, Aerobika®, Cornet®
	Intrapulmonary percussive ventilation
	High frequency chest wall oscillation

The use of either the forced expiratory technique (FET) or huffing is now accepted as a key component of the majority, if not all, of the ACT options listed in Table 1.1.[29] The traditional form of the FET consisted of forced expirations from varying lung volumes, interspersed with periods of diaphragmatic breathing, whilst huffing referred specifically to forced expirations alone.[71, 72] Whilst huffing is technically just one component of the FET as described above, these terms are often used interchangeably.[29, 69, 71]

The forced expirations in FET and huffing are based on the equal pressure point (EPP) theory. When an active expiration occurs, the point within the airway where the airway pressure equals the surrounding pleural pressure is referred to as the EPP.[73] Narrowing of the airway occurs just central (or downstream) to the EPP and it is at this point where turbulent airflow may result in an increase in MCC.[73] During the FET, the forced expirations occur initially at lower lung volumes so that the EPP is located more peripherally, before the lung volume at which the expirations occur increases in order to move the EPP more centrally. Whilst it is proposed from this theory that forced expirations from a mid to low lung volume will increase peripheral secretion clearance, several studies have failed to show that forced expirations from mid to low lung volumes result in increased radioaerosol clearance from the peripheral regions compared to resting breathing or coughing.[74, 75] Regardless, the use of the FET or huffing is believed to be an important component of any ACT routine as it helps to increase the rate of expiratory airflow, thereby promoting the movement of secretions from the central and intermediate regions more proximally so they can be expectorated, and may be associated with less effort than coughing.

1.3.4 Evidence supporting the use of airway clearance techniques

Evidence from short-term studies support the use of ACTs in the management of CF respiratory disease and is discussed below. A key consideration when interpreting this body of evidence is the outcome measure selected, some of which have well documented limitations. In this section, findings are discussed according to the outcome measures commonly used in studies investigating ACTs in CF.[76]

1.3.4.1 Expectorated sputum

A systematic literature review of ACTs versus no ACTs in CF found an increase in expectorated sputum weight with ACTs in four out of the five studies that included this outcome measure.[76] There was a notable variability in the sputum weights reported between the different studies, with the authors of the review not conducting a meta-

analysis due to insufficient data.[76] However, sputum weight as an outcome measure has substantial limitations as there may be contamination with saliva and/or secretions may be inadvertently swallowed by the participant, both of which may affect accuracy and reliability.[5, 76] These factors may explain, at least in part, the large variation in expectorated sputum weights reported in these trials.

1.3.4.2 Direct measures of mucociliary clearance

Measurement of MCC by radioaerosol clearance may provide a more accurate method for assessing ACTs when compared to sputum weight.[77] The systematic review comparing ACTs to no ACTs in CF reported that four of the five studies which included MCC measured via radioaerosol clearance as an outcome found that ACTs increased MCC compared to no ACT.[76] It is of interest that the one study which did not find a difference in MCC did not include coughing as part of the ACT regimen, whilst the four studies finding a benefit did so. This therefore raises the question about the role of coughing alone in increasing MCC. Another study comparing 30 minutes of rest to matched coughing and various ACTs found that whilst there was a trend toward greater radioaerosol clearance with matched coughing and the ACTs compared to rest, the only intervention to significantly improve radioaerosol clearance was PD with percussion and vibration.[78] This study did not mention if FET or huffing were used during any of the interventions. As all of the studies in the systematic review which found in favour of using ACTs to improve MCC included the use of huffing, FET or coughing as part of the ACT regimen, it is likely that these three components are vital in any regimen aimed at increasing MCC.

1.3.4.3 Pulmonary function tests

The impact of ACTs on PFTs is unclear. The four studies included in the systematic literature review of ACTs versus no ACTs found inconsistent effects on PFTs, with one study reporting an improvement in FEV_1, one noting a fall in FEV_1 30 minutes post-ACT and two finding no difference.[76] A small cross-over trial involving eight participants found

that cessation of PD combined with percussion and vibrations, deep breathing and coughing for a three-week period resulted in a significant reduction in forced vital capacity (FVC) (mean change [SD] = -4.4 [5.0]%, p <0.025), FEV_1 (mean change [SD] = -7.7 [6.5]%, p < 0.025) and FEF_{25-75} (forced expiratory flow at 25-75% of vital capacity) (mean change [SD] = -19.4 [12.6]%, p < 0.005).[79] Interestingly, it appeared that a single ACT session after the three-week withholding period used in this study resulted in the FVC and FEV_1 returning to a level similar to that seen at baseline.[79] The FEF_{25-75} however remained significantly lower for those who had not performed any ACT in the preceding three weeks when compared to the those who had, with the values returning to baseline after the resumption of ACT for a further three weeks.[79] This finding that ACTs may improve FEF_{25-75} may be important, as CF respiratory disease is recognised as starting in the small airways, as previously discussed, and therefore this reduction may be an early sign of mucus retention when ACTs are withheld. There remains a paucity of long term data on the impact of ACTs on PFTs when compared to no ACT, largely owing to ethical concerns around the withholding of ACTs over the long term.[55]

1.3.5 Adherence with airway clearance techniques by people with cystic fibrosis

Adherence with ACTs is commonly reported as being lower than that seen with other CF therapies, with a wide range of adherence rates reported.[42, 43, 48, 80, 81] One of the earliest reports of ACT adherence found that 41% of participants reported performing an ACT every day or almost every day.[47] Using a similar classification of adherence (i.e. ACT performed most days), other studies have reported adherence rates varying between 38-84%.[46, 82-86] The percentage of people with CF who reported not performing any traditional ACT also varies widely, with estimates ranging between 10-21%.[48, 85, 87, 88] Making direct comparisons however between studies is challenging due to differences in adherence level definitions and recall periods.

There are few published data on adherence to ACTs in Australia. Unlike in the United Kingdom and Canada, the Australian CF Data Registry does not collect any information

about ACT utilisation.[2, 87] Previous research has shown that the types of ACTs used and the rates of adherence with ACTs varies between countries.[87] The largest study to date of adherence rates in Australia was a single-centred study conducted in 2007.[89] In this study, the most commonly reported ACT was exercise (used by 79% of respondents when they were well), which historically is considered an adjunct to, but not an alternative to traditional ACTs.[55, 89] The most commonly utilised traditional ACT was PEP (used by 42% when well). An ACT was performed at least once a day by 67% of the participants, however the inclusion of exercise as a form of ACT may explain why the rate of adherence was higher than that seen in the majority of previous reports. As this was only a single-centred study and practice may vary between centres, the adherence to ACT recommendations by Australian adults with CF remains unknown. This topic was investigated in a national survey of ACT practices in adults with CF, reported in Chapter 4 of this thesis.

The factors underlying the low levels of adherence with ACT are multiple and complex. Reasons for non-adherence can be divided into several key themes: lack of time, lack of perceived benefit, resentment or general dislike of the treatment, undesirable or unpleasant adverse effects and simply forgetting to undertake the treatment.[48, 83-85, 88, 89] With the increasing number of treatments available to people with CF, the treatment regimen has become increasingly complex.[26] Airway clearance has been reported as one of the more burdensome components of the therapeutic regimen in CF.[40] The performance of ACTs is time-intensive, with a lack of time being one of the most commonly cited reasons (reported by 20-65% of participants) for non-adherence with ACTs.[48, 83-85, 88, 89] As life-expectancy has increased and people with CF move into adulthood with normal or only mild reduced PFTs, there is an ever increasing competition between the time demands associated with CF treatments and normal societal expectations, such as maintaining relationships and work/study commitments. As a lack of time is so commonly reported as a reason for non-adherence with the overall therapeutic regimen in CF, rationalisation and simplification of the treatment regimen

where possible may help to improve adherence. Given that some people with CF report considering exercise as an alternative to traditional ACTs, or a reason for not performing traditional ACTs (estimates range between 4-48%), further investigation of the suitability of this practice is required given the treatment-related time saving this may offer to people with CF.[47, 48, 83, 88-90]

1.4 Exercise as an alternative to traditional airway clearance techniques in cystic fibrosis

Regular and frequent performance of exercise is routinely recommended for people with CF due to the potential benefits summarised in the narrative review presented in Chapter 2 of this thesis. In addition to the respiratory and non-respiratory benefits of exercise, it has also been suggested that exercise may act as an alternative to traditional ACTs. In a survey conducted at one UK CF centre, which included 50 participants, 26% of participants indicated that they thought exercise could be used as an alternative to traditional ACTs.[91] Another study from a single Australian CF centre found that 79% of the 57 participants considered exercise as one of their ACTs.[89] Despite these studies reporting that people with CF may consider exercise as an alternative to traditional ACTs, there were, prior to the study reported in Chapter 4 of this thesis, no data on the nature (i.e. type, duration and intensity) of exercise people with CF considered as an alternative to traditional ACTs. Given that a notable proportion of people with CF are already using exercise as alternative to traditional ACTs, its efficacy when compared to traditional ACTs needs to be investigated.

For exercise to function as an alternative to traditional ACTs, there needs to be an underlying physiological rationale by which exercise will increase MCC and reduce airway obstruction. The mechanisms by which exercise may increase MCC and reduce obstruction, which will be discussed in more detail below, are: a direct effect on the epithelium, mechanical effects on the sputum, alterations in expiratory airflow and stimulation of cough.[5, 92, 93]

1.4.1 Physiological rationale for the use of exercise as an airway clearance technique in cystic fibrosis

1.4.1.1 Nasal transepithelial potential difference and sodium conductance

Exercise may directly affect the airway surface liquid by altering the regulation of ion transport across the epithelial luminal surface. As outlined previously, CF is characterised by both a reduction in Cl^- conductance and an upregulated rate of Na^+ resorption, with the combined result being a larger negative nasal transepithelial potential difference (TPD) when compared to individuals without CF.[94] Moderate to vigorous intensity cycling has been shown to result in the nasal TPD becoming less negative in individuals with CF.[93, 95, 96] The degree of change in nasal TPD was to the extent that, in two of the three studies, the nasal TPD in participants with CF at the completion of exercise was not significantly different to that of the control 'normal' participants.[93, 95]

This effect of exercise on nasal TPD is believed to be as a result of changes in Na^+ conductance.[93, 96] In a small study of 10 participants with CF, 20 minutes of submaximal cycling exercise (workload that resulted in a 1mM increase in blood lactate) resulted in a significant decrease in Na^+ resorption.[96] Neither submaximal nor maximal exercise on a bicycle altered Cl^- transport.[96] These findings are supported by another study which also found a reduction in Na^+ transport, but no effect on Cl^- transport, associated with moderate intensity cycling (85% of ventilatory threshold) in people with CF.[93] These changes in Na^+ resorption are believed to result from inhibition of the epithelial sodium channel by adenosine triphosphate mediated pathways.[93, 96] Within 20 minutes of resting, nasal TPD was found to return to baseline levels, indicating that any effect on Na^+ transport is likely to be of relatively short duration.[93, 96] Changes in Na^+ resorption associated with exercise may potentially affect the retention of water within the airway, thereby improving the airway surface liquid hydration.[96]

1.4.1.2 Sputum solids content

By reducing Na^+ resorption, it is hypothesised that there will be an increase in the water content of the airway surface liquid. Given the difficulty of measuring airway surface liquid in vivo, the water content, or inversely the sputum solids content, reported as a percentage of expectorated sputum weight, is commonly used as a surrogate measure.[92, 97, 98] Whilst exercise may decrease sputum solids content by increasing water content as a consequence of inhibiting Na^+ resorption, theoretically the additional airflow associated with exercise may conversely result in a drying of the secretions, countering any potential gains in water content. Indeed, the potential airway drying effect from airflow during exercise is believed to be the cause of exercise-induced asthma.[99]

Several studies have investigated the impact of exercise on sputum solids content in CF with mixed results. Cycling for 20 minutes at 75% peak heart rate resulted in a significant increase in sputum solid content compared to the pre-exercise level (median [IQR]: pre-exercise = 5.3 [3.9-7.4]%, post-exercise = 6.2 [4.2-9.7]%, 45 min post exercise = 6.5 [4.4-8.1]; p = 0.038).[98] This is the opposite of what was expected based on the previous studies indicating a reduced Na^+ resorption (i.e. it was expected that sputum solids content would decrease, not increase). Another study, comparing treadmill and cycling exercise (20 min at 60% VO_2peak) to resting, found no significant difference in the change in sputum solid content between any of the interventions.[92] In a subsequent study by the same research group, no significant difference was found in the change in sputum solids content when comparing treadmill exercise to rest or use of the Flutter® device.[97] However, the sub-group of participants who spontaneously expectorated a sputum specimen following exercise did have a significant reduction in their pre- to post-sputum solids content with treadmill exercise compared to resting (mean difference 1.2%, 95%CI 0.4 to 1.9%), with a trend to a lower sputum solids content with treadmill exercise compared to the Flutter®.[97] The authors of this study noted that the magnitude of change in percent sputum solids seen was similar to that seen with inhaled Mannitol, an inhaled osmotic agent used to increase MCC.[97] Further research is required to

confirm the effect of exercise on the water content of the airway surface liquid in CF and the relationship this may have with clinical outcomes. Until these studies are completed, the initial findings that treadmill exercise may reduce percent sputum solids, at least in those who spontaneously expectorate sputum, provides some rationale for investigating exercise as an alternative to traditional ACTs.

1.4.1.3 Sputum rheology

Aside from affecting the water content of the airway surface liquid, exercise may have a direct effect on the rheological properties of the sputum in people with CF. Sputum rheology is commonly described in terms of viscosity, elasticity and/or spinnability.[92, 97, 98, 100] Mechanical impedance, as reported in several studies investigating the effects of ACT and/or exercise on sputum properties, is the vector sum of viscosity and elasticity.[100] A high mechanical impedance is likely to adversely affect MCC (measured at slow speeds e.g. 1rad/s) and cough clearance (measured at higher speeds e.g. 100rad/s) based on evidence from laboratory studies.[100-102] Exercising on a treadmill for 20 minutes, at a work rate equivalent to 60% VO_2peak, resulted in a significant reduction in sputum mechanical impedance at both 1 rad/s (mean decrease [95%CI] = 6.3 [0.9 to 11.7]Pa; p = 0.025) and 100 rad/s (mean decrease [95%CI] = 53.5 [11.6 to 95.4]Pa; p = 0.016) when comparing the change between pre- to post-recovery levels relative to those seen with resting.[92] The treadmill exercise also resulted in a change in sputum mechanical impedance at 1 rad/s (mean difference [95%CI] = 5.3 [0.8 to 9.8]Pa; p = 0.026) between pre- and immediately post-exercise values when compared to a control intervention. This change in mechanical impedance was not seen when comparing cycling to rest and the differences between cycling and treadmill exercise did not reach statistical significance.[92] These results are supported by another study which found that cycling did not result in a significant difference in sputum viscoelasticity measured at 1 rad/s and 10 rad/s immediately post-exercise or 45 minutes post-exercise.[98] More recent research has shown that treadmill exercise resulted in significant reductions in sputum mechanical impedance similar to that achieved with the Flutter®.[97] The exact reasons why treadmill

exercise, but not cycling, may cause a reduction in sputum mechanical impedance have not been investigated. However, it has been postulated that the trunk oscillations associated with walking/running or similar activities, but not seen to the same extent with cycling, may exert a direct mechanical effect on the sputum, breaking chemical bonds and thereby causing a reduction in mechanical impedance.[92] Whilst the exact reason has not been definitively established, the cumulative results from the studies discussed above suggest that exercise which involves chest oscillations (e.g. walking/running) is likely to improve the mechanical impedance of sputum which in turn may improve MCC.

1.4.1.4 Expiratory flow

The physiological demands that result from exercise lead to changes in the ventilatory pattern. As mentioned previously, it is proposed that the PEFR must exceed 30 to 60L/min in order to result in the cephalad movement of secretions secondary to the TPGLF mechanism. It has also been proposed that generation of an expiratory flow bias (i.e. PEFR:PIFR >1.1) will result in a cephalad movement of respiratory secretions.[68] Table 1.2 summarises the current evidence on the effect of exercise and traditional ACTs on expiratory flow. Both cycling and treadmill exercise at a moderate intensity are likely to result in an increase in PEFR above the minimum proposed threshold for secretion movement.[92, 97] Furthermore, the PEFR generated during exercise may exceed that seen with commonly used traditional ACTs (e.g. PEP and Flutter®). The effects on PEFR:PIFR are more mixed, with neither exercise or some traditional ACTs (e.g. PEP) consistently reported as achieving a flow bias of >1.1. Nevertheless, based on the available data, it would seem that exercise, performed to at least a moderate intensity, is likely to result in sufficient expiratory airflow to promote an increase in MCC.

Table 1.2: Effects of exercise and traditional ACTs in CF on expiratory flow.

Intervention	Study	n	PEFR (L/min)	PEFR:PIFR
Cycling	Dwyer et. al.[92]	14	109.2 ± 28.2	0.93 ± 0.08
Treadmill	Dwyer et. al.[92]	14	107.4 ± 31.2	0.92 ± 0.11
	Dwyer et. al.[97]	24	100.8 ± 30.6	0.90 ± 0.10
Huff	McCarren and Alison[103]	17	302 ± 138	2.80
	McIlwaine et. al.[104]	14	249 ± 160	-
AD	McIlwaine et. al.[104]	14	47.7 ± 17 to 115 ± 31.7	-
PEP	McCarren and Alison[103]	18	26.4 ± 9	0.47
Flutter®	Dwyer et. al.[97]	24	91.8 ± 15	1.13 ± 0.37
	McCarren and Alison[103]	17	67.8 ± 18	1.15
Aerobika®	O'Sullivan et. al.[105]		105.2 ± 40.8	-

Data are mean (SD); AD: autogenic drainage; PEFR: peak expiratory flow rate; PEP: positive expiratory pressure; PIFR: peak inspiratory flow rate.

1.4.1.5 Stimulation of cough

It has been suggested that exercise may stimulate cough, which in turn may help to improve MCC. The evidence to support an increased rate of coughing with exercise however is inconclusive. Two studies comparing 20 minutes of rest to treadmill exercise at moderate intensity (60% VO_2peak) found no significant difference between rest and treadmill for the total number of coughs either during exercise or the subsequent recovery period.[92, 106] Another study found a small but statistically significant increase in the number of spontaneous coughs during treadmill exercise compared to rest (median [IQR]: treadmill = 4 [1 to 9], rest = 2 [0 to 5]; $p < 0.01$) but the difference in the number of coughs was probably below a clinically meaningful threshold.[97] A separate study found that cycling exercise did not increase the number of spontaneous coughs compared to rest (median [IQR]: cycling = 3 [0 to 19], rest = 5 [1 to 7]; $p > 0.3$).[92] Based on these

studies, it appears that exercise alone may not increase the number of coughs and therefore if exercise is to be used as a form of secretion clearance, people with CF may need to be encouraged to specifically cough in order to clear secretions.

1.4.2 The effects of exercise on secretion clearance compared to rest

The evidence presented in the previous sections suggests that exercise is likely to improve MCC by increasing expiratory airflow and by reducing the viscosity and mechanical impedance of sputum. However, to be confident that exercise can be used as an alternative to traditional ACTs, direct comparison in clinical trials is required. This will be discussed in the following sections.

Chapter 3 of this thesis is a systematic review of the literature comparing exercise to rest in people with CF with regards to PFTs, HRQOL and measures of sputum clearance. Randomised and quasi-randomised trials were eligible for inclusion, as were cross-over trials. This review identified five trials that compared exercise to rest, all of which were of short duration and cross-over in design. From this systematic review, it can be concluded that exercise is likely to be more effective than rest with regards to improving ease of expectoration, weight of expectorated sputum and radioaerosol clearance without acutely changing FVC or FEV_1.[92, 97, 106-108] The full details and results of this review can be found in Chapter 3 of this thesis.

1.4.3 The effects of exercise on secretion clearance compared to traditional airway clearance techniques

The initial reports describing the use of exercise as an alternative to traditional ACTs date back to the early 1980s. One of the first reports detailed an uncontrolled trial recruiting 12 children with CF who were admitted to a rehabilitation hospital for 17 days, during which the inhalation and traditional ACT regimens were stopped.[109] The participants instead undertook an intensive exercise and physical activity program which included swimming, jogging, hiking and a variety of other physical activities. Over the 17

days, PFTs from 10 of the 12 participants (one became unwell and needed to resume the usual ACT routine and the other was too young to perform spirometry) revealed a significant increase in percent predicted FVC (pre: 88.0 [14.7]%, post: 93.8 [13.7]%; $p < 0.05$), FEV_1 (pre: 70.6 [21.7]%, post: 79.2 [22.7]%; $p < 0.01$) and FEF_{25-75} (pre: 41.6 [31.5]%, post: 52.9 [33.5]%; $p < 0.05$). Eight weeks after finishing the intervention phase and resuming their normal inhalation therapy, traditional ACT and exercise routines, the PFT values had returned to baseline. A subsequent longer term trial over 30 months recruited seven participants with CF and also suggested that using exercise alone as a form of ACT may be effective in maintaining various PFT measures.[110] Following recruitment, participants commenced a daily exercise routine whilst continuing their traditional ACT. After 12 months, the traditional ACT was stopped and for the remaining 18 months, the participants continued the exercise program alone. At the end of the 30 month study period, there was no significant change in FEV_1 but there was a significant reduction in gas trapping when compared to baseline.[110] Whilst both of these studies have important limitations, including but not limited to the lack of a control group, their positive findings contribute to the equipoise for the further investigation of exercise as an alternative to traditional ACTs.

The systematic literature review presented in Chapter 3 of this thesis reviews the scientific literature for the use of exercise as an alternative to traditional ACTs. Nine studies were identified that compared exercise to at least one traditional ACT. Conclusions regarding the short-term clinical suitability of using exercise as an alternative to traditional ACTs were limited by conflicting results, with the full results of this review presented in Chapter 3 of this thesis.

1.4.4 Summary of exercise as an airway clearance technique

The current published evidence provides a physiological rationale for the use of exercise as a method to improve MCC in CF. As presented in the systematic literature review in Chapter 3 of this thesis, evidence directly comparing exercise to traditional ACTs is

limited by small, short duration studies with considerable heterogeneity in design and conflicting results. Nonetheless, there is sufficient evidence to provide equipoise for the further investigation of exercise as an alternative to traditional ACTs in CF. Well-designed, sufficiently powered, medium to long term clinical trials are required.

Clarifying whether or not exercise can be used as an alternative to traditional ACTs has been identified as one of the top 10 research priorities by clinicians and people with CF.[111] A recent survey of healthcare professionals revealed considerable endorsement for such a trial, with 72% indicating they would support a trial of this nature.[90] Given the relatively small size of the CF population, these studies will need to be multi-centred. Prior to undertaking these studies, identifying a feasible study design, including selection of the most appropriate ACT and exercise interventions, as well as relevant outcome measures, is crucial. These considerations will be discussed in the following section.

1.5 Study design considerations

1.5.1 Protocol

The design of clinical trials investigating exercise as an alternative to traditional ACTs comes with some unique challenges. Firstly, it is likely that potential participants would already be using one or both of these treatments. Given the wide variety of traditional ACT and exercise options available in clinical practice, participants recruited to the study will likely enter the study with a very heterogeneous treatment regimen. Not only may the type of traditional ACT or exercise differ, but the frequency with which they are performed may also be highly variable. These differences in baseline regimens may lead to concerns regarding a carry-over effect in terms of PFTs and symptoms if participants are enrolled directly into the intervention phase of the study. However, an inactive run-in period to counter this wide variation in routine practice, where participants did neither exercise nor ACT, would be ethically inappropriate. Therefore, an active run-in period is required. This period could be used to establish a standardised traditional ACT and

exercise routine across all participants, as well as reducing the confounding risk of any carry-over effect from differing baseline practices. The active run-in period would also allow the identification of participants who do not adhere to the protocol and may therefore be withdrawn from the study prior to randomisation. Chapter 6 of this thesis describes a feasibility study adopting such a protocol.

Any study investigating the use of exercise as an alternative to traditional ACTs will be unable to have a traditional ACT-alone (i.e. no exercise) comparator group. As discussed in Chapter 2 of this thesis, exercise is likely to have a multitude of benefits for people with CF beyond solely improving MCC including improved physical fitness, improved cardiometabolic health and possibly improved survival. It would therefore be considered unethical to withhold exercise from any traditional ACT-alone group. Therefore, such a study would need to compare an exercise-alone intervention versus traditional ACT and exercise. The feasibility study reported in Chapter 6 of this thesis used this approach.

1.5.2 Selection of trial interventions

When designing a study to investigate exercise as an alternative to traditional ACTs, careful consideration needs to be given to which exercise and traditional ACT interventions will be used during the study. As discussed previously, there are a wide variety of traditional ACT and exercise options available for people with CF to use. The current evidence does not generally support one type of ACT over another.[112-116] The one notable exception to this is the recommendation to use PEP instead of high frequency chest wall oscillation (HFCWO).[115] This recommendation is largely based on the results from a single, 12 month study, which found the PEP group had fewer respiratory exacerbations than the HFCWO group, despite there being no difference in PFTs.[117] The narrative literature review presented in Chapter 2 of this thesis also highlighted that there is no one type of exercise which has been found to be most beneficial. The decision regarding which traditional ACT and types of exercise a person chooses to use is commonly based on individual preference and the experience of the clinician prescribing

the intervention. As summarised in Section 1.3.5, adherence remains a challenge with traditional ACTs in CF. Therefore, when considering which traditional ACT and exercise to include in a study investigating exercise as an alternative to traditional ACTs, those techniques that people with CF are satisfied with and already adhering to in routine clinical practice are possibly going to optimise adherence during the study.[118] Chapter 4 of this thesis reports a study investigating the current practices of adults with CF in Australia in relation to exercise and traditional ACTs, providing a valuable insight into which exercise and traditional ACT modalities are currently being used by people with CF. These data may guide the choice of which exercise and traditional ACT modalities to use in future traditional ACT and exercise studies, including any study investigating exercise as an alternative to traditional ACTs.

1.5.3 Outcome measures for clinical trials in cystic fibrosis

When designing studies to investigate the effectiveness of using exercise as an alternative to traditional ACTs, the selection of appropriate outcomes measures is vitally important. It is therefore worthwhile reviewing the current outcomes measures available for use in CF clinical studies and considering their usefulness when evaluating exercise as an alternative to traditional ACTs.

1.5.3.1 Mortality

When CF was first described in the 1930s the average life expectancy was approximately six months.[9] The initial focus of clinical care and research in CF was on improving the mortality rate. As the therapeutic options for CF have expanded, the life expectancy of people with CF has improved markedly. Over 50% of people with CF in Australia are adults, with the median predicted survival increasing from 29 years in 1986-1990 to 46 years for those born between 2013-2017.[1, 2] Improved survival has meant that the use of mortality as a primary outcome measure for CF clinical studies is no longer

feasible as studies would need to be of very long duration or require a prohibitively large sample.[119, 120]

1.5.3.2 Pulmonary function tests

One of the most commonly utilised outcome measure in CF studies over the last 20-30 years has been FEV_1.[119, 120] The FEV_1 is determined by spirometry which is a relatively quick and easy test to perform, with children above the age of six years generally able to perform the technique reliably, and the equipment is commonly available.[119] Changes in FEV_1 can either be analysed according to the absolute values or by conversion to a percentage of predicted values or the lower limit of normal, based on gender, age and height.[120] One reason FEV_1 has become accepted as the primary outcome measure of choice is due to the fact that a low percent predicted FEV_1 is a strong predictor of poor survival.[121, 122] While other values determined by spirometry, such as FVC and FEF_{25-75}, have been suggested as possible outcomes of interest, they are not commonly utilised as a primary outcome measure due to a large degree of within subject variability necessitating larger study sample sizes.[65, 119]

At the present time, FEV_1 remains the most commonly used primary outcome in CF studies. However, as the rate of decline in FEV_1 has slowed with improvements in therapies, the usefulness of this measure in CF clinical studies has been questioned.[65, 118-120] With the advent of effective disease modulators, as discussed in Section 1.1.4, it is likely the rate of decline in FEV_1 will be even further reduced as these therapies become established in routine clinical care. Therefore, the feasibility of recruiting a sufficient number of participants to a non-inferiority study to achieve statistical power for a change in FEV_1 is now even more questionable. Alternative outcome measures to FEV_1 may be required in future CF clinical trials.

Interest in newer PFTs which may be more sensitive than FEV_1 in CF is increasing. The lung clearance index (LCI), which is measured by the multiple breath washout test, was

originally developed in the 1960s and assesses the degree of ventilation inhomogeneity.[119, 123] Renewed interest over the last 10-15 years has led to the finding that LCI may be more sensitive than FEV_1 at detecting early CF-related respiratory disease.[124, 125] Unlike spirometry, LCI is independent of patient effort and can be performed by young children. However, performing LCI requires more equipment than spirometry and is therefore generally only performed in PFT laboratories. Due to the costs associated with the equipment, it has only recently started to be incorporated into paediatric clinical practice and has yet to be widely adopted in adult CF centres. While the use of LCI as a primary outcome measure in CF studies is emerging, the evidence has not yet reached a point where it can be considered an alternative to FEV_1 as the primary outcome of choice in studies recruiting adults with CF.[119]

1.5.3.3 Respiratory exacerbations

Respiratory exacerbations are a hallmark feature of CF and are associated with a worsening of PFTs and reduced HRQOL.[126-129] Reducing the rate of respiratory exacerbations is therefore potentially a valuable target when developing new therapies in CF. Whilst numerous studies have reported respiratory exacerbation rates as an outcome, there is currently no consensus on what constitutes a respiratory exacerbation and as such, a variety of definitions have been used.[120, 130, 131] A wide range of a combination of features, such as a change in symptoms, decrease in FEV_1 (absolute or relative) and/or physician decision to treat with additional antibiotics has been used to define the occurrence of a respiratory exacerbation.[132] One of the most commonly used respiratory exacerbation definitions is that developed for a trial of Dornase alfa, where a respiratory exacerbation was defined as treatment with parenteral antibiotics for a change in at least four out of 12 signs or symptoms (i.e. change in sputum; new or increase haemoptysis; increased cough; increased dyspnoea; malaise, fatigue or lethargy; temperature > 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in FEV_1 by 10 percent or more from a previously recorded value; or radiographic changes indicative of

respiratory infection).[133] More recently, several large trials have expanded this definition to include treatment with oral or inhaled antibiotics in addition to parenteral antibiotics.[134] Given the importance of respiratory exacerbations to people with CF and the healthcare system, there is clear value in studies collecting as much data regarding respiratory exacerbation occurrence and management as possible. Given the lack of agreement on a respiratory exacerbation definition, there may be value in specifying a priori several exacerbation outcome definitions (e.g. any use of additional antibiotics [oral, inhaled or parenteral] versus use of oral, inhaled or parenteral antibiotics due to a change in at least four of 12 pre-specified signs or symptoms). Even with utilising a broad definition of a respiratory exacerbation, the feasibility of using respiratory exacerbation rate as a primary outcome in future CF clinical trials needs to be questioned as a result of the significant reduction in respiratory exacerbations seen with effective disease modulators.[37, 38]

1.5.3.4 Expectorated sputum and mucociliary clearance

The volume or weight of expectorated sputum has been commonly used as an outcome for ACT studies.[76, 80, 135] The weight of sputum expectorated is typically calculated by one of two methods: either by weighing the wet sputum or by drying the sputum and then weighing it.[135] However, sputum weight may be unreliable as participants may swallow some of the secretions that have been cleared and/or there may be contamination with saliva.[5, 80, 135, 136] Another factor that needs to be considered is the duration of sputum collection, as there may be a delay between the performance of the ACT and the sputum being expectorated.

The use of radioaerosol clearance has become accepted as a more accurate and reliable measure of MCC compared to sputum weight.[77] Participants inhale a radioactive aerosol tracer, with the amount of radioactivity then measured by either a gamma camera or scintillation counters.[77, 137] Measurements over time are taken, with changes in radioaerosol activity expressed as either the percentage retained or percentage

decreased. The use of radioaerosol tracer clearance has become more widely accepted and used as an outcome in ACT studies.[76] However, this technique requires considerably more equipment and involves radiation exposure to the participants. Whilst sputum weight and radioaerosol clearance may have value when comparing two interventions over a short time period, the usefulness of these measures in longer duration studies is unclear.

1.5.3.5 Exercise testing

Assessment of exercise capacity is a valuable outcome measure in CF clinical studies. The current gold standard for assessing exercise capacity is full cardiopulmonary exercise testing (CPET), most commonly performed on a cycle ergometer, with gas exchange measurement.[138] This allows for determination of parameters including VO_2peak, peak work (Wpeak), maximum heart rate and anaerobic threshold.[138] Whilst recommended as the gold standard, CPET is still not widely available or utilised in CF clinics because of its requirement for specialised equipment and trained staff.[138] Other exercise tests, including field tests such as the six-minute walk test, modified shuttle walk test and the incremental shuttle test are available, but their usefulness in assessing outcomes in studies and clinical care in CF is debated.[139] Whilst VO_2peak and Wpeak have been linked to survival in CF, the responsiveness of CPET measures to interventions evaluated over the short to medium term is less clear.[52] Therefore, whilst exercise testing, particularly CPET, has potential to be used as a primary outcome, and may represent as an alternative to FEV_1 in the future, at the present time it is generally reserved as a secondary outcome measure.

1.5.3.6 Patient-reported outcomes

A patient-reported outcome (PRO) has been defined as "… a measurement based on a report that comes directly from the patient (i.e. study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response

by a clinician or anyone else." (US FDA, p.32).[140] The use of PROs allows for the assessment of the impact of interventions beyond that which is gleaned by physiological measurements alone. Single symptoms through to multi-domain HRQOL may be measured using PROs.[141] To be considered as an outcome measure in clinical studies, any PRO must be valid, reliable and responsive to change.[141]

The most commonly used PRO in CF is the Cystic Fibrosis Questionnaire (Revised) (CFQ-R), a disease-specific HRQOL measure. The CFQ-R has several different versions: children (6-11 years) and their parents, adolescents (12-13 years) and adults (14 years and older).[142, 143] The adult version of the CFQ-R comprises 50 questions divided into 12 domains. Each domain is scored on a 0-100 scale. The respiratory domain of the CFQ-R, comprising six questions, is the most widely reported domain of the CFQ-R and has been used as an outcome measure in clinical trials of both inhaled and oral medications.[144, 145] The test-retest reliability and minimal important difference, during both well and unwell periods, for the respiratory domain has been established.[146, 147]

Cough is the most frequently reported and also the most bothersome symptom reported by people with CF.[148, 149] Changes in cough (e.g. increased frequency) often precipitate a medical review to assess for a potential respiratory exacerbation.[148] To date there has been no specific validation of a PRO questionnaire examining cough-related quality of life in CF. The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that was developed for use in people with chronic cough. It has been validated for use in non-CF bronchiectasis and used in an airway clearance trial evaluating the Acapella® device in non-CF bronchiectasis. The LCQ has not been validated in the CF population. Despite the lack of confirmation of the psychometric properties of the LCQ in CF, it has been used in a small study investigating the response to Nissen fundoplication in six people with CF.[150] Given that cough is one of the dominant symptoms of CF and changes in cough may be a useful outcome in traditional ACT and exercise trials, determination of

the psychometric properties of the LCQ as a cough-based PRO in CF is warranted. This has been examined in the study reported in Chapter 5 of this thesis.

1.5.3.7 Summary of outcome measures in cystic fibrosis studies

There are a broad range of outcome measures available for use in CF studies. Whilst LCI and CPET may prove to be highly useful outcome measures in the future, further work is required to confirm their utility in CF clinical studies. At the present time, FEV_1 remains the primary outcome of choice for CF clinical studies, with assessment of respiratory exacerbations and PROs also highly recommended.[119, 120]

1.5.4 Measuring adherence to exercise and traditional airway clearance techniques

Measuring adherence with interventions is an important aspect of both clinical studies and day-to-day clinical practice. Self-recall by the participant of adherence over a specified preceding time period (e.g. 1 day, 2 weeks, 6 months), by either interview, questionnaire or diary, is the easiest and most commonly used method to measure treatment adherence.[151] These methods however are potentially susceptible to recall bias.[81, 152] Alternatively, daily phone diaries where participants are called, potentially without advanced warning, and asked for a detailed recall of the preceding 24 hours may be slightly more accurate than other self-reported methods.[153] Adherence with medication use has been measured using the degree of prescription collection, also known as the medication possession ratio, and may be more accurate than self-reported methods.[45, 81, 153] Newer methods, such as the Medication Event Monitoring System (MEMS™), rely on electronic sensors connected to data loggers located within the caps of medication bottles to record adherence.[81, 153] However, even these methods may not be accurate as filling the prescription or removing the medication for use does not necessarily mean that it was actually taken.

It is generally accepted that self-reports, either via verbal interviews or questionnaires, are the least reliable method of adherence assessment and may overestimate the actual level of adherence.[151-154] A small study of people with CF taking Ivacaftor found that the average adherence over 118 days was 61% when measured by electronic means, 84% as determined by pharmacy refill data and 100% based on self-report.[45] There was no correlation between the electronic measurement adherence and pharmacy refill history or self-report. Similarly, over-estimation of self-reported adherence with the Vest® ACT system when compared to electronic assessment methods has been reported.[155]

Exercise adherence measurement has historically relied upon participant self-report via either verbal, questionnaire or diary-based methods. Measuring adherence with exercise has evolved over the last 15-20 years, with objective measurement of physical activity and exercise, including the frequency, duration and intensity, using electronic accelerometer-based methods now possible.[156] There are research-based (e.g. ActiGraph®, SenseWear Pro®) and commercially available devices used by the general population (e.g. Fitbit®, Garmin® activity trackers) that can be used to measure adherence with exercise and physical activity. Whilst the use of accelerometers to record physical activity has expanded substantially, it must be recognised that data derived from accelerometers are not necessarily conceptually equivalent to data gleaned from questionnaires and therefore direct comparisons between the two methods is challenging.[156] For example, the ability to differentiate between types of activities and also patterns of differing intensities is likely to be different between questionnaires and accelerometers. It also needs to be noted that the various devices record physical activity differently based on their own unique algorithms used to define activity and therefore the validity of devices in each specific cohort may need to be considered.[157-159] It is likely that a combination of accelerometer and self-reported physical activity and exercise levels may represent the most appropriate method for assessing physical activity and exercise adherence in clinical trials.

Evaluation of adherence to traditional ACTs has historically relied upon self-report. Any assessment of adherence with traditional ACTs needs to consider two important components: 1) whether there has been an attempt to perform the traditional ACT and 2) the within-session quality of that attempt. It is important to assess both of these components to ensure that performance of a traditional ACT occurs using the recommended technique, and thus the treatment has been delivered as intended.

There have been several preliminary attempts to develop an electronic recording device for objectively measuring adherence with positive pressure ACTs. These electronic devices measure and record the rate of airflow and/or pressure generated when a person uses a positive pressure ACT device. These data can then be used to determine attempts to perform a positive pressure ACT as well as the quality of those attempts. A small feasibility study, where a flow-based electronic recording device was connected to an Acapella®, found that participants over-estimated adherence with self-reporting compared to data from the electronic device and that only 67% of expirations were considered satisfactory, based on the participant's ability to achieve the target expiratory duration and flowrate.[160] Several other exploratory studies have used computer games, controlled by either a pressure or flow sensor connected to an ACT device and a computer, to record within session data and to guide the performance of the ACT.[161-164] A flow-based device, aimed at improving performance of forced expiratory techniques, found that whilst participants managed the technical requirements of using the device, there was no significant difference in the total number of sessions or expiratory manoeuvres performed between the gaming and control periods.[161, 162] Another study used changes in pressure associated with use of a PEP device, measured via a pressure sensor connected by USB cable to a computer, to control actions in a video game.[163, 164] Due to the design of the device and sensor chosen, the first breath was used as a calibration breath, meaning the game control and therefore technique feedback, was dependent on the first breath being correct, which may adversely affect the utility of this device.[163, 164] Whilst these initial attempts to develop an electronic method of measuring

adherence with ACTs are noteworthy, further development of an electronic device to measure ACT adherence is required to improve device functionality and patient useability.

The initial electronic devices described above have generally relied upon the use of a sensor connected to a computer.[161-164] This adversely affects the portability of the device and increases its complexity of use.[50] Whilst these preliminary attempts have shown potential, at the present time there is no validated electronic device for measuring adherence with traditional ACTs. There is a clear need, in both routine clinical practice and for research purposes, for an electronic device to be developed that can objectively record both session attempts and within session quality.[165] Any such device should be portable, easy to use and compatible with the broad range of ACT devices currently available for use by people with CF. The development and testing of such a device are reported in Chapter 7 of this thesis.

1.6 Summary

Over the last 20-30 years there have been enormous changes in CF treatments and outcomes. There are now more adults living with CF than ever before and many of these may have normal or only mildly impaired PFTs. Over the same time period, the treatment burden has substantially increased and reports confirm that people with CF struggle to maintain adherence with the recommended optimal treatment regimen. Where possible, rationalisation of the components of the therapeutic regimen may help to improve overall adherence.

Whilst it is routinely recommended that people with CF perform traditional ACTs on a daily basis, many struggle to do so. Many also report that they consider exercise to be a suitable alternative to traditional ACTs. A physiological rationale exists to support the use of exercise as a form of airway clearance. Short-term studies also suggest that there is potentially a role for exercise as an alternative to traditional ACTs. Currently, there are no

medium or long term data to support or refute this practice. Prior to conducting a multi-centred, longer term trial, which is expensive and complex to run, it is necessary to establish the feasibility of the trial protocol, clarify the utility of potential outcome measures, and test methods to measure adherence with the trial interventions.

Thesis aims and outline

The overarching objective of this thesis was to investigate the use of exercise as an alternative to traditional ACTs for people with CF. Specifically, this thesis aimed to:

- Review the evidence for exercise as a therapeutic modality in CF.
- Systematically review the evidence for the use of exercise as an alternative to traditional ACTs.
- Identify the current beliefs and practices of adults with CF in Australia with respect to the use of exercise as an ACT.
- Confirm the psychometric properties of the LCQ in CF so that it can be used as an outcome measure in CF trials.
- Determine the feasibility of a clinical trial protocol investigating the use of exercise as an alternative to traditional ACTs in adults with mild CF-related respiratory disease.
- Develop a device to objectively measure adherence with positive pressure ACT devices.

Outline of thesis chapters and individual study aims

This chapter has provided an overview of CF, including the pathophysiology of respiratory disease resulting from CF gene mutations and the complex treatment regimen that people with CF are required to undertake. The physiological rationale and proposed mechanisms for improving MCC in CF have been discussed, including how these mechanisms may apply to traditional ACTs and exercise. Considerations for outcome measures in clinical trials in CF, as relevant to a study comparing exercise to traditional ACTs, has been summarised. The following chapters, as outlined below, will address in more detail the specific aims of this thesis.

Chapter 2 – Exercise as a therapeutic intervention in cystic fibrosis: a narrative literature review

Chapter 2 presents a narrative literature review of the role of exercise as a therapeutic intervention in CF.[166] It summarises the current evidence for the use of exercise in CF with regards to physical fitness, PFTs, use as an alternative or adjunct to traditional ACTs, HRQOL and mental health, CF-related diabetes and bone mineral density. The safety of exercise, exercise and physical activity assessment methods and the evidence for which type of exercise may be the most effective are reviewed. Finally, current and possible future research directions, with regards to exercise in CF, are discussed.

Chapter 3 – Exercise as an alternative to traditional airway clearance in cystic fibrosis: a systematic literature review

This chapter presents a systematic literature review and meta-analysis of randomised controlled clinical trials investigating the use of exercise as an alternative to traditional ACTs.[167] The systematic review aimed to:

1) Determine the effects of exercise compared to resting on PFTs, respiratory exacerbations, HRQOL, MCC, expectorated sputum weight / volume, ease of expectoration, participant preference and adverse events.
2) Determine the effects of exercise compared to traditional ACTs on PFTs, respiratory exacerbations, HRQOL, MCC, expectorated sputum weight / volume, ease of expectoration, participant preference and adverse events.

Chapter 4 – Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice

This chapter presents an Australian-wide cross-sectional survey of adults with CF.[168] This study aimed to identify what exercise and traditional ACTs adults with CF in Australia are using, the frequency with which they perform these techniques, their beliefs and practices about exercise as an alternative to traditional ACTs and their beliefs and practices about exercise as an adjunct to traditional ACTs.

Chapter 5 – Assessment of respiratory symptoms in cystic fibrosis

Chapter 5 presents a study that aimed to evaluate the psychometric properties of the LCQ in adults with CF to determine if it is suitable to be used as an outcome measures in future CF clinical trials.[169]

Chapter 6 – Airway clearance by exercising in mild cystic fibrosis (ACE-CF): a feasibility study

This Chapter presents a feasibility study of a protocol for a randomised controlled trial investigating exercise as an alternative to traditional ACTs in adults with mild CF-related respiratory disease.[170] This study aimed to determine the feasibility of the protocol and to provide preliminary clinical data on the use of exercise as an alternative to traditional ACTs.

Chapter 7 – Development of the positive expiratory pressure therapy recorder for assessing adherence (PEPtrac)

Chapter 7 presents a study describing the development and initial clinical testing of an electronic device to objectively measure adherence, both session attempts and within session quality, when positive pressure ACT devices are used by adults with CF for airway clearance.[171] This study aimed to validate an electronic device that can be used to objectively measure adherence in future clinical trials investigating the use of positive pressure ACT devices, which may include studies investigating exercise as an alternative to traditional ACTs where a positive pressure ACT device is used as part of the traditional ACT regimen.

Chapter 8 – Conclusions and future directions

A summary of the main findings of the thesis, including clinical implications and directions for future research, are discussed.

CHAPTER 2: EXERCISE AS A THERAPEUTIC INTERVENTION IN CYSTIC FIBROSIS: A NARRATIVE LITERATURE REVIEW

Declaration of authorship – Chapter 2

Student's Declaration

The nature and extent of contributions to Chapter 2 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Writing of manuscript and review	80%	
Kathy Stiller	Review of manuscript	10%	
Anne Holland	Review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 2 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

Title: Exercise as a therapeutic intervention for people with cystic fibrosis.

Authors:

Nathan Ward

Adult Cystic Fibrosis Service, Royal Adelaide Hospital and Physiotherapy, La Trobe University

8E055.08, Royal Adelaide Hospital, Port Rd, Adelaide, SA, Australia 5000

[redacted]

nathan.ward2@sa.gov.au

Kathy Stiller

Allied Health Research Coordinator, Central Adelaide Local Health Network

7F060, Royal Adelaide Hospital, Port Rd, Adelaide, SA Australia 5000

[redacted]

Anne E Holland

La Trobe University and Alfred Health

La Trobe University Clinical School, Alfred Health, Level 4, The Alfred Centre, 99 Commercial Rd,

Melbourne, Vic, Australia 3004

[redacted]

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Corresponding author: Nathan Ward; nathan.ward2@sa.gov.au; c/o Physiotherapy, 8E055.08, Royal Adelaide Hospital, Port Rd, Adelaide, SA, Australia 5000; [redacted]

Title: Exercise as a therapeutic intervention for people with cystic fibrosis.

Keywords: Cystic Fibrosis; Exercise Therapy; Physical Therapy Modalities

Abstract

Introduction: The complex multisystem nature of cystic fibrosis (CF) commonly results in reduced exercise tolerance, which is independently associated with poor clinical outcomes. Exercise is routinely recommended as part of the therapeutic regimen in CF to improve both respiratory and non-respiratory impairments.

Areas covered: This article summarises the most recent evidence regarding the use of exercise as a therapeutic intervention in CF and discusses some of the practical considerations for exercise prescription in this setting. Clinical trials in progress and future research priorities are outlined.

Expert opinion: On the balance of available evidence, exercise is likely to assist in improving physical fitness and health-related quality of life (HRQOL) and may be associated with a slower rate of decline in respiratory function in CF. Limitations to current studies include small sample sizes, study durations insufficient to achieve a training effect and difficulty distinguishing the effects of exercise training from that of other interventions implemented as part of a package of care. Larger, multi-centred trials are required to clarify the role of exercise in CF in improving physical fitness, respiratory function, HRQOL, as a substitute for traditional airway clearance techniques and in the management of common CF-related comorbidities.

1. Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic condition affecting the Caucasian population [1]. Whilst historically considered a disease of childhood, survival rates have improved to the point where there are now as many adults with CF as there are children in some countries [2, 3]. This improvement in life-expectancy is attributable to a large increase in the available treatment options over the last three decades. Pivotal new therapies have been introduced over this period adding to the existing therapeutic options, meaning people with CF are now often required to perform a complex, time-intensive treatment regimen as part of their daily care. In addition to oral and inhaled medications and performance of airway clearance techniques (ACTs), regular exercise is a routinely recommended component of CF treatment [4, 5, 6]. Exercise is recommended in order to improve physical fitness, respiratory function and quality of life in individuals with CF (Figure 1). An additional benefit of exercise in CF is also its potential to supplement or replace traditional ACTs, representing a potential means of reducing overall treatment burden. However, given the time and energy required to undertake regular exercise, in addition to the other components of care, there is value in evaluating the evidence underpinning this recommendation.

Recently revised physical activity guidelines recommend that children and adolescents in the general population should achieve 60 minutes of moderate to vigorous physical activity daily, whist adults should perform at least 150-300 minutes of moderate intensity or 75-150 minutes of vigorous aerobic physical activity per week [7]. Physical activity may be defined as "… any bodily movement produced by skeletal muscles that results in energy expenditure.", whilst the commonly accepted definition of exercise is "… physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective." [8,p.126 & 128]. Whilst dating approximately 30 years ago, these definitions remain a common basis for defining physical activity and exercise in clinical practice, research and health policy statements. Many contemporary guidelines refer to moderate and vigorous physical activity,

instead of exercise specifically, when describing activity levels related to improving or maintaining population health outcomes [7, 9]. For the purpose of this review, exercise is considered as including moderate or vigorous physical activity that is undertaken with the explicit purpose of improving one or more specific health outcomes.

The cardiovascular and musculoskeletal benefits of exercise in the general population are widely acknowledged [10]. Whilst exercise has been a recommended component of CF care since the 1980s, it was a pivotal study in 1992 that found a link between VO_2peak and survival in CF, independent of FEV_1, that precipitated the increasing interest in exercise as a therapeutic intervention [11]. This link between VO_2peak and survival was supported by a recent systematic review and meta-analysis, which found a significantly increased risk of mortality in people with CF who have a reduced VO_2peak [12]. Meta-analysis revealed that non-survivors had a reduction in VO_2peak compared to survivors in the two included studies (standardised mean difference of -0.606, 95%CI -0.993 to -0.219), whilst individuals with a VO_2peak < 45ml/kg/min or < 82%pred had a relative risk of mortality of 4.896 (95%CI 1.086 to 22.072) compared to those individuals with a VO_2peak above this threshold [12]. Supporting these findings, a recent multi-centred retrospective review of cardiopulmonary exercise testing (CPET) data from 2000-2007 confirmed that, even in the modern era of CF management, VO_2peak (hazard ratio 0.964, 95%CI 0.944 to 0.986) and peak work rate (hazards ratio 0.969, 95%CI 0.951 to 0.988) remain significant predictors of mortality or need for transplant over the subsequent 10 years in people with CF [13].

Exercise intolerance in CF has historically been attributed to reduced respiratory function and physical inactivity [14, 15, 16, 17]. However it is now clear that exercise intolerance in individuals with CF is multifactorial, with additional factors beyond reduced respiratory function and physical inactivity all potentially adversely affecting skeletal muscle function and exercise tolerance [18]. For example, nutritional status, as reflected by body mass index and fat free mass, may be associated

with reduced peak exercise capacity [15, 19]. It has also been demonstrated, relatively recently, that cystic fibrosis transmembrane conductance regulator (CFTR) is directly expressed in skeletal muscle, potentially adversely affecting muscle contractility and metabolism [20, 21]. However it is unclear if this relates to any functional impact as recent research has failed to find a link between genotype and VO_2peak, with the exception of those with F508del and a class V mutation having reduced VO_2peak [18, 19]. Given the multifactorial causes of exercise intolerance, including nutritional status, direct skeletal muscle CFTR and physical inactivity, it is therefore plausible that exercise may be one of the therapeutic options available to improve exercise tolerance in people with CF.

The purpose of this review is to provide an overview of the current understanding of the rationale and evidence for exercise as a therapeutic intervention for people with CF. Particular emphasis will be given to the impact of exercise on physical fitness and respiratory function. The evidence supporting the role of exercise as an ACT in CF will also be reviewed.

2. Exercise and physical fitness

A recent systematic review concluded that there is some evidence, albeit limited, demonstrating that aerobic exercise training improves physical fitness in CF [22]. Four out of the seven studies included in the review found that exercise had a positive effect on VO_2peak [22]. However, the strength of the evidence for exercise improving VO_2peak was only rated as very low to low, largely attributable to the fact that the studies were of low to moderate methodological quality as a result of small sample sizes and potential bias from the randomisation and allocation concealment methods adopted [22]. It is likely that the variable effect of exercise on VO_2peak seen in current studies arises in part from the small sample sizes, heterogeneous interventions and differing intervention durations [22]. A lack of effect of exercise on VO_2peak may also result from exercise training intensities being below the optimal intensity required to see an improvement in VO_2peak, especially if the individuals had a moderate level of fitness capacity at baseline [22]. Whilst

assessment of physical fitness has historically focussed on measuring VO_2peak, assessment of other measures of fitness, such as endurance/constant workload tests or lactate concentrations levels at specific workloads, may be of value in future studies to determine if they are positively impacted by exercise interventions.

As well as decreased physical fitness, limb muscle mass and strength are often reduced in individuals with CF compared to age-matched peers [23, 24]. Whilst reduced muscle mass has historically been linked to malnutrition and physical inactivity in the setting of CF, recent evidence supports the direct expression of CFTR in skeletal muscle [20, 25]. Indeed, leg fatigue/symptoms may be the limiting factor during maximal exercise testing in people with CF, suggesting a potential peripheral limitation to exercise [26, 27]. However, despite any deficiencies arising from direct CFTR expression in skeletal muscle, the endurance and fatigability of skeletal muscle in people with CF appears similar to that of normal controls when allowing for a reduction in muscle mass, indicating that strength deficits in individuals with CF may be more related to reduced muscle mass as opposed to an intrinsic muscle dysfunction [21]. Therefore, another physiological rationale for the recommendation of exercise as a therapeutic intervention in CF is to address this loss of muscle mass and strength. A small trial found that participants who underwent targeted muscle training (via neuromuscular electrical stimulation) and cycle training had greater increases in muscle strength and thigh circumference compared to the participants who only undertook the cycle training program [28]. Two of the larger trials that have examined the effects of exercise on muscle strength and mass in people with CF showed conflicting results, with one finding short-term resistance training during an inpatient admission for an acute respiratory exacerbation resulted in a mean 18% increase in lower limb strength on discharge, whereas a 6-month, partially supervised aerobic or resistance exercise intervention did not show an increase in muscle strength or mass, even in the resistance training group [29, 30]. Due to the heterogeneity in both training and strength assessment protocols, meta-analysis of strength-based outcomes was not possible [22].

3. Effect of exercise on respiratory function

Exercise may have the potential to effect respiratory function in CF. It has been shown that a single bout of moderate intensity exercise may have an acute bronchodilator effect, increasing both FEV_1 and FEF_{27-75}, with the changes in FEF_{25-75} being similar to that seen 60 minutes post albuterol administration [31]. Recent research has also found a correlation between self-reported physical activity levels and the rate of decline in respiratory function in adults with CF [32]. Individuals with CF with a higher level of habitual physical activity may have a slower rate of decline in respiratory function [33]. Indeed, exercise has long been promoted as a means of maintaining respiratory function in the setting of CF [34]. However, the quality of the evidence demonstrating a beneficial effect of implementing an exercise intervention on respiratory function, particularly FEV_1, is rated as low. A recent systematic review examining the effect of exercise interventions in CF found that the effect of exercise on FEV_1 was unclear, with only two out of the 11 included studies finding a benefit [22]. As noted by the authors, it is not clear if the lack of effect of exercise on FEV_1 resulted from an actual ineffectiveness of exercise or if methodological issues, such as poor adherence, insufficient training load and/or lack of statistical power explained the lack of effect [22]. Those studies which found a benefit of exercise on FEV_1 used a variety of exercise regimens and therefore, at this time, there is no one specific exercise regimen that appears most effective at increasing or maintaining FEV_1 [29, 30]. Other measures of respiratory function, such as lung clearance index (LCI) or impulse oscillometry (IOS) may be more sensitive to change than spirometry and may therefore have a role in assessing the respiratory effects of exercise interventions. Data from a single centred study involving 33 participants with CF, found that a single bout of maximal exercise improved LCI without changing IOS values [35]. We are unaware of any studies investigating the long-term effect of exercise interventions on LCI or IOS and there would be value in using these measures as outcomes in future long-term exercise studies.

4. Exercise and ACTs

4.1. Exercise as a stand-alone form of airway clearance

The potential use of exercise as a form of stand-alone airway clearance in CF was considered as far back as the early 1980s, with various reports suggesting that exercise could be substituted for at least some airway clearance sessions without adversely affecting respiratory function [36, 37, 38]. Since these initial reports, several short-term crossover studies have reported positive effects associated with exercise that support a physiological rationale regarding the use of exercise as a form of airway clearance (Figure 2). Exercise in CF may inhibit sodium channel conductance, increasing sputum water content and reducing nasal potential difference [39, 40]. This increased sputum water content and resultant reduction in sputum viscosity has been postulated to improve mucociliary clearance. Whilst laboratory studies have suggested a change in sodium conductance following exercise may result in an increased sputum water content and therefore a change in the percentage of solids within the sputum, there are conflicting results from clinical studies, with the change in the percentage of sputum solids resulting from exercise varying from a reduction to a small increase (Table 1) [39, 40, 41, 42, 43].

Exercise may increase the ease of expectoration and volume of airway secretions cleared by people with CF by altering the rheological properties of the airway secretions. Treadmill exercise has been shown to result in a reduction in sputum mechanical impedance, with the degree of reduction in mechanical impedance similar to that seen with the use of the Flutter® [42, 43]. However, cycling does not appear to result in the same changes to mechanical impedance as seen with treadmill exercise, perhaps because the trunk oscillations associated with treadmill walking/running may be an important component of this exercise intervention [41, 42, 43]. Cycling, when compared to rest, has been shown to result in an increased ease of expectoration of airway secretions during the post-exercise recovery period, with this improvement not seen with treadmill use [41, 42]. It is unclear what the underlying physiological cause of the difference found between cycling and treadmill

exercise for ease of expectoration would be. Exercise such as cycling or trampolining has also been shown to increase the volume of sputum expectorated when compared to a sham exercise [44].

Exercise may have positive effects on ventilation, which may make secretion clearance easier. For example, cycling and treadmill exercise may facilitate airway clearance by increasing expiratory flow rates above the suggested flow rate required to achieve an increase in secretion movement [42, 45]. However, it is not clear whether the change in expiratory flow rate associated with exercise is sufficient to achieve the expiratory flow bias that is required for a cephalad movement of secretions (i.e. ratio of peak expiratory flow to peak inspiratory flow did not exceed 1.1) [42, 45]. Nevertheless, the combined potential effects of exercise on expiratory flow rate, mechanical impedance and water content provides a physiological rationale for using exercise as a form of airway clearance.

Whilst several short-term crossover trials have suggested that exercise can be used as a substitute for traditional ACTs, other studies have concluded that exercise sessions may not clear the same weight of sputum as compared to traditional ACT sessions [37, 44, 46, 47, 48, 49]. These inconsistent findings may result from the fact that the reliability of sputum weight as an outcome measure may be affected by potential contamination with saliva or swallowing of sputum [50, 51]. At present, there is a lack of research regarding the medium to long-term efficacy of exercise as a stand-alone form of ACT as highlighted by a recent systematic review of ACTs in CF, thus precluding the ability to make firm recommendations for clinical practice [52]. We recently published a feasibility trial investigating the medium-term effectiveness of exercise as a stand-alone form of airway clearance [53]. This study provides a framework for a future multi-centre trial, but was not powered to detect effects on clinical outcomes [53].

Despite the lack of evidence for exercise as a form of stand-alone airway clearance, this practice is commonly reported in the clinical setting. Some patients may prefer undertaking exercise compared

to traditional ACTs, with recent data from the UK CF data registry suggesting that 16% of registrants reported exercise as their primary form of airway clearance [54]. We recently reported the findings of a survey conducted across all Australian adult CF centres, where 44% reported using exercise as a substitute for traditional ACTs at some stage during the preceding three months [55]. This finding that patients accept and use exercise as a substitute for traditional ACTs is important, as patient preference may be critical to long-term adherence to therapy. Given the relatively high rates of people with CF already choosing to use exercise as a substitute for traditional ACTs, the need to reduce patients' treatment burden where possible and evidence of a physiological rationale, further research investigating the efficacy of exercise as a stand-alone form of airway clearance should be a high priority [56].

4.2. Exercise to improve the effectiveness of traditional ACTs

As well as a stand-alone form of airway clearance, exercise is also promoted as an adjunct intervention to improve the effectiveness of traditional ACTs [6]. Our recent survey of Australian adults with CF found that 57% had used exercise (most often walking) to improve the effectiveness of their traditional ACT over the preceding three months [55]. Exercise undertaken immediately prior to traditional ACTs has been shown to increase expectorated sputum weight, although results are conflicting [44, 47, 57], likely due to the differing exercise regimens. It is possible that exercise that results in more marked chest oscillation (e.g. walking, jogging, trampoline jumping), may be more effective than exercise with less chest oscillation (e.g. cycling, other non-impact based exercise) [42, 44, 47, 57].

5. Exercise, health-related quality of life (HRQOL) and mental health

Adolescents and adults with CF have worse HRQOL and higher rates of symptomatic depression and anxiety compared to their age-matched peers [58, 59]. A 12-week study, where participants exercised at least three times per week for 30 minutes, demonstrated significantly improved HRQOL

in the domains of treatment burden and emotional functioning but no significant change in overall HRQOL [60]. Another study found that increases in self-reported physical activity over six months was associated with improved HRQOL in domains such as role limitations and feelings of embarrassment, however objectively measured (via an accelerometer) moderate to vigorous physical activity were not correlated with HRQOL [61]. A recent systematic review of exercise in CF found that exercise may improve HRQOL in individuals with CF (based on 2 out of 7 included studies) but there was no clear evidence regarding the optimal type, intensity, duration or frequency of exercise required to achieve this benefit [22]. We were unable to identify any current trials examining the role of exercise in CF with the primary aim of improving symptoms of anxiety or depression in CF and believe this should be a priority for researchers in the coming years, given the elevated prevalence of these symptoms in CF and the potential adverse effect these symptoms may have on overall treatment adherence and clinical outcomes. The ACTIVATE-CF trial, a large multi-centred exercise trial currently in progress, includes assessment of anxiety and depression, using the Depression and Anxiety Stress Scale (DASS), as a secondary outcome and, whilst not necessarily powered to detect change in the DASS, this should provide an insight into the potential role of exercise in treating these important comorbidities [62].

6. Exercise and CF-related diabetes

CF-related diabetes (CFRD) is increasing in prevalence as the lifespan of individuals with CF increases, with impaired glucose tolerance occurring in as many as 50% of some age groups [2, 3]. While exercise is recommended as part of the therapeutic regimen for people with type one (T1DM) and type two diabetes mellitus (T2DM), it is unclear if the benefits of exercise can be extrapolated to individuals with CFRD [63]. A recent paediatric CF study found a significant relationship between poor glucose tolerance and reduced exercise capacity [64]. After for controlling for age and FEV_1, glucose and insulin levels at 120min during an oral glucose tolerance test in those participants who did not have CFRD were found to be significant predictors of reduced percent predicted VO_2peak.

However, whilst it could be hypothesised that better physical fitness might improve longer-term glycaemic control, this study found no correlation between glycated haemoglobin (HbA1c) and percent predicted $VO_{2\%}$peak [64]. A recent cross-sectional study involving 18 adults with CFRD reported no significant difference in HbA1c between those who did or did not meet the Canadian Diabetes Association aerobic training guidelines (150min of moderate to vigorous exercise per week with no more than two consecutive days without exercise) based on responses to the Seven-Day Physical Activity Recall interview [65]. A small study (n = 14), recruiting sedentary adults with CF and abnormal glucose tolerance, found that those completing a 12-week mixed exercise program (3 sessions per week of aerobic and resistance training) had a significant improvement in their 2hr plasma glucose level (-2.34 ± 1.26 mmol/L, $p < 0.01$) on the oral glucose tolerance test and a 17.2% reduction in overall glucose excursion (as measured by the glucose area under the curve, $p < 0.02$) whilst the control group remained stable for both measures [66]. The investigators concluded this reduction was probably due to an increase in insulin sensitivity as opposed to an increase in insulin secretion. Whilst providing a potential insight into the role of exercise in managing CFRD, this study was underpowered and did not compare between-group changes [66]. There are no long-term data on the impact of exercise on maintaining or improving long-term glycaemic control in CFRD. A planned randomised controlled trial aims to investigate if a home cycling program, performed three times per week, will improve insulin sensitivity [67]. In the absence of CF-specific data, it seems appropriate to base clinical recommendations for exercise in CFRD on the guidelines for T1DM and T2DM until such time that CFRD-specific evidence is obtained.

7. Exercise and bone mineral density (BMD)

Osteopenia and osteoporosis are becoming increasingly prevalent in CF, largely attributable to the increase in lifespan of affected individuals. The cause of reduced BMD is likely to be multifactorial, with reduced physical activity and weight bearing commonly cited contributing factors [68]. Current international CF guidelines regarding bone mineralisation recommend that children and adolescents

achieve 20-30 minutes of exercise, which includes high impact weight bearing activities, three times per week, in order to promote increased bone strength [68]. These guidelines do not specify a frequency or duration for adults with CF, simply stating they should perform regular weight bearing and impact activities. A recent cross-sectional study involving 50 adolescents and adults with CF found a significant correlation between the time spent in moderate and vigorous physical activity and femoral BMD and biochemical markers of bone formation [69]. Whilst not establishing causation, these findings suggests that ensuring people with CF meet exercise and activity guidelines may have at least a protective role with regards to maintaining BMD. Although a prospective trial investigating exercise and BMD in CF has been registered, at present there are no prospective published data specifically investigating the role of exercise in maintaining or increasing BMD in CF [70]. Until such data exists, extrapolation of research from other cohorts would suggest that exercise is unlikely to do harm and indeed is more than likely to be of benefit with respect to BMD in CF [71].

8. Safety of exercise in CF

As with any therapeutic intervention, exercise may have undesirable side-effects. Beyond the risks of exercise applicable to the general population, people with CF have several factors that need specific attention when prescribing exercise as a therapeutic intervention. The potential for oxygen desaturation is a well-known side effect of exercise, particularly in those with more severe disease [72]. Cardiac arrhythmias associated with exercise have also been reported, with a lower oxygen saturation at rest and during exercise a potential risk factor [72]. Malnutrition is a hallmark of CF, primarily attributable to malabsorption [73, 74]. Nutritional status, particularly energy balance/requirements, should be considered when prescribing an exercise regimen for a person with CF and is best done through an interdisciplinary model, where both the exercise and nutrition prescriptions can occur concurrently [74]. Exercise has the potential to affect hydration and electrolyte balance, particularly in hot or humid conditions. People with CF are particularly vulnerable to sodium depletion due to an increased sweat sodium loss during exercise and

potentially a reduced thirst drive [75, 76]. Current guidelines cite insufficient evidence to provide specific CF hydration or sodium-replacement recommendations other than to note that clinicians should be aware of the issues of energy requirements and fluid/electrolyte balance and provide education to individuals with CF accordingly, particularly for those exercising in hot or humid conditions [74].

In healthy adults, exercise is known to affect immune cell function and inflammatory cytokine levels [77]. Whilst single bouts of exercise may be pro-inflammatory, regular medium intensity exercise is believed to have an anti-inflammatory effect in the healthy population [77]. However, insufficient rests between higher intensity exercise sessions may have a negative effect on immune cell function and the inflammatory response [77]. People with CF generally have an elevated baseline level of inflammation and therefore there is a theoretical risk of exercise increasing this inflammatory load [78]. The evidence concerning the inflammatory response to exercise in CF is insufficient at this time to enable definitive conclusions to be made [79, 80, 81].

9. Exercise and physical activity assessment

As recommended by the European Cystic Fibrosis Society (ECFS), exercise testing should be a component of the regular assessment of people with CF, especially in people aged 10 years or more [82]. Exercise testing allows for the evaluation of physical limitations and exercise-related symptoms, to screen for potential adverse effects from exercising and also as a basis for prescribing and monitoring prescribed exercise interventions [82]. Suitable tests for use in CF populations include full CPET protocols or field tests such as the six minute walk test (6MWT) or incremental shuttle tests. Full CPET using the Godfrey cycling protocol should be the preferred choice of testing where possible as it allows for measurement of VO_2peak, identification of factors limiting exercise capacity, the evaluation of exercise-associated adverse reactions (e.g. cardiac arrhythmias) and the prescription of exercise training loads at a percentage of peak capacity [82]. Other tests, such as the one minute sit

to stand, the three minute step test and the stair-climb power test are currently being investigated for potential use in CF but at present lack sufficient evidence to be recommended as routine assessments. The 6MWT is considered the test of choice when assessing people with CF for potential lung transplantation, with current guidelines suggesting those with a 6MWT of <400m should be considered for referral to a transplant centre [83]. It is recommended that exercise testing should be undertaken upon the reporting of new exercise-related symptoms and as part of the exercise prescription process. There is currently insufficient evidence to make any recommendations regarding the benefit of routine use of exercise testing in CF outside of these situations [82].

Whilst exercise testing is useful for assessing exercise capacity, it does not provide a measure of physical activity participation. There are a variety of methods available for assessing daily physical activity, with the position statement from the ECFS providing recommendations for the assessment of physical activity in the CF context [84]. Whilst objective measures may provide a more accurate assessment of physical activity compared to patient self-reports via questionnaires, they can be expensive and onerous to use [85]. As commercial devices improve their accuracy in the future, they may become a viable option. At present, the ECFS recommends motion sensors, such as the ActiGraph® or DigiWalker®, be considered for objective physical activity assessment whilst the Habitual Activity Estimation Scale (HAES) questionnaire may be useful for the subjective assessment of physical activity [84].

The ideal frequency of assessment of exercise capacity and physical activity is yet to be determined. As both formal exercise testing and physical activity assessment may be dependent upon equipment and the availability of clinicians with the appropriate training, each CF centre must adapt the recommendations from the position statements for day to day use in their centre [82, 84]. The prescription of an exercise regimen should be personalised with regards to type, setting and

intensity of exercise based upon the results from both an exercise test and physical activity assessment and through a collaborative approach between the person with CF and clinical team.

10. What is the optimal exercise regimen?

Current CF-specific recommendations are generally drawn from guidelines for the general population [4, 86]. Current recommendations are that, unless contraindicated due to specific comorbidities, children with CF should exercise in a similar way to their age-matched peers, achieving at least 60 minutes of daily moderate physical activity [7, 86]. Similarly, adults with CF should ideally achieve at least 150 minutes of moderate or 75 minutes of vigorous physical activity per week, achieved by exercising at least five times per week [4, 7, 86]. Exercise should consist of both aerobic (e.g. walking/jogging or cycling) and anaerobic (e.g. resistance, bodyweight) training [4, 86]. Weight-bearing forms of exercise (e.g. walking, jogging) may be preferred over non-weight bearing forms (e.g. swimming) due to the potential beneficial effects on BMD and the effects on mucus associated with truck oscillations [42, 68]. Specific considerations, such as resistance training in young children, adjustment of insulin and carbohydrate intake in those with CFRD and the use of supplemental oxygen should be done on an individualised basis [4, 86, 87]. The optimal exercise regimen for people with CF is unclear [4, 22, 86]. As such, the specific exercise training regimen (type, intensity, frequency and duration) should consider the broad recommendations above, be based upon a comprehensive assessment of the individual and be tailored to the individual's circumstance and preferences. Once prescribed as a therapeutic intervention, exercise regimens should be reviewed on a regular basis to evaluate efficacy and adherence, progress components as required and to monitor for unwanted side effects.

The ideal location (e.g. hospital, community health centre or commercial gym) and method for prescribing and/or modifying an individual's exercise prescription has yet to be determined and can differ between healthcare centres. Historically, the approach has been for an individual with CF to

attend their local CF clinic for the purposes of undergoing an exercise assessment, receiving initial instruction in the exercise program and then undertaking this exercise program either at home or by attendance at local gyms. While some individuals may receive regular supervised exercise sessions, depending on service availability, the infection control requirements associated with CF care mean that people with CF may be excluded from group-based programs such as that offered by the traditional pulmonary rehabilitation model [88]. Telehealth and web-based approaches present an opportunity to overcome some of the issues associated with infection control requirements as well as the burden associated with travelling to healthcare centres for supervised exercise sessions. Two recent studies have proven the feasibility of using a web-based tool to promote physical activity as well as real-time screening of exercise sessions via a telemedicine application [89, 90]. Further research however is required to compare the use of telehealth and web-based interventions for exercise prescription and/or supervision to current models of care.

Given the limitations in the current literature, large, well designed and adequately powered prospective randomised controlled trials are required to clarify both the benefits and optimal regimen of exercise in CF. One such trial currently being conducted is the ACTIVATE-CF trial which is being conducted across CF centres from eight countries, recruiting people with confirmed CF who are ≥12 years of age and have an FEV_1 ≥35% predicted [62]. Participants are randomised to either usual care or three hours per week of vigorous physical activity, aided by counselling, pedometer use, a web-based diary and monthly telephone support. The primary endpoint is the difference in change in FEV_1 from baseline to six months. Secondary outcomes include changes in VO_2peak, physical activity, HRQOL, oral glucose tolerance and frequency of respiratory exacerbations. The results of ACTIVATE-CF will be important to see if they confirm the benefits of exercise reported by the previous studies. Until ACTIVATE-CF and other larger exercise trials are completed, the current evidence demonstrating physical fitness and HRQOL benefits arising from exercise provides a

sufficient rationale for recommending exercise as a routine component of the CF therapeutic regimen [4, 86].

Expert opinion:

Exercise intolerance and reduced muscle mass are commonly reported in cystic fibrosis (CF). Exercise is a routinely recommended component of the CF therapeutic regimen. Whilst the strength of the evidence supporting exercise as a method of improving physical fitness and respiratory function is constrained by methodological limitations (e.g. small sample sizes), on the balance, it seems likely that exercise may assist in improving these important outcomes. Short-term studies provide a physiological rationale for the use of exercise as a form of airway clearance however there are no medium or long-term data upon which clinical recommendations can be made. Exercise may play a role in the optimisation of bone mineralisation and may also help in the management of CFRD, but further research is required. Until such time that larger, multi-centred, exercise-based trials are conducted, there is sufficient evidence to continue recommending exercise as a routine therapeutic intervention in CF.

The next five years are a potentially exciting time for clarifying the role of exercise as a therapeutic intervention in CF. The results of the ACTIVATE-CF trial may help to clarify the role of exercise with regards to respiratory function and exacerbation rate. It will also be interesting to see if the ACTIVATE-CF study confirms a role for exercise in CF with respect to improving anxiety and depressive symptoms in CF. Through a better understanding of alternative approaches where preliminary data has shown some promise, such as high intensity interval training and inspiratory muscle training, the methods for optimising exercise prescription in CF may become clearer [91, 92, 93, 94]. It is expected that trials investigating the use of exercise as a substitute for traditional ACTs will be conducted within the next five years, as this is clearly an area of high priority for both patients and clinicians. The future for CF care is exciting, with the new disease modifier medications

(e.g. Ivacaftor, Ivacaftor/Lumacaftor) representing a fundamental shift in how CF is managed. With the increase in body weight and nutrition seen with these new therapies, the benefit and importance of exercise may only be increased, particularly as more people with CF may start to be classified as overweight as a result of improved gastrointestinal absorption. Exercise may have an increasing role in management of cardiometabolic risk in this setting. Finally, strategies to improve treatment adherence, including the use of new and emerging technologies including telehealth, is likely to gain increased attention.

Key issues:

- Exercise is routinely recommended for people with cystic fibrosis (CF)
- Evidence supporting the use of exercise as a therapeutic is generally considered to be of low quality due to methodological limitations
- Exercise may improve health-related quality of life (HRQOL) for people with CF and may improve physical fitness and respiratory function
- Whilst some people with CF may choose to use exercise as a substitute for traditional airway clearance techniques (ACTs), further evidence is required before this can be recommended as part of routine care
- Exercise performed prior to traditional ACTs may improve the effectiveness of the traditional ACTs
- The impact of exercise, when prescribed as a therapeutic intervention, on nutritional status, hydration and blood glucose level management needs to be assessed and tailored on an individual basis
- Several trials in progress may help to provide clarity on the role of exercise as a therapeutic intervention in CF for maintaining respiratory function, physical fitness and HRQOL

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Figure 1: Potential benefits of exercise in CF.

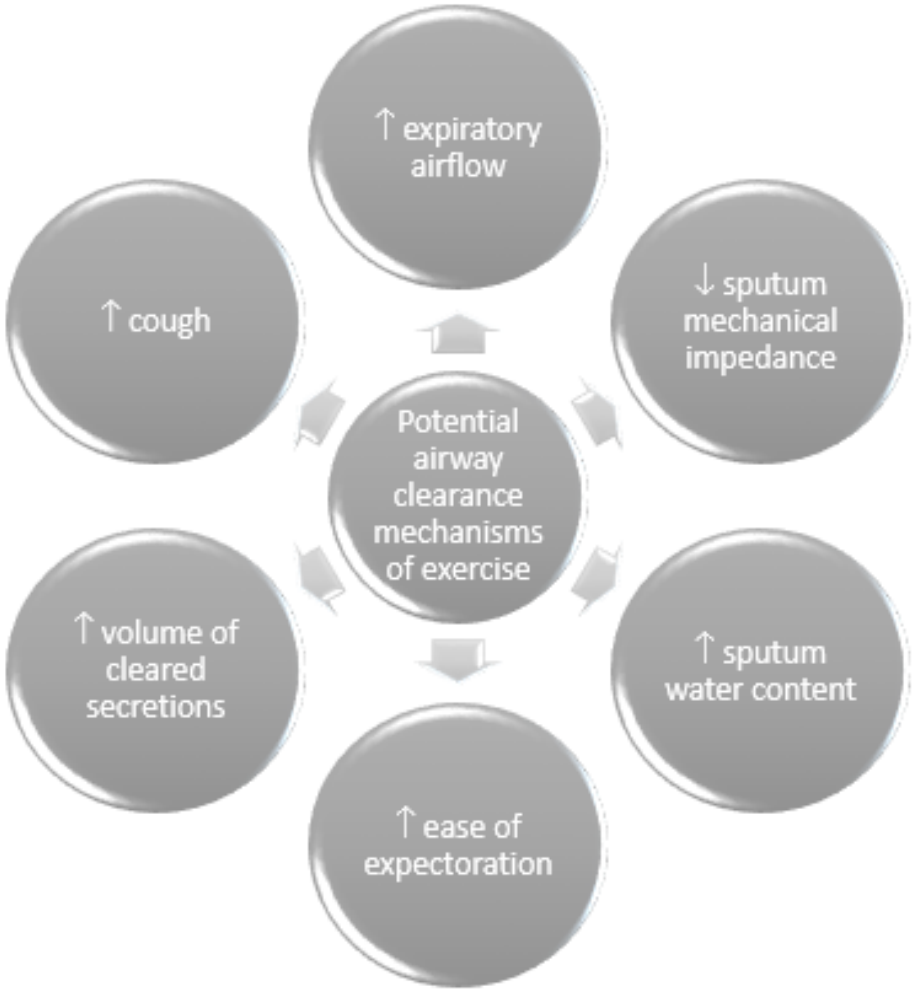

Figure 2: Physiological rationale for exercise as a form of airway clearance in CF.

Table 1: Effect of exercise on percent sputum solids and sputum mechanical impedance.

Study	Interventions	Results
Dwyer et al [28]	Treadmill vs cycling vs rest	*Sputum solids* No significant difference in change between treadmill or cycling compared to rest ($p > 0.4$) or between cycling and treadmill ($p > 0.6$). *Mechanical impedance** Treadmill resulted in a significant reduction compared to rest (mean differences range = 5.3 to 53.5Pa). There was no significant difference between cycling and rest ($p > 0.06$) or treadmill and cycling ($p > 0.06$).
Dwyer et al [29]	Treadmill vs Flutter® vs rest	*Sputum solids* No significant differences between conditions tested at the end of the intervention or after 20min recovery. Those who expectorated spontaneously within 5min of stopping exercise: treadmill resulted in a 1.2% (95%CI 0.4-1.9) reduction in percent sputum solids compared to rest. There was a trend towards reduced percent sputum solids with treadmill compared to the Flutter® (1.1%, [95%CI -0.1 to 2.3]). *Mechanical impedance** Treadmill resulted in a significant reduction compared to rest at the end of the intervention and after 20-min recovery (mean differences range = 7.1 to 12.3Pa). There were no significant differences between the treadmill and Flutter®.
Radtke et al [27]	Cycling vs cycling + Flutter®	*Sputum solids* Cycling: significantly increased percent sputum solids post cycling (pre = 5.3% [3.9-7.4%], post = 6.2% [4.2-9.7%], 45min recovery = 6.5% [4.4-8.1%], $p = 0.038$). Cycling + Flutter®: no significant difference post cycling + Flutter® (pre = 4.5% [3.6-5.8%], post = 6.2% [4.1-7.5], 45min recovery = 6.9% [3.8-8.4%], $p = 0.672$). Cycling vs Cycling + Flutter®: no significant difference between the two interventions for absolute change in percent sputum solids. *Mechanical impedance*** No significant difference between pre to post for either intervention ($p > 0.057$) or between interventions ($p > 0.237$).

*measured at 1 rad/s and 100 rad/s; ** measured at 1 rad/s and 10 rad/s.

CHAPTER 3: EXERCISE AS AN ALTERNATIVE TO TRADITIONAL AIRWAY CLEARANCE IN CYSTIC FIBROSIS: A SYSTEMATIC LITERATURE REVIEW

Declaration of authorship – Chapter 3

The nature and extent of contributions to Chapter 3 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Study concept and protocol development, data extraction and analysis, writing of manuscript and review	70%	
Scott Morrow	Data extraction and analysis, review of manuscript	10%	
Kathy Stiller	Study concept and protocol development, review of manuscript	10%	
Anne Holland	Study concept and protocol development, review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 3 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

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Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review

Nathan Ward[a,b], Scott Morrow[a], Kathy Stiller[c], Anne E Holland[b,d,e]

[a]Physiotherapy, Central Adelaide Local Health Network, Adelaide, Australia
[b]Physiotherapy, La Trobe University, Melbourne, Australia
[c]Allied Health, Central Adelaide Local Health Network, Adelaide, Australia
[d]Physiotherapy, Alfred Health, Melbourne, Australia
[e]Allergy, Immunology and Respiratory Medicine, Monash University, Australia

Corresponding author: Nathan Ward, c/o Physiotherapy, 8E055.08, Royal Adelaide Hospital, Port Road, Adelaide, SA, Australia 5000, nathan.ward2@sa.gov.au

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Keywords: Cystic fibrosis; Exercise; Physical therapy modalities; Respiratory therapy

Word Count: 4447

Key Messages:

What is the key question?

Whilst people with cystic fibrosis commonly report using exercise as a substitute for traditional airway clearance techniques, is there evidence to support this practice?

What is the bottom line?

Short-term studies indicate exercise improves mucociliary clearance compared to resting. Exercise may be as effective as traditional airway clearance techniques however the evidence is limited by short-term studies and conflicting results. There is no medium or long-term evidence to guide clinical practice.

Why read on?

This review systematically evaluates the evidence for using exercise as a substitute to traditional airway clearance techniques in people with cystic fibrosis and provides insight for clinical practice and future studies in this area.

Abstract

Background: Exercise and traditional airway clearance techniques (ACTs) are both routinely recommended for people with cystic fibrosis (CF), with some people using exercise as a substitute for traditional ACTs. The effectiveness of this is unclear. We systematically reviewed the evidence for using exercise as a substitute for traditional ACTs in people with CF.

Methods: A systematic database and literature search was undertaken of studies comparing exercise to rest or traditional ACTs. Primary outcomes were respiratory function, respiratory exacerbations and health-related quality of life. Secondary outcomes included mucociliary clearance (MCC), sputum weight and ease of expectoration. Data are mean difference (95%CI).

Results: A total of 12 studies (15 reports) were included, all of short duration (single session to two weeks). In crossover trials, exercise did not improve FEV_1 in comparison to rest, but peak expiratory flow (PEF) was increased during treadmill exercise (MD range 1.00 to 1.16L/s) and cycle ergometry (1.19 [0.96 to 1.42]L/s). Treadmill exercise improved MCC (2.6 [1.6 to 3.6]%) and ease of expectoration (MD range 1.3 to 1.8cm) compared to rest. No consistent differences in respiratory function were evident when exercise was compared to traditional ACTs (4 crossover studies). There was no significant difference in MCC or sputum weight in studies where forced expirations were included in the exercise intervention.

Conclusions: Exercise improves ease of expectoration and sputum clearance compared to rest. Exercise, incorporating forced expirations, may have similar effects to traditional ACTs over the short-term. There are no data comparing exercise to traditional ACTs over the longer-term.

Exercise as a means of airway clearance in cystic fibrosis: a systematic review

INTRODUCTION

Historically, people with cystic fibrosis (CF) have been prescribed a daily routine of airway clearance techniques (ACTs) with the aim of reducing symptoms and slowing decline in respiratory function. Traditional ACTs included postural drainage (PD), percussion and vibrations (P&V), but have evolved to include breathing techniques (e.g. active cycle of breathing technique [ACBT], autogenic drainage [AD]) and device-based ACTs such as positive expiratory pressure (PEP) and oscillating PEP. It is recommended that people with CF undertake regular exercise, to improve aerobic fitness and muscle strength, in addition to performing ACTs.[1-4] However, a recent survey of Australian adults with CF found that 43% of the participants agreed or strongly agreed that exercise could be used as a substitute for traditional ACTs, whilst analysis of the United Kingdom CF data registry found that 16% of patients reported exercise was their primary method of airway clearance.[5, 6]

The physiological rationale for using exercise as a substitute for traditional ACTs includes that moderate intensity exercise reduces epithelial sodium conductance and nasal potential difference in people with CF, potentially increasing sputum water content and subsequently mucociliary clearance (MCC).[7, 8] Exercise may also increase respiratory flow, promoting the cephalad movement of respiratory secretions. Substituting exercise for traditional ACTs may reduce the treatment burden in CF, with recent data suggesting up to 96% of people of CF already exercise and 48% may omit their traditional ACT if they have exercised.[9] Determining the suitability of using exercise as a substitute for traditional ACTs has been identified as one of the top 10 research priorities in CF.[10] To date no literature review has specifically reviewed the effectiveness of using exercise as a substitute for traditional ACTs.[11, 12] Therefore, the aim of this review is to examine the evidence for using exercise as a substitute for traditional ACTs in people with CF.

METHODS

We performed a systematic review of the scientific literature investigating the role of exercise as a substitute for traditional ACTs in people with CF. The review was prospectively registered on PROSPERO (available from: https://www.crd.york.ac.uk; ID=CRD42018102780) and undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Search strategy

The following electronic databases were searched from the earliest available time until May 2020: MEDLINE, Pubmed, Cochrane (CENTRAL) and CINAHL. Table 1 summarises the

search strategy. Reference lists of included studies were screened to identify potentially relevant studies not identified through the database search.

Table 1: Search strategy

#	Searches
1	cystic fibrosis
2	exercise therapy OR physical exertion OR exercis* OR walk* OR jog* OR run* OR bicycl* OR cycl*
3	physical therapy modalities OR mucociliary clearance OR mucus OR sputum OR respiratory therapy OR chest physical therapy OR physiotherapy OR airway clearance OR active cycle of breathing technique OR ACBT OR autogenic drainage OR AD OR positive expiratory pressure OR PEP OR oscillating PEP OR OPEP OR flutter OR acapella OR percussion OR vibration OR drainage, postural OR intrapulmonary percussive ventilation OR IPV OR chest wall oscillation OR HFCWO OR bottle PEP OR bubble PEP OR underwater PEP OR uPEP OR rest
4	1 AND 2 AND 3

Inclusion and exclusion criteria

Studies recruiting participants with a diagnosis of CF were included if they compared (1) exercise to rest, in order to evaluate the effects of exercise alone, or (2) to a traditional ACT (e.g. PD, P&V, ACBT, AD, PEP, oscillating PEP), in order to directly compare the two treatment strategies.

Exercise was defined as the purposeful movement of the upper or lower limbs or both. Exercise interventions could include periodic huffing and coughing to clear secretions. Studies where exercise solely involved breathing techniques (e.g. breathing control, thoracic expansion exercises) were excluded. Randomised controlled trials (RCTs) or quasi-RCTs, either parallel or crossover in design were eligible. Studies published in English, of any duration and disease phase (e.g. stable, unstable), were included. Full text studies and those published in abstract form only were included.

The outcomes of primary interest were: respiratory function tests (e.g. FEV_1, FVC, FEF_{25-75}, lung clearance index), acute respiratory exacerbations (defined by symptoms or initiation of antibiotics based on medical practitioner assessment) and health-related quality of life

(HRQOL) measured by generic or disease-specific questionnaires. Secondary outcomes of interest were: MCC (assessed by radioaerosol clearance or mucus transport rate), ventilation scans (radiological or nuclear medicine), expectorated sputum weight or volume (wet or dry), perceived ease of expectoration, participant preference and adverse events.

Study selection and data extraction

After removal of duplicates, two reviewers (NW and SM) independently identified potentially eligible studies by evaluating the title and abstract against the inclusion and exclusion criteria. Full texts of potentially eligible reports were reviewed and a final decision made regarding eligibility. Where both reviewers could not agree, a third reviewer (KS) assisted in achieving consensus.

Two reviewers (NW and SM) independently evaluated each included study for methodological quality. Data were extracted using a standardised data extraction table, with the reviewers blinded to the other's extracted data. Study design, technique descriptions, participant characteristics and outcome data were recorded. No attempt was made to contact the authors of studies where insufficient detail was provided in the report as most of the studies where data were missing were published more than 20 years previously.

Risk of bias assessment

Risk of bias was independently determined by two reviewers (NW and SM) according to the Risk of Bias Assessment Tool included in the Cochrane Handbook for Systematic Reviews of Interventions.[14] Where there was disagreement, a third reviewer (KS) undertook the assessment and, if required, the three reviewers discussed the assessment to achieve consensus.

Data analysis

Data for exercise versus the two comparators (rest or traditional ACT) were analysed separately. Given the potentially differing physiological effects of the various exercise modalities available (e.g. running, cycling, resistance training) and ACTs (e.g. ACBT, PEP), data from studies utilising different exercise modalities or ACTs were not combined for meta-analysis. When multiple RCTs comparing the same exercise regimen and ACT were available, and the studies homogeneous, meta-analyses were conducted using a fixed-effect model, with results reported as mean difference (MD) between groups [95% confidence interval]. If substantial heterogeneity was identified, a random-effect model was utilised. Heterogeneity was defined as low if I^2 was < 25%, moderate if I^2 was 25-50% and substantial if I^2 was > 50%.[14] Continuous variables were analysed as mean differences

and 95% confidence intervals. Continuous data from cross-over trials were analysed using a generic inverse-variance method where sufficient data were reported. RevMan software was used for the risk of bias table and all meta-analyses. For each of the primary outcomes, the quality of the body of evidence was rated using GRADE.[15]

RESULTS

Flow of studies through the review

After screening the titles and abstracts of identified reports, 199 full reports were reviewed (Figure 1). Of these, 184 reports were excluded. Twelve studies, comprising 15 reports, met the eligibility criteria.

Description of the included studies

Of the 12 studies identified, only one was an RCT, with the remainder crossover trials. Nine of the 12 studies were conducted when participants were clinically stable, two occurred during inpatient treatment for an acute respiratory exacerbation and one did not specify.

Five studies compared the effects of exercise to rest (Table 2).[16-20] All were crossover in design with small sample sizes (n = 8 - 24) and comprised a single session of each intervention/comparator. Participants' ages ranged from 15-48 years, with percent predicted FEV_1 ($ppFEV_1$) ranging from 19-113%. Exercise consisted of treadmill (n = 3), cycle ergometry (n = 2), trampolining (n = 1) and mixed exercise (n = 1) with durations ranging from 20-40 minutes, with two studies comparing multiple forms of exercise to rest. Prescribed exercise intensities were: 60% of peak oxygen consumption (VO_2peak) (n = 3) and heart rate of 140-160bpm (n = 1), whilst one study did not report exercise intensity. Rest interventions, of similar duration to the exercise interventions, included sitting quietly, playing billiards or limiting activity without being confined to bed. None of the studies included instructions to use huff, the forced expiratory technique (FET) or cough during exercise or rest.[16-20] One of the five studies occurred during a period of hospitalisation, however other differences in study design (e.g. differing exercise interventions) meant a comparison based on clinical stability could not be undertaken.[16]

Table 2: Summary of included studies

Reference	Study design	Exercise	Comparator	Sample size		Age (yrs)*		$ppFEV_1$*		Clinical stability	Relevant outcomes
				Ex	Com	Ex	Com	Ex	Com		
Exercise vs rest											
Baldwin et al 1994 [16]	Crossover	Mixed	Rest	8		18-27		63.6 (6.6)#		Acute exacerbation	Respiratory function tests, sputum weight
Dwyer et al 2011 [17]	Crossover	Cycle ergometry Treadmill	Rest	14		18-44, 27 (7)^		19-108, 55 (27)^		Stable	Respiratory function tests, participant ease of expectoration
Kreimler et al 2016 [19] (Radkte et al 2015)	Crossover	Cycle ergometry Trampoline	Rest (billiards)	12		15.9-28.9, 20.8 (3.5)^		33.3-89.9, 62.8 (17.7)^		Not specified	Respiratory function tests, sputum weight
Exercise vs rest/traditional ACT											
Dwyer et al 2017 [18]	Crossover	Treadmill	Rest Flutter®	24		19-48, 30 (8)^		28-86, 51 (18)^		Stable	Respiratory function tests, participant ease of expectoration, adverse events
Dwyer et al 2019 [20]	Crossover	Treadmill	Rest PEP	15		18-48, 27 (9)^		31-113, 65 (23)^		Stable	Mucociliary clearance, adverse events
Exercise vs traditional ACT											
Aquino et al 2006 [21]	Crossover	Active video game	PEP	13		7-29		46-102		Stable	Sputum weight
Balestri et al 2004 [22]	Crossover	Cycle ergometry	Bubble PEP	13		10-41		54-95		Stable	Sputum weight
Bilton et al 1992 [23] (Bilton et al 1990)	Crossover	Cycle ergometry	ACBT with PD	18		16-34		18-98		Stable	Respiratory function tests, sputum weight, participant perception and

											treatment preference, adverse events
Cerny 1989 [24]	RCT	Cycle ergometry	PD with P&V	9	8	15.4^ (4.9)	15.9^ (4.9)	NS	NS	Acute exacerbation	Respiratory function tests, sputum weight
Falk et al 1988 [25]	Crossover	Cycle ergometry	PEP	12		NS		NS		Stable	Respiratory function tests, sputum weight
Lannefors et al 1992 [26]	Crossover	Cycle ergometry	PEP	9		12-36		20-78,		Stable	Mucociliary clearance
			PD with TEE					51 (NS)^			
Reix et al 2012 [27] (Reix et al 2009)	Crossover	Mixed	mACBT	32		12 (3)^		93 (14)†	94 (14)†	Stable	Respiratory function tests, sputum weight, participant satisfaction, adverse events

*range unless otherwise specified; #mean (SEM); ^mean (SD); †mean (95%CI); PEP: positive expiratory pressure; ACBT with PD: active cycle of breathing technique with postural drainage; PD with P&V: postural drainage, percussion and vibration; CPET: cardiopulmonary exercise testing; PD with TEE: postural drainage and thoracic expansion exercises; mACBT: modified active cycle of breathing technique; NS: not specified

Nine studies (13 reports) were identified that compared exercise to a traditional ACT,[18-30] with two also comparing exercise to rest.[18, 20] Eight studies were of crossover design, with sample sizes ranging from 9-32, and comprised a single session of each intervention. The other was a RCT, recruiting 17 participants during a hospital admission (mean length of stay [SD] = 13.0 [2.6] days).[24] Participants in the nine studies included children and adults, with ppFEV_1 ranging from normal to severely impaired. Exercise interventions included cycle ergometry, walking/running on a treadmill, mixed exercise and active video gaming. Target exercise intensities were: 60%VO_2peak (n = 3), ½ W/kg (n = 1), 80% maximum working capacity (n = 1), >40% heart rate reserve (n = 1) or 'submaximal' (n = 1) and unclear in two studies. ACT interventions included PEP (n = 4), bubble PEP (n = 1), oscillating PEP (n = 1), ACBT (n = 1), a modified form of ACBT (n = 1), PD with P&V (n = 1) and PD with thoracic expansion exercises (n = 1). Treatment durations were inconsistently reported, ranging from 4 sets of 15 breaths to a total duration of 20-40 minutes. Three studies did not mention whether huffing/FET or cough were incorporated into either intervention,[21, 22, 24] four studies used huffing/FET as part of ACT but not the exercise intervention,[18, 20, 23, 25] whilst two studies incorporated huffing/FET with both interventions.[26, 27] Only one of the nine studies occurred during a respiratory exacerbation, with the rest occurring during a stable phase, with other differences in study design (e.g. differing exercise/ACT interventions) precluding a comparison of results based on clinical stability.[24]

Figure 2 presents the risk of bias assessment for all 12 studies. Insufficient details regarding study methodology meant it was not possible to classify risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment for the majority of the studies.

Exercise vs rest

Primary outcomes

Two studies (n = 20 participants) reported on the effect of exercise (cycle ergometer and trampolining, mixed exercise) compared to a period of rest on spirometry (Figure 3a and 3b).[16, 19] The intervention duration differed between studies (30min vs. 60min) and neither study reported if huffing/FET was used in either group. There was no significant effect on FVC or FEV_1 in either study. The mean changes in FEV_1 with exercise ranged from -0.05 to 0.01L and from -0.02 to -0.01L for rest.[16, 19] Meta-analysis was not possible due to the different types of exercise investigated. The quality of the evidence (GRADE) was assessed as being low for both FVC and FEV_1 due to unclear blinding and imprecision.

Peak expiratory flow (PEF) rates and peak expiratory to peak inspiratory flow ratios (PEF:PIF) were reported by two studies undertaken by the same research group (Figure 3c and 3d).[17, 18] Treadmill exercise resulted in a significantly higher PEF than rest in both studies, with mean differences ranging from 1.00 to 1.16L/sec. The PEF:PIF was higher with treadmill compared to rest (MD 0.05 to 0.12), demonstrating a peak expiratory flow bias. Compared to rest, one study found cycle ergometry improved PEF (MD 1.19 (0.96 to 1.42)L/s) and PEF:PIF (MD 0.13 [0.04 to 0.21]).[17] The quality of the evidence (GRADE) for PEF and PEF:PIF was assessed as being moderate due to indirectness.

No studies comparing exercise and rest reported on respiratory exacerbations or HRQOL.

Secondary outcomes

Treadmill exercise resulted in significantly greater mucus clearance from the whole lung immediately after the 20 minute intervention period (mean difference [95%CI] = 2.6% [1.6-3.6], 1 study, 15 participants).[20] When analysed by lung region, treadmill exercise also resulted in significantly greater mucus clearance from the intermediate and peripheral regions but not the central region. These differences were maintained over 60 minutes post-intervention except for the central region, where rest resulted in greater mucus clearance during this period.[20]

No studies reported on the relative effects of exercise compared to rest on ventilation scans.

Sputum weight was reported in two studies (n = 20 participants).[16, 19] One study (n = 8 participants) found a trend towards mixed exercise (including walking, cycling, step ups, star jumps) producing a greater sputum weight than rest (MD 4.4 [-0.07 to 8.8]g).[16] In the other study (n = 12 participants), trampoline exercise resulted in more sputum being expectorated (7.60 [SD 4.5]g) than the control period (billiards) (3.8 [SD 2.2]g) (p = 0.021).[19] There was also a trend for cycling to result in more sputum being expectorated (6.0 [SD 3.9]g) compared to a control period (p = 0.074).[19] Given the different types of exercise used in these two studies, meta-analysis was not possible.

Two studies (n = 38 participants) compared exercise and rest on participant-reported ease of expectoration, measured via a 10cm visual analogue scale.[17, 18] Immediately after treadmill exercise, neither study found a significant difference in ease of expectoration (Figure 4a). After a 20 minute recovery period however, there was improvement in ease of expectoration with treadmill exercise compared to rest in one study (Figure 4b). Similarly, the study (n = 14 participants) comparing cycle ergometer exercise to rest found no significant

difference in ease of expectoration immediately post exercise, however there was a significant improvement in ease of expectoration after a subsequent 20 minute rest period in favour of exercise (MD 2.0cm, [0.2 to 3.8]) (Figure 4a and 4b).[17]

No studies reported participant preference for exercise versus rest. Two studies (n = 39 participants) measured adverse events, with both finding no adverse events in either the exercise (treadmill) or rest groups.[18, 20]

Exercise vs ACT

Primary outcomes

Five studies were identified that reported on the effect of exercise compared to traditional ACTs on respiratory function (Figure 5).[18, 23-25, 27] Due to differences in exercise and traditional ACT regimens and limited published data provided in some study reports, meta-analyses were not possible. One study (n = 12 participants) noted that cycle ergometry resulted in an increase in lung clearance index (LCI) which was not seen with PEP but did not provide data.[25] These authors also reported no significant difference between cycle ergometry and PEP for FVC, FEV_1, FRC, TLC, MEF_{25}, MEF_{50} and RV without providing data. Another study (n = 18 participants) comparing cycle ergometry to ACBT reported that exercise resulted in an immediate increase in FEV_1 post exercise ($p < 0.05$), with no change in FVC or FEV_1 for either intervention at 30 minutes post treatment but did not provide the data.[23] In another study (n = 32 participants), mixed exercise improved $ppFEV_1$ compared to modified ACBT (MD 3 [0 to 6]%) when measured after a 40 minute recovery period.[27] Both the exercise and traditional ACT groups performed the FET. The only study (n = 17 participants) to compare exercise (cycle ergometry) to a traditional ACT (PD with P&V) for longer than a single session of each intervention (a two week hospitalisation period) found no significant difference between interventions for the mean change in percent predicted FVC (14.6% vs 22.4%), FEV_1 (11.3% vs 18.4%), FEF_{25-75} (4.1% vs 9.6%) or FRC (-19.4% vs -10.1%).[24] The quality of the evidence (GRADE) for FVC and FEF_{25-75} were both assessed as being very low due to imprecision and unclear blinding and allocation concealment. The quality of the evidence (GRADE) for FEV_1 was assessed as being low due to unclear blinding and imprecision.

Peak expiratory flow and PEF:PIF bias were compared between treadmill exercise and the Flutter® in one study (n = 24 participants).[18] No significant difference between treadmill and Flutter® was found for PEF (Figure 5d). Whilst not included in the original study report, a paired samples t-test of the raw data provided in a supplement by the study authors for PEF:PIF revealed a significant difference in favour of the Flutter® (Figure 5e).[18] The

quality of the evidence (GRADE) for both PEF and PEF:PIF was assessed as being moderate due to indirectness.

No studies comparing exercise and ACT reported HRQOL or respiratory exacerbation rates.

Secondary outcomes

Two studies (n = 24 participants) investigated the effect of exercise compared to traditional ACTs on MCC.[20, 26] There was a trend towards lower MCC following cycle ergometry, when compared to PEP and PD with thoracic expansion exercises, but this did not reach statistical significance (n = 9 participants).[26] The FET was included with both the exercise and traditional ACT interventions. In another study (n = 15 participants) that compared treadmill exercise to PEP, treadmill exercise resulted in significantly less overall MCC.[20] Mucus clearance from the peripheral and intermediate regions were similar between interventions, with the central region displaying greater clearance with PEP compared to treadmill. Importantly, the PEP intervention included the use of FET, whilst the treadmill intervention did not.[20]

No studies reported on the relative effects of exercise compared to traditional ACTs on ventilation scans.

Sputum weight was measured in six studies.[21-25, 27] Four studies (n = 75 participants) reported no significant difference between exercise and traditional ACT. [21, 22, 24, 27] One of these studies (n = 32 participants) however did report a non-significant trend favouring more sputum being produced with exercise (MD 0.6 [-0.2 to 1.4]g), with this study being the only study to include huffing/FET during the exercise intervention.[27] Two studies (n = 30 participants) found that exercise produced significantly less sputum during the intervention period compared to traditional ACT.[23, 25] Both of these studies included FET in the ACT intervention but not the exercise intervention. These two studies reported no significant difference in the weight of sputum expectorated during the post-intervention follow-up period (15 minutes in one study and 23 hours in the other).

There was no significant difference in change in ease of expectoration between treadmill and Flutter®, either during the intervention or recovery (1 study, n = 24 participants).[18]. Patient preference was reported in one study (n = 18 participants) however the design and reporting method means a direct comparison of exercise to traditional ACT could not be made.[23]

Adverse events were reported by four studies (n = 89 participants).[18, 20, 23, 27] Two studies (n = 39 participants), which compared treadmill to either Flutter® or PEP reported no adverse events.[18, 20] No adverse effects on heart rate or oxygen saturation during exercise were reported in another study (n = 18 participants) however the authors did not comment on any adverse events in the ACT group (ACBT with PD).[23] One study (n = 32 participants) reported four adverse events in the exercise group (mixed exercise) compared to one in the traditional ACT group (modified ACBT) however this did not reach statistical significance (relative risk [95%CI] = 4.00 [0.47-33.86]).[27] The adverse events reported were fatigue, breathlessness and oxygen desaturation (SpO_2 < 92%) which resolved rapidly with interruption of the intervention.[27] The authors did not specify which events occurred with each intervention.

DISCUSSION

The aim of this systematic review was to examine the evidence for exercise as a substitute for traditional ACTs in people with CF. The review identified 12 studies comparing exercise to either rest or traditional ACTs. The studies were of short duration and heterogeneous in design. When compared to rest, exercise increased PEF, improved MCC and increased the ease of expectoration. The evidence comparing exercise to traditional ACTs was mixed, which may reflect variability in the use of huffing/FET during the exercise routine.

Compared to rest, both cycling and treadmill exercise significantly increased PEF, with the PEF being in excess of the 30-60L/min that is proposed as the minimum expiratory flow required for cephalad secretion movement.[17, 18, 31] Whilst these findings support the physiological rationale for exercise as a potential ACT substitute, the PEF:PIF for both treadmill exercise and cycling did not exceed the proposed PEF bias of >1.1. The implications of not achieving this bias are unclear as not all traditional ACTs achieve this.[31] Meta-analysis also found that ease of expectoration was improved by treadmill exercise when compared to rest. Interestingly, this improvement was not evident immediately post-intervention but occurred after a 20 minute recovery period. The single study comparing ease of expectoration between cycle ergometry and rest also found an improvement in ease of expectoration 20 minutes after exercise but not immediately after.[17] The differences in ease of expectoration that were documented (mean differences ≥1.4cm) may be clinically meaningful. Whilst the cause of the delayed response in ease of expectoration is unclear, it is potentially an important finding for clinical practice in that patients should be counselled that changes in ease of expectoration associated with exercise may not occur immediately post exercise when judging its effectiveness as a substitute for traditional ACTs.

Based on the results of this review, it is possible that in the short term, exercise may have a similar effect as traditional ACTs on FVC, FEV_1 and FEF_{25-75}.[23-25, 27] These findings provide equipoise for exploring the effectiveness of exercise as a substitute for traditional ACTs over the medium to longer term in parallel-group randomised controlled trials. Whilst assessment of respiratory function in such a study would likely include FEV_1, there is potentially a role for the use of other outcomes, such as LCI, which may be more sensitive to change. The effect of substituting exercise for traditional ACTs on respiratory exacerbation rates, HRQOL, treatment burden and adherence with the overall treatment regimen needs to be further investigated. The design of future trials comparing exercise with traditional ACTs should consider whether huffing/FET is incorporated as part of the exercise regimen, as this may be a key determinant of outcome. The one study including huffing/FET in both the exercise and traditional ACT groups found no significant difference between the interventions in sputum weight.[27] Conversely, the two studies which found in favour of traditional ACTs both incorporated huffing/FET as part of the ACT regimen but not the exercise regimen.[23, 25] Findings were similar for MCC.[20, 26] It is unclear if the difference in MCC found in the study favouring traditional ACT over exercise was clinically meaningful as there are no published data indicating a minimal important difference for MCC.[20] Likewise, it is unclear if the higher sputum weight achieved with ACBT compared to cycling is of clinical importance given the lack of data for a minimum important difference for sputum weight.[23] These findings suggest that if exercise is to be used as a substitute for traditional ACTs, huffing/FET should also be included as part of the exercise regimen.[31] Several, but not all, current clinical guidelines make reference to including huffing/FET when exercise is used to promote secretion clearance, and the evidence from this review would support this being included as a recommendation in future clinical guidelines.[1, 2, 32, 33]

There were several limitations to this review. A lack of detail in some included studies limited the ability to determine the risk of bias. It is possible that publication bias could have affected the conclusions of the review if negative studies were not published, however the inclusion of studies reported only in abstract form may have mitigated this risk. We were unable to formally assess publication bias using funnel plots due to the small number of included studies for each comparison. The study designs were heterogeneous, with a wide variety of exercise and traditional ACT interventions and studies recruited a mixture of adult and paediatric patients, all of which may affect interpretation of the results. Combined with minimal data provided by some studies, the ability to perform meta-analyses was limited and where undertaken, the results should be interpreted in the context of only two included studies. The majority of studies were of short duration, hence it is not possible to make any conclusions on the medium to long term effects of exercise versus traditional ACTs. All of

the studies had small sample sizes (n ≤ 32) and were likely underpowered, so small differences between exercise and ACTs cannot be excluded.

Whilst longer term studies comparing exercise alone to traditional ACTs as a form of airway clearance are required, there are unique considerations that will need to be accommodated in the clinical trial design. Firstly, exercise is likely to have multiple benefits for people with CF beyond just improving airway clearance. Exercise improves aerobic capacity and higher aerobic capacity has been linked to improve survival in CF.[4, 12] Exercise is therefore likely to remain a component of the CF treatment regimen into the foreseeable future, even in the age of modulator therapy. There would be ethical concerns around withholding exercise from the ACT group in a true exercise versus traditional ACT study due to the non-respiratory benefits of exercise.[34] Therefore it is likely that future studies will take the form of exercise versus ACT and exercise. Secondly, measuring adherence with both exercise and traditional ACTs will be important in future studies given the often poor adherence with these interventions. Electronic methods of objectively measuring adherence with both exercise/physical activity (e.g. activity monitors) and traditional ACTs (e.g. in-line devices to measure pressure and flow) are available and should be considered an essential component in any future studies investigating exercise as a substitute for traditional ACTs.[35, 36] The results of a feasibility trial investigating such a study design have been recently published and may provide the basis for a larger multi-centred trial.[37]

This systematic review found that, based on short-term studies, exercise may have a similar effect to traditional ACTs on respiratory function and may produce a similar weight of expectorated sputum when combined with huffing/FET. It also found that treadmill exercise improves the ease of sputum expectoration compared to rest. Longer duration studies are required to determine if exercise can be used as a substitute for traditional ACTs in the modern era of CF management.

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List of figures:

Figure 1: Flow of studies through the review

Figure 2: Risk of bias assessment for the 12 included studies

+ = low; - = high; ? = unclear;

Figure 3: Exercise versus rest - pulmonary function tests.

FVC: forced vital capacity (L); FEV_1: forced expiratory volume in one second (L); PEF: peak expiratory flow (L/sec); PEF:PIF: peak expiratory flow to peak inspiratory flow ratio

Figure 4: Exercise versus rest – ease of expectoration.

Mean difference in cm measured on a visual analogue scale

Figure 5: Exercise versus traditional airway clearance technique – pulmonary function tests

FVC: forced vital capacity (percent predicted); FEV_1: forced expiratory volume in one second (percent predicted); FEF_{25-75}: mean forced expiratory flow between 25-75% of FVC (percent predicted); PEF: peak expiratory flow (L/sec); PEF:PIF: peak expiratory flow to peak inspiratory flow ratio; ACBT: active cycle of breathing technique; ACT: airway clearance technique

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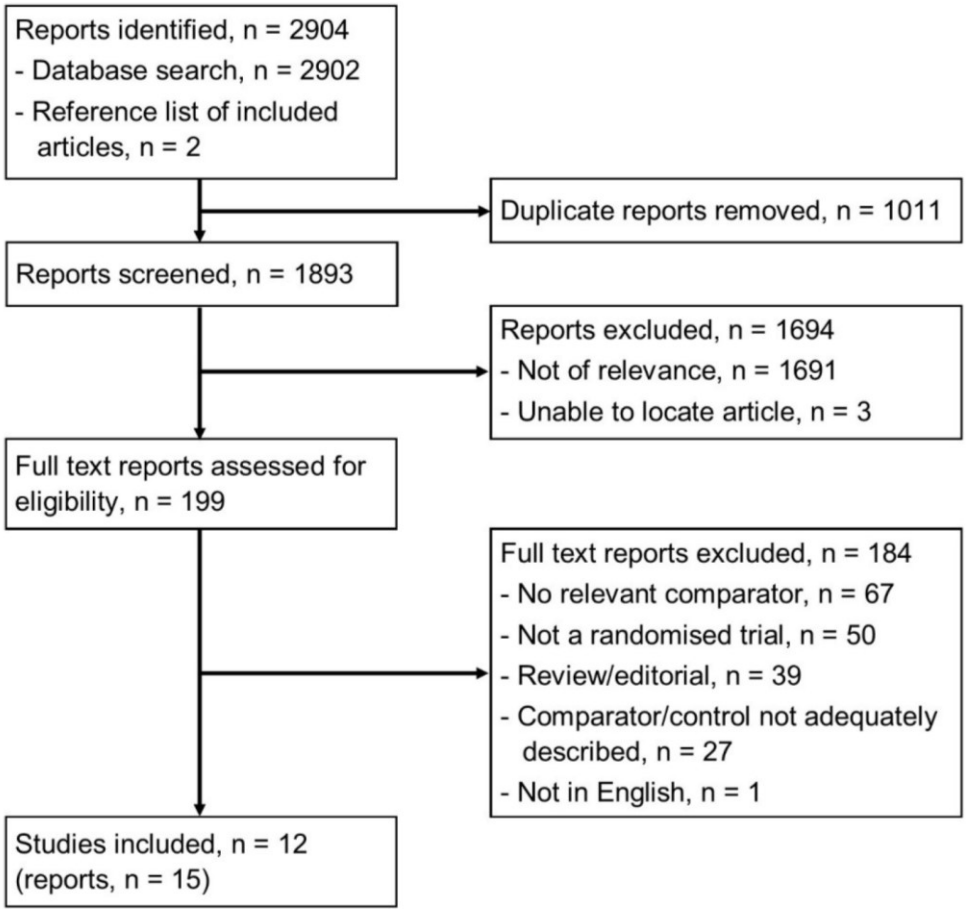
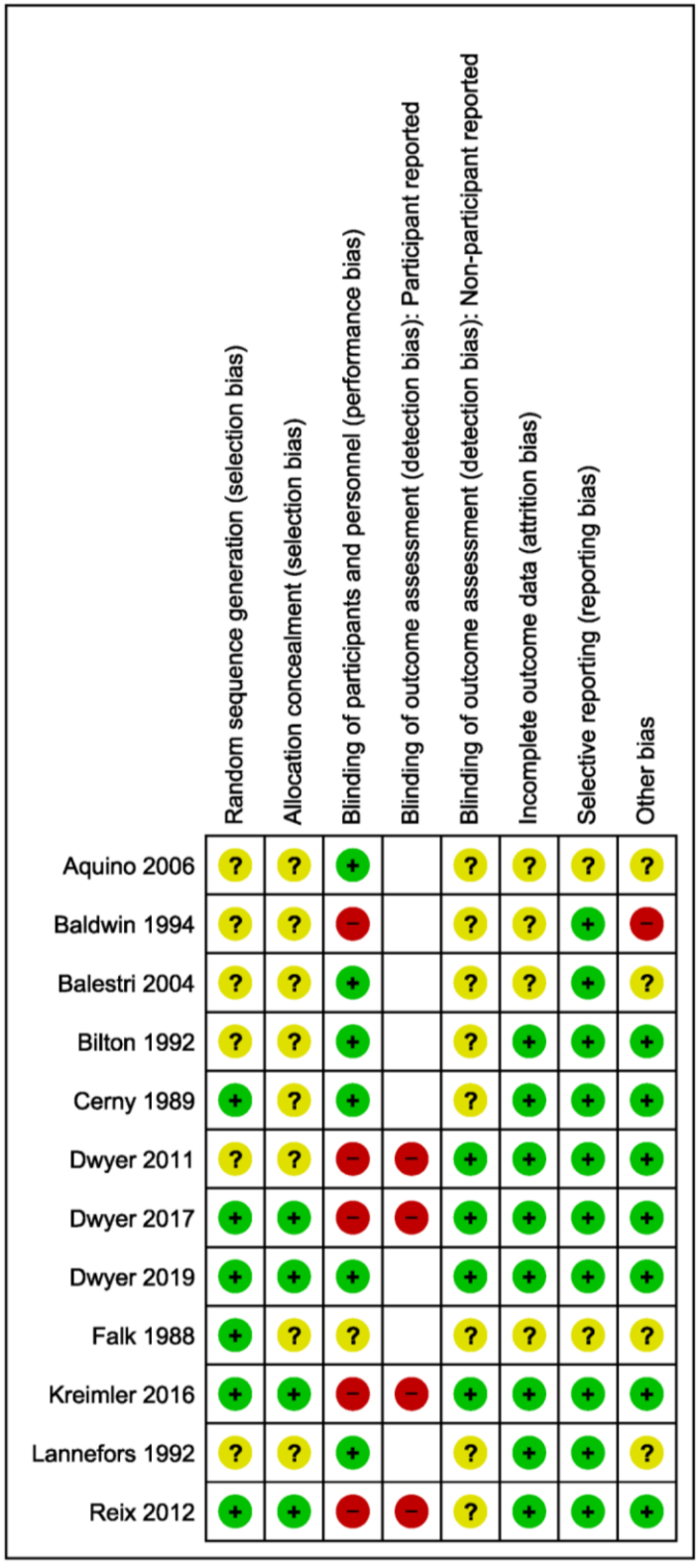


Figure 1: Flow of studies through the review



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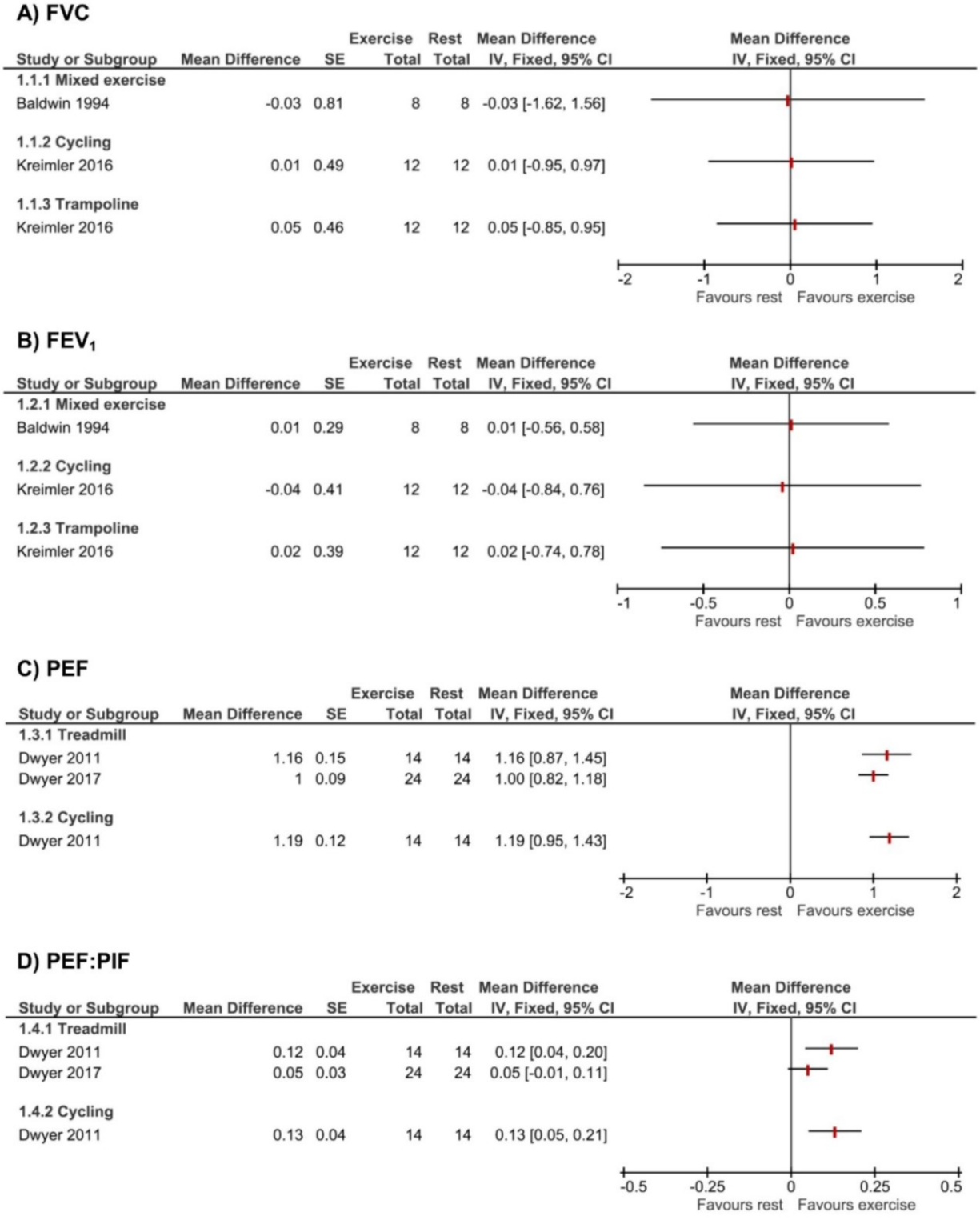
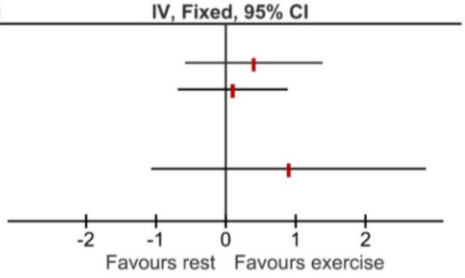


Figure 3: Exercise versus rest - pulmonary function tests. FVC: forced vital capacity (L); FEV_1: forced expiratory volume in one second (L); PEF: peak expiratory flow (L/sec); PEF:PIF: peak expiratory flow to peak inspiratory flow ratio.

A) Immediately post exercise

Study or Subgroup	Mean Difference	SE	Exercise Total	Rest Total	Mean Difference IV, Fixed, 95% CI
1.5.1 Treadmill					
Dwyer 2011	0.4	0.5	14	14	0.40 [-0.58, 1.38]
Dwyer 2017	0.1	0.4	24	24	0.10 [-0.68, 0.88]
1.5.2 Cycling					
Dwyer 2011	0.9	1	14	14	0.90 [-1.06, 2.86]



B) Post recovery

Study or Subgroup	Mean Difference	SE	Exercise Total	Rest Total	Mean Difference IV, Fixed, 95% CI
1.6.1 Treadmill					
Dwyer 2011	1.8	1.1	14	14	1.80 [-0.36, 3.96]
Dwyer 2017	1.3	0.5	24	24	1.30 [0.32, 2.28]
1.6.2 Cycling					
Dwyer 2011	2	0.9	14	0	2.00 [0.24, 3.76]

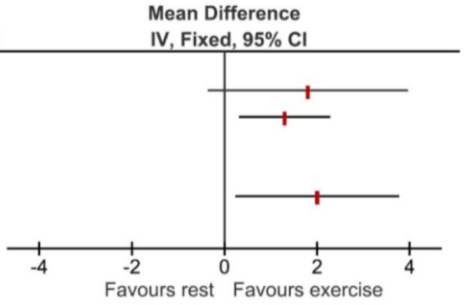
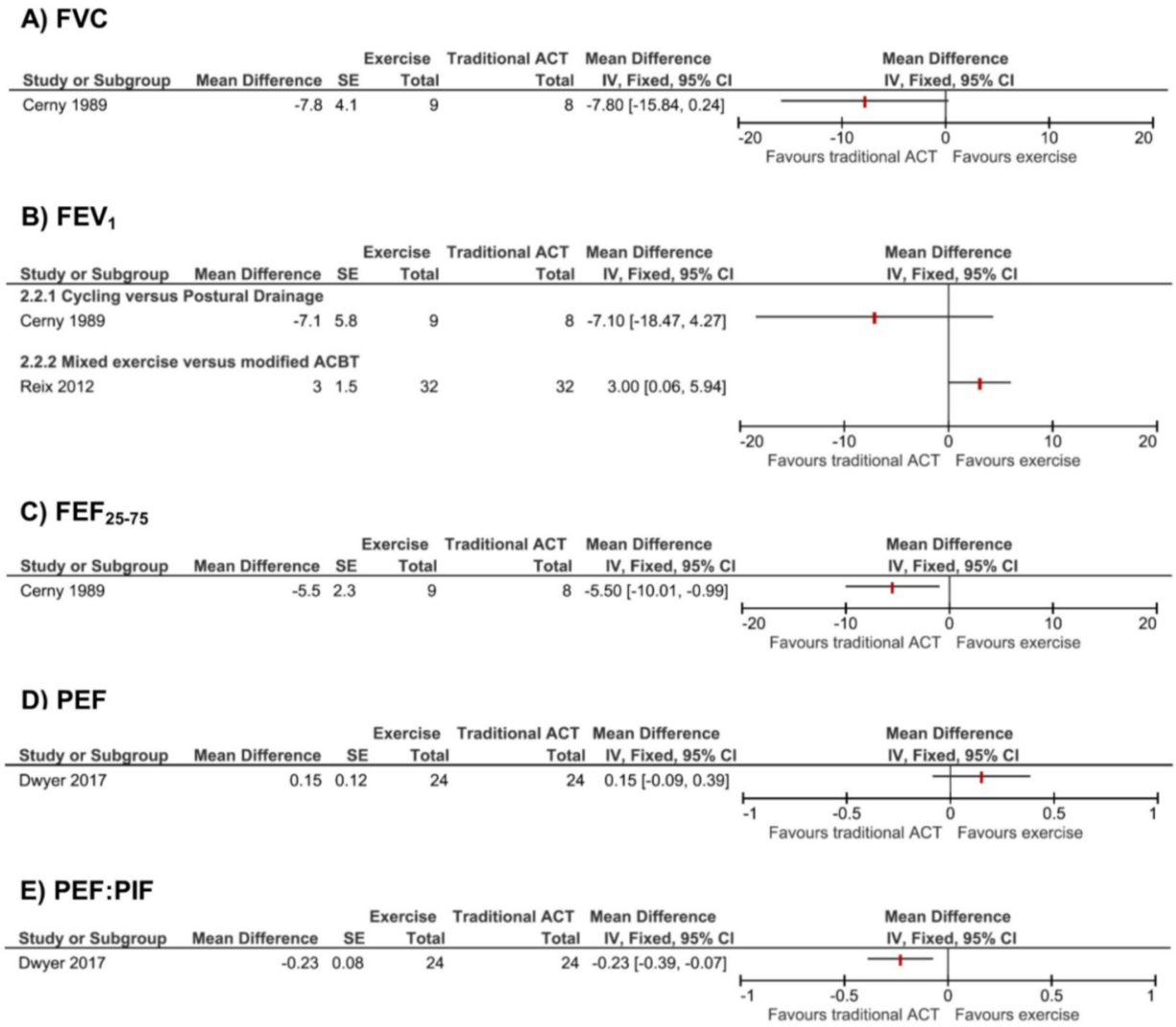


Figure 4: Exercise versus rest – ease of expectoration. Mean difference in cm measured on a visual analogue scale.



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CHAPTER 4: EXERCISE AND AIRWAY CLEARANCE PRACTICES OF ADULTS WITH CYSTIC FIBROSIS: CURRENT AUSTRALIAN PRACTICE.

Declaration of authorship – Chapter 4

The nature and extent of contributions to Chapter 4 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Study concept and protocol development, data collection and analysis, writing of manuscript and review	70%	
Kathy Stiller	Study concept and protocol development, review of manuscript	10%	
Anne Holland	Study concept and protocol development, review of manuscript	10%	
Australian Cystic Fibrosis Exercise Survey group	Review of protocol, data collection, review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 4 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

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Research

Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey

Nathan Ward [a,b], Kathy Stiller [c], Anne E Holland [b,d], and the Australian Cystic Fibrosis Exercise Survey group[1]

[a] Cystic Fibrosis Service, Royal Adelaide Hospital; [b] Physiotherapy Department, School of Allied Health, La Trobe University, Melbourne; [c] Central Adelaide Local Health Network; [d] Physiotherapy, Alfred Health, Melbourne, Australia

KEY WORDS

Cystic fibrosis
Exercise
Physical therapy modalities
Respiratory therapy

ABSTRACT

Questions: What airway clearance techniques and exercise regimens are used by adults with cystic fibrosis (CF) in Australia when well or unwell? What proportion of these adults believe that exercise can be used as a substitute for traditional airway clearance techniques, and how have they come to this belief? What type of exercise is used as a substitute for traditional airway clearance techniques? **Design**: Cross-sectional survey at 13 CF centres in Australia, using a purpose-designed questionnaire. **Participants**: Six hundred and ninety-two adults with CF completed the questionnaire. **Outcome measures**: The questionnaire included questions about: the participants' current use of traditional airway clearance techniques and exercise, when well and unwell; and beliefs regarding the use of exercise as a substitute for traditional airway clearance techniques. **Results**: Coughing, huffing and positive expiratory pressure were the most commonly used airway clearance techniques. Walking, jogging and lifting weights were the most commonly used forms of exercise. Overall, 43% of participants believed that exercise could be used as a substitute for traditional airway clearance techniques, with 44% having substituted exercise for traditional airway clearance techniques in the previous 3 months. Personal experience was the most commonly reported factor influencing participants' beliefs about the use of exercise as a substitute for traditional airway clearance techniques. **Conclusion**: Exercise is commonly used as a substitute for traditional airway clearance techniques. Physiotherapists should advise patients that whilst there is some research suggesting a possible mechanism for exercise as a form of airway clearance, there are currently no medium-term to long-term data supporting exercise as a stand-alone form of airway clearance. These results suggest that future research to investigate the clinical effectiveness of exercise as a substitute for traditional airway clearance techniques should be a priority. **Registration**: ACTRN12616000994482. **[Ward N, Stiller K, Holland AE, and the Australian Cystic Fibrosis Exercise Survey group (2019) Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey. *Journal of Physiotherapy* 65:43–50]**

Introduction

Survival among people with cystic fibrosis (CF) has improved over the last few decades, largely due to an increase in the range of treatment options. As a result, there has been a rise in the complexity and time-burden of clinical care and self-management. As with any complex treatment regimen for any chronic disease, it is well recognised that treatment adherence varies widely between individuals with CF.[1–4]

There are now more adults with CF who have mild respiratory disease than ever before, with approximately 42% of adult males and 44% of adult females with CF in Australia having normal or only mildly impaired lung function, defined as forced expiratory volume in one second (FEV_1) > 70% predicted.[5] Historically, people with CF have been advised to perform airway clearance techniques on a daily basis to aid the clearance of thick respiratory secretions. Exercise is also routinely recommended due to its beneficial effects on aerobic exercise capacity, muscle strength, bone mineral density and mental health.[6] Current international guidelines either recommend exercise as an adjunct to, but not a replacement for, traditional airway

[1] Jenn Bingham, Royal Hobart Hospital; Jennifer Bishop, Westmead Hospital, Sydney; Brenda Button, The Alfred Hospital and Monash University, Melbourne; Rebecca Chambers, The Prince Charles Hospital, Brisbane; Clare Chung, Gosford Hospital; Robyn Cobb, The Prince Charles Hospital, Brisbane; Jennifer Corda, Monash Medical Centre, Melbourne; Ruth Dentice, Royal Prince Alfred Hospital, Sydney; Margot Green, Canberra Hospital; Kathleen Hall, The Prince Charles Hospital, Brisbane; Jenny Hauser, Royal Hobart Hospital; Scott Morrow, Royal Adelaide Hospital; Rebecca Netluch, John Hunter Hospital, Newcastle; Amanda Nichols, Monash Medical Centre, Melbourne; Hilary Rowe, Royal Adelaide Hospital; Andrew Shaw, Gold Coast University Hospital; Danielle Shortall, Mater Hospital Brisbane; Tara Smith, John Hunter Hospital, Newcastle; Jamie Wood, Sir Charles Gairdner Hospital, Perth, Australia.

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clearance techniques, or do not mention exercise in relation to airway clearance.[7–9]

It is well documented that people with CF have lower adherence to traditional airway clearance techniques than other therapies, with daily adherence as low as 40%.[2,3] There are many reasons for non-adherence with airway clearance techniques, including a sense of feeling well without performing airway clearance techniques, insufficient time, and the perceived effort and energy required.[1] Previous studies have reported that some patients (4 to 80%) consider exercise as a form of airway clearance or that exercising regularly means that they do not need to perform traditional airway clearance techniques.[1,2,10–13] The nature of exercise (type, frequency, duration and intensity) that people with CF do when exercising as a form of airway clearance has yet to be documented. This information would be of value as it would help to inform the exercise prescription chosen for any future studies investigating exercise as a stand-alone airway clearance technique.[14]

The main aims of this study were to identify in adults with CF in Australia: current use of exercise and airway clearance techniques during well and unwell periods; whether exercise is used as a substitute for, or to enhance the effectiveness of, traditional airway clearance techniques; and how their beliefs regarding the use of exercise as a substitute for traditional airway clearance techniques were formed.

Therefore, the research questions for this cross-sectional survey were:

1. What airway clearance techniques and exercise regimens are used by adults with CF in Australia when well or unwell?
2. What proportion of these adults believe that exercise can be used as a substitute for traditional airway clearance techniques, and how have they come to this belief?
3. What type of exercise is used as a substitute for traditional airway clearance techniques?

Method

Design

A multicentre cross-sectional survey was undertaken. All centres that provide data about adults with CF to the Australian Cystic Fibrosis Data registry participated. Recruitment was open at each centre for 3 months, with all centres commencing recruitment between February and May 2017. Consecutive patients attending for care during the recruitment period were screened for eligibility by the investigators at each site. Participants provided informed consent prior to completing the questionnaire independently.

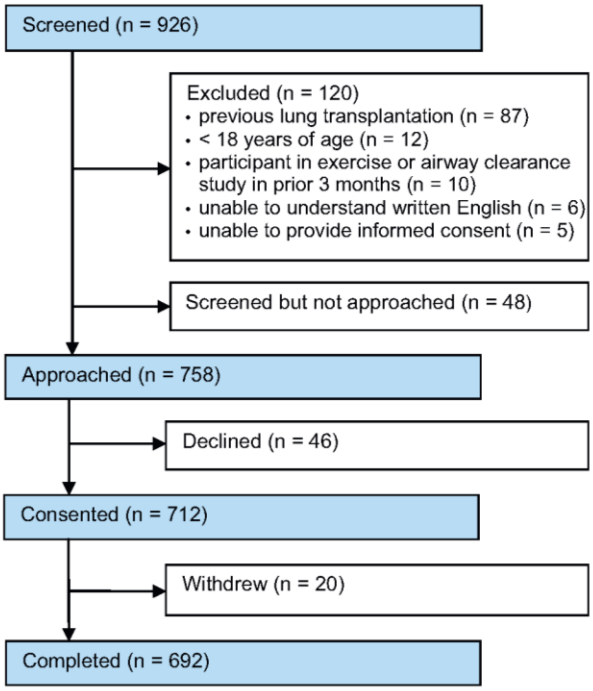

Figure 1. Flow of participants through the study.

Table 1
Characteristics of the participants.

Characteristics	Participants (n = 692)
Age *(yr)*, mean (SD)	31 (11)
Gender, n male (%)[a]	395 (57)
Body mass index *(kg/m²)*, mean (SD)[b]	22.8 (3.6)
Most recent FEV_1 *(l)*, mean (SD)[b]	2.40 (1.05)
Most recent FEV_1 *(% predicted)*, mean (SD)[c]	63 (23)
Best FEV_1 in the past year *(l)*, mean (SD)	2.62 (1.06)
Best FEV_1 in the past year *(% predicted)*, mean (SD)[d]	69 (23)
Lung disease/symptoms visual analogue scale *(0 to 10)*, mean (SD)	3.8 (2.5)
Sputum volume visual analogue scale *(0 to 10)*, mean (SD)[b]	3.4 (2.2)
Pseudomonas aeruginosa, n (%)[c]	513 (74)
Using dornase alfa, n (%)	435 (63)
Using nebulised saline, n (%)	451 (65)
6.0%	294 (42)
3.0%	78 (11)
0.9%	49 (7)
Antibiotics for respiratory exacerbation in past 3 months, n (%)[d,e]	495 (72)
intravenous	232 (34)
inhaled	312 (45)
oral	377 (55)
Social situation, n (%)[b]	
living with parent(s)	222 (32)
living with partner/spouse with no dependent children	206 (30)
living with partner/spouse and dependent children	140 (20)
living alone	54 (8)
living with friend(s)	46 (7)
living with dependent child/children	5 (1)
other	18 (3)
Employment, n (%)	
working or studying full time	328 (47)
working or studying part time	131 (19)
disability pensioner	90 (13)
disability pensioner and working part time	48 (7)
unemployed	34 (5)
stay-at-home parent	23 (3)
other	38 (5)

[a] n = 689.
[b] n = 691.
[c] n = 690.
[d] n = 688.
[e] Participants were able to select multiple options if applicable.

Participants

The inclusion criteria were: age ≥ 18 years, diagnosis of CF, and attendance at the participating adult CF centre. Exclusion criteria

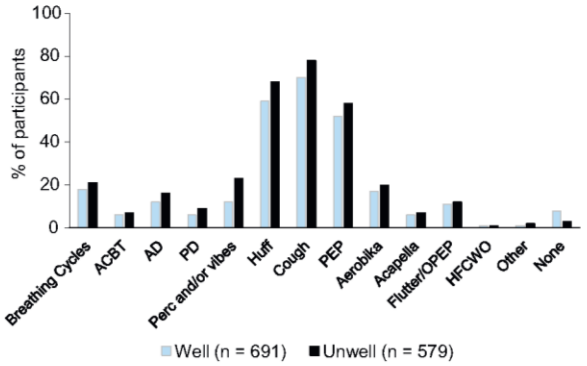

Figure 2. Airway clearance techniques reportedly used over the preceding 3 months for all participants when well and unwell.
ACBT = Active Cycle of Breathing Technique, AD = autogenic drainage, PD = postural drainage, Perc and vibes = percussion and/or vibrations, PEP = positive expiratory pressure, OPEP = oscillating positive expiratory pressure, HFCWO = high-frequency chest wall oscillation.

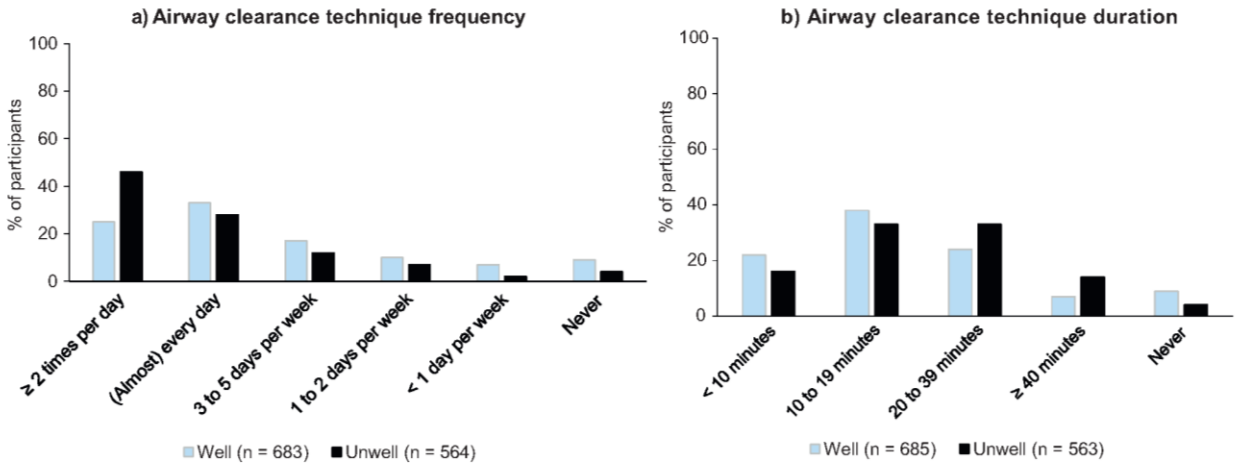

Figure 3. Reported (a) frequency and (b) duration of airway clearance techniques for all participants when well and unwell over the preceding 3 months.

were: inability to provide informed consent; being critically unwell or receiving end-of-life care; inability to understand written English; previous lung transplantation; or participation in an interventional study of exercise or an airway clearance technique in the previous 3 months.

Outcome measures

A purpose-designed questionnaire was developed by the investigators. The draft questionnaire underwent several rounds of pilot testing, with two to three young adults with CF involved in each round. The feedback on the questionnaire's clarity, ease of completion and content was used to make further refinements. The final questionnaire comprised seven sections. The participant completed six sections, which elicited: demographic data; symptom severity; current airway clearance techniques and exercise use during both well and unwell periods; and beliefs and practices regarding exercise as a form of airway clearance. Perceived severity of lung disease/symptoms was marked on a 10-cm visual analogue scale ranging from 0 'not severe at all' to 10 'extremely severe'. Estimated daily sputum volume was marked on a similar scale from 0 'no sputum' to 10 'extreme amount'. After this, the site investigator checked for missed questions and then entered the participant's clinical data in the seventh section. The full questionnaire is available in Appendix 1 on the eAddenda.

Data analysis

The raw data were entered into an electronic spreadsheet[a] for data cleaning prior to importing into statistical software[b] for analysis. Demographic data were summarised with descriptive statistics. Responses about the types of airway clearance techniques and exercise used were summarised as number (%) of respondents. Responses about the frequency and duration of those regimens have been categorised and then also reported as number (%) of respondents. For the questions examining airway clearance techniques and exercise regimens when participants had been unwell, percentages were calculated based on the number of participants indicating that they had been unwell in the preceding 3 months, as elicited by the questionnaire. Participants' beliefs were grouped into the following categories for analysis: agreed/strongly agreed, neutral, and disagreed/strongly disagreed. Correlations were determined using either Pearson's or Spearman's correlations depending on normality of the data distribution. T-tests and ANOVAs were used to determine differences between groups. Categorical data were analysed using Chi-square and Tukey post-hoc comparisons. Significance was determined as $p < 0.05$.

Results

Compliance with the study protocol

Of the 806 eligible patients screened, 758 were approached regarding participation. The remaining 48 (6%) eligible patients were not approached due to the competing clinical requirements of the investigators, meaning that these patients left their appointments prior to being approached regarding study participation.

Flow of participants through the study

Figure 1 summarises the flow of participants through the study. One hundred and twenty patients were excluded, most often because they had undergone a lung transplant. Of the 758 patients approached for participation in the study, 712 provided informed consent, with 692 completing the questionnaire (completion rate = 91%). Twenty patients chose to withdraw after consenting to participate.

Characteristics of the participants

The characteristics of the participants are summarised in Table 1. Based on the most recent spirometry, 127 (18%) participants had severe lung disease (FEV_1 < 40% of predicted), 278 (40%) had moderate lung disease (FEV_1 = 40 to 69% of predicted), 190 (27%) had mild lung disease (FEV_1 = 70 to 89% of predicted), and 95 (14%) had normal lung function ($FEV_1 \geq 90\%$ of predicted).

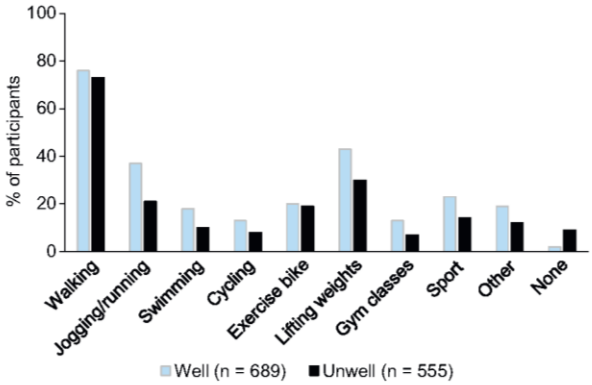

Figure 4. Reported exercise types for all participants when well and unwell over the preceding 3 months.

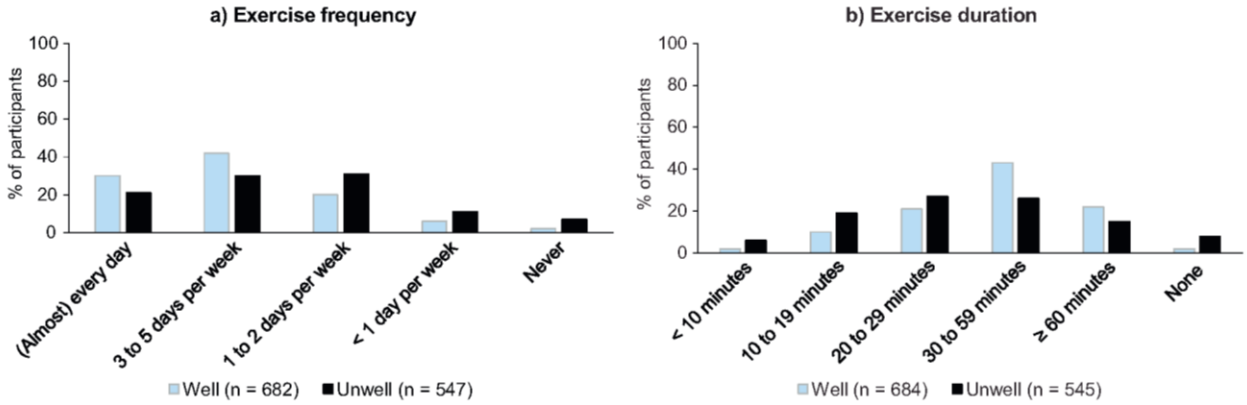

Figure 5. Reported (a) frequency and (b) duration of exercise for all participants when well and unwell over the preceding 3 months.

Airway clearance techniques and exercise regimens

The most commonly used airway clearance techniques were coughing, huffing and positive expiratory pressure during both well and unwell periods (Figure 2). A total of 396 (58%) participants were performing an airway clearance technique most days when well (Figure 3). Walking, lifting weights and jogging/running were the most commonly reported forms of exercise performed when well and unwell (Figure 4). The majority of participants reported using more than one form of exercise when both well and unwell: 546 (79%) when well and 315 (57%) when unwell. The recommended frequency of exercising (ie, at least three times per week)[15] was achieved by 490 (72%) of participants when they were well, with exercise duration most often 30 to 59 minutes (n = 293, 43%) (Figure 5). Reduced chest congestion and less coughing were the most commonly reported benefits for both airway clearance techniques and exercise (Table 2). The use of huffing to clear respiratory secretions during exercise was reported by 371 (54%) participants, with 218 (61%) only doing so when they felt the need. See Appendix 2 on the eAddena for further analyses of airway clearance techniques and exercise practices, the perceived benefits, and the use of huffing during exercise.

Table 2
Participant-reported respiratory symptom benefits from performing airway clearance techniques and exercise over the preceding 3 months.

Reported benefits	Airway clearance techniques (n = 691)	Exercise (n = 682)
Identified respiratory symptom benefits, n yes (%)		
yes	574 (83)	533 (78)
no	73 (11)	130 (19)
not applicable	44 (6)	19 (3)
Symptom benefits, n (%)		
less coughing	318 (46)	272 (40)
less chest congestion	405 (59)	355 (52)
less likely to cough up sputum	227 (33)	170 (25)
less short of breath	223 (32)	223 (33)
less chest pain	61 (9)	74 (11)
less chest tightness	211 (31)	212 (31)
less wheeze	178 (26)	136 (20)
other	26 (4)	60 (9)
Time to onset, n (%)		
within a few minutes of starting	89 (13)	66 (10)
by end of treatment	224 (32)	189 (28)
within 30 minutes of finishing	157 (23)	143 (21)
> 30 minutes after finishing	61 (9)	80 (12)
other	13 (2)	13 (2)
unsure	13 (2)	23 (3)
Duration of benefits, n (%)		
< 30 minutes	10 (1)	6 (1)
30 to 59 minutes	16 (2)	21 (3)
1 to 2 hours	74 (11)	71 (10)
3 to 12 hours	263 (38)	201 (29)
> 12 hours	87 (13)	127 (19)
unsure	103 (15)	95 (14)

Beliefs about exercise and its relationship to airway clearance

Almost half of the participants (n = 296, 43%) agreed or strongly agreed that exercise could be used as a substitute for traditional airway clearance techniques, and 456 (66%) participants believed that exercising before or during traditional airway clearance techniques could enhance their effectiveness (Figure 6). The most commonly reported reasons underlying participants' beliefs about exercise and its role in airway clearance were: personal experience (n = 584, 85%), advice from an unspecified health professional (n = 83, 12%), advice from physiotherapists (n = 51, 7%), and advice from doctors (n = 29, 4%). Multiple reasons for their beliefs were provided by 144 (21%) participants. Tukey post-hoc analysis (Table 3) revealed that participants who agreed/strongly agreed that exercise could be used as a substitute for traditional airway clearance techniques had significantly higher FEV_1 % predicted (mean 68%, SD 23) than those who were neutral (62%, SD 22) or disagreed/strongly disagreed (58%, SD 23), $p < 0.049$. Those who disagreed/strongly disagreed had a significantly higher perceived daily sputum volume (mean 4.0, SD 2.0) than those who were neutral (3.2, SD 2.2) or agreed/strongly agreed (3.0, SD 2.2), $p < 0.001$.

A significant association was demonstrated between participants' beliefs about exercise being an alternative to traditional airway clearance techniques and the adoption of this in clinical practice. The proportion of participants who had used exercise as a substitute for traditional airway clearance techniques was higher in the agreed/strongly agreed group (68%) compared with the neutral group (42%) or the disagreed/strongly disagreed group (16%), $p < 0.001$. Participants who agreed/strongly agreed that exercise could enhance the effectiveness of traditional airway clearance techniques were more likely to have used exercise to improve the effectiveness of their traditional airway clearance techniques in the previous 3 months (68%) than those who were neutral (33%) or disagreed/strongly disagreed (47%), $p < 0.001$.

Use of exercise as a substitute or alternative to traditional airway clearance techniques

Three hundred (44%) participants reported having used exercise as a substitute for traditional airway clearance techniques over the past 3 months. Figure 7 presents the types, frequencies and durations of exercise reported by participants when using exercise as a substitute for traditional airway clearance techniques. Participants who reported using exercise as a substitute for traditional airway clearance techniques were asked to identify the single most effective form of exercise and, of the 174 participants who did so, 53 (30%) reported that jogging/running was the most effective, followed by sport

Figure 6. Participants' beliefs about exercise and its relationship to traditional airway clearance techniques, indicated by the degree of agreement with statements (a) and (b).

(n = 25, 14%), other (n = 20, 11%) and swimming and walking fast (each n = 17, 10%). When exercising as a substitute for traditional airway clearance techniques, the majority of participants reported exercising at moderate to strong perceived exertion intensity and experiencing moderate to severe shortness of breath (Table 4). When participants who used exercise as a substitute to traditional airway clearance techniques were unwell, 63 (21%) stopped using exercise as a substitute for traditional airway clearance techniques, 45 (15%) continued using exercise as their only airway clearance technique, and 187 (63%) continued using exercise as an alternative to traditional airway clearance techniques but also added in a traditional airway clearance technique whilst unwell.

Participants who reported using exercise as a substitute for traditional airway clearance techniques had: significantly higher FEV_1 % predicted (mean 68%, SD 22) than the other participants (60%, SD 24), $p < 0.001$; significantly lower perceived severity of respiratory disease (3.4 cm, SD 2.3) than the other participants (4.2 cm, SD 2.5), $p < 0.001$; and significantly lower sputum load (3.1 cm, SD 2.2) than other participants (3.6 cm, SD 2.2), $p = 0.002$. There was no association between the CF centre the participants attended and their use of exercise as a substitute for traditional airway clearance techniques ($p = 0.354$). The proportion of participants who reported not using any traditional airway clearance techniques when well was significantly higher in the subgroup that reported using exercise as a substitute for traditional airway clearance techniques (10% versus 6%, $p = 0.048$).

Exercise to improve the effectiveness of traditional airway clearance techniques

In the preceding 3 months, 394 (57%) participants reported using exercise to improve the effectiveness of their traditional airway clearance techniques, with 342 (87%) using more than one form of exercise (Figure 8). Participants were evenly divided between those who exercised before versus after airway clearance techniques: n = 106 (27%) and n = 107 (27%), respectively. There were 18 (5%) who reported exercising during their airway clearance techniques to improve the techniques' effectiveness. Despite this, 144 (37%) reported exercising at a time unrelated to their airway clearance techniques and 19 (5%) did not indicate when they exercised in relation to the techniques. The majority of participants reported exerting themselves moderately to strongly when using exercise to improve airway clearance effectiveness (Table 5).

Table 3
Relationship of disease characteristics to beliefs about using exercise as a substitute for traditional airway clearance techniques.

Disease severity marker	Belief about whether exercise can substitute for traditional airway clearance techniques	Mean (SD)
FEV_1 *(% predicted)*	disagree/strongly disagree	58 (23)
	neutral	62 (22)
	agree/strongly agree	68 (23)[a]
Participant-perceived severity *(0 to 10)*	disagree/strongly disagree	4.4 (2.4)
	neutral	3.8 (2.4)
	agree/strongly agree	3.3 (2.5)
Participant-perceived sputum volume *(0 to 10)*	disagree/strongly disagree	4.0 (2.0)[a]
	neutral	3.2 (2.2)
	agree/strongly agree	3.0 (2.2)

[a] Significant difference ($p < 0.05$) when compared to the 'neutral' respondents.

Discussion

This is the first study that has investigated the airway clearance techniques and exercise practices of adults with CF across Australia. It is also believed to be the first multicentre study to carry out an in-depth investigation of the current practices of adults with CF regarding the use of exercise as a substitute for traditional airway clearance techniques. It was found that 43% of participants believed that exercise could be used as a substitute for traditional airway clearance techniques and 44% of participants had used exercise as a substitute for such techniques in the preceding 3 months.

The proportion of participants reporting using exercise as a substitute for traditional airway clearance techniques in this study is much higher than that reported in the majority of previous studies, where rates have generally been < 30%.[1,2,10,13,16] Current international guidelines recommend exercise as an adjunct to traditional airway clearance techniques or do not mention exercise in relation to them.[8,9,15] Whilst several short-term studies provide a potential physiological rationale for using exercise as a form of secretion clearance, to date there is no medium-term to long-term evidence supporting the clinical efficacy of such practice.[17–19] Given that nearly half of the participants in this study were already choosing to substitute exercise for traditional airway clearance techniques, further research investigating the clinical efficacy of exercising as a substitute for traditional airway clearance techniques over the medium to longer term should be considered a high priority.

Walking fast or jogging were the two most commonly reported types of exercise that participants used as a substitute for traditional airway clearance techniques. Whilst lacking medium-term to long-term data to support this practice, several short-term crossover trials have suggested that walking/jogging may have a role in promoting secretion clearance.[17,18,20] Walking/jogging may increase expiratory airflow and have a beneficial effect on sputum mechanical impedance.[17] Lifting weights was the third most commonly reported type of exercise used as a substitute for traditional airway clearance techniques in this study. We are unaware of any research investigating the effect of lifting weights on secretion clearance, and further investigation into the clinical effectiveness of this practice may be warranted.

Prior to the study it was anticipated that patients' beliefs and practices regarding the use of exercise as a substitute to traditional airway clearance techniques may have been influenced by the clinical advice imparted from their treating multidisciplinary team. However, the most common reason stated by participants for their beliefs about the suitability of exercise as a substitute for traditional airway

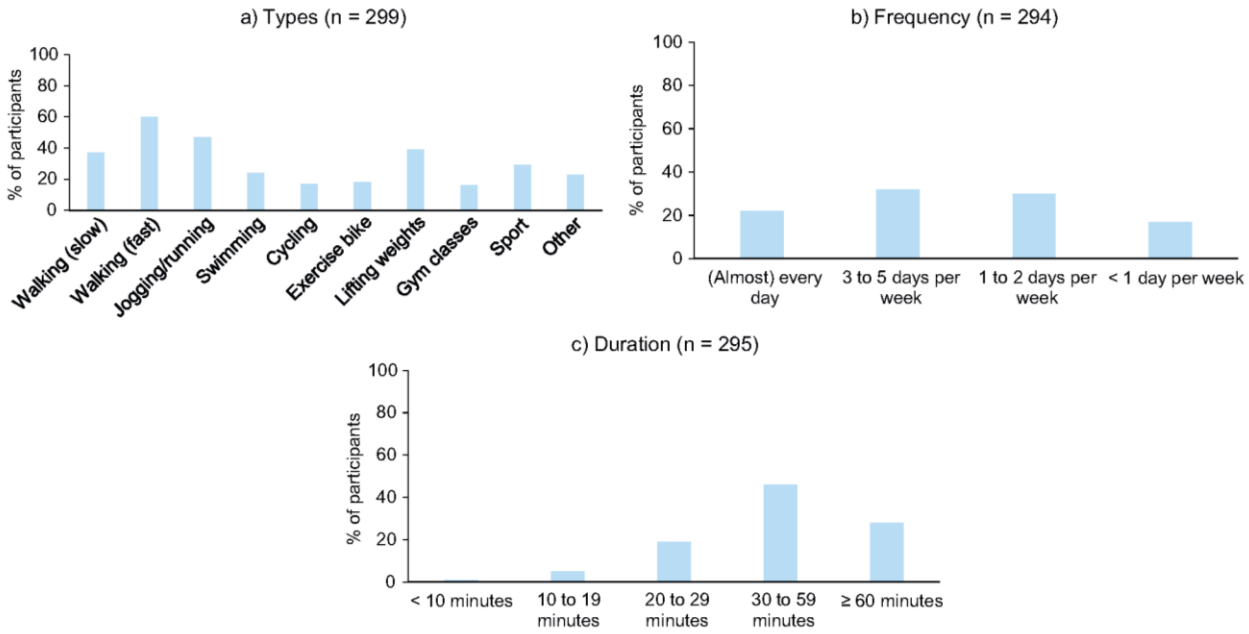

Figure 7. Reported exercise routines when exercising as a substitute for traditional airway clearance techniques: a) type of exercise, b) frequency and c) duration of exercise sessions.

clearance techniques was personal experience. These beliefs were widespread across Australia and independent of the CF centre that the participant attended. Given that a sizeable cohort of patients are already choosing to use walking/jogging as a substitute for traditional techniques based on personal experience and in view of the physiological data suggesting a potential mechanism of action, it would seem appropriate that walking/jogging be the forms of exercise used for studies investigating the impact on clinical outcomes such as lung function and exacerbation rate.

The results of this study have several implications for clinical practice. It is evident from this study that a large number of people with CF are choosing to use exercise as a substitute for traditional airway clearance techniques, based largely on their personal experience. Therefore, when prescribing new exercise regimens to people with CF, in addition to outlining the non-respiratory benefits of exercise (eg, muscle strength, bone mineral density), clinicians should also advise patients that whilst there is some research suggesting a possible mechanism for exercise as a form of airway clearance, there are currently no medium-term to long-term data supporting exercise as a stand-alone form of airway clearance. Similarly, when reviewing an individual's current exercise regimen, specific questioning should occur to determine if the individual is using exercise as a substitute for airway clearance techniques, and if so, further education should be provided by the clinician regarding the evidence for this practice. When a person chooses to use exercise as a substitute for airway clearance techniques when well, clinicians should also take the time to discuss that he/she may need to use traditional airway clearance techniques when unwell to improve airway clearance.

Another clinical implication relates to the finding that personal experience of participants was such a dominant driver of their decision-making. A total of 7% of participants reported that advice from a physiotherapist was a basis for their beliefs, as opposed to 85% who cited personal experience. This finding highlights that clinicians should take the time to explore a patient's beliefs and personal experience as part of the process for prescribing new or modified exercise and airway clearance techniques regimens. Despite this study relying on participant self-report, which may have overestimated adherence, a notable number of participants were not achieving the current recommended frequency of airway clearance techniques and exercise. Whilst clinicians consider longer term outcomes, such as rate of lung function decline and respiratory exacerbation rates, to be highly important when prescribing airway clearance techniques and exercise, patients may consider outcomes with a more immediate benefit, such as reducing the time burden of treatment or immediate symptom relief, as being more important when deciding on their therapeutic regimen. However, there are no studies demonstrating the outcomes that people with CF value most highly. It is clear from this study that clinicians should explore a patient's underlying beliefs, values and previous personal experience regarding airway clearance techniques and exercise in order for the treatment regimen to be optimised to achieve both short-term (eg, reduced time burden, immediate symptom relief) and long-term term goals (eg, reduced rate of decline in lung function) for both the patient and the clinician.

This study had several limitations. First, whilst the protocol was for consecutive recruitment, 6% of screened patients were not invited to participate, as they left their appointment prior to being approached, due to the competing clinical demands of the investigators. This was unlikely to be related to the patients' clinical status or use of airway clearance techniques or exercise. Second, the study relied upon participants' self-reporting and, given that patients with CF may overstate their level of adherence, the data presented may represent an over-estimation.[21] Third, as with most questionnaire-based studies, there was a variable degree of missing data. However, given the relatively small amount of missing data for any one individual question relative to the total sample size, it is felt that missing data were unlikely to have made a large impact on the results and conclusions from this study. Finally, as this study only

Table 4
Shortness of breath and perceived exertion reported by participants who used exercise as a substitute for traditional airway clearance techniques.

Perceived exercise intensity	n (%)
Shortness of breath[a]	
very, very slight to slight	122 (42)
moderate to severe	158 (54)
very severe to maximal	12 (4)
Rating of perceived exertion[b]	
very, very weak to weak	11 (4)
moderate to strong	200 (67)
very strong to maximal	87 (29)

[a] n = 292.
[b] n = 298.

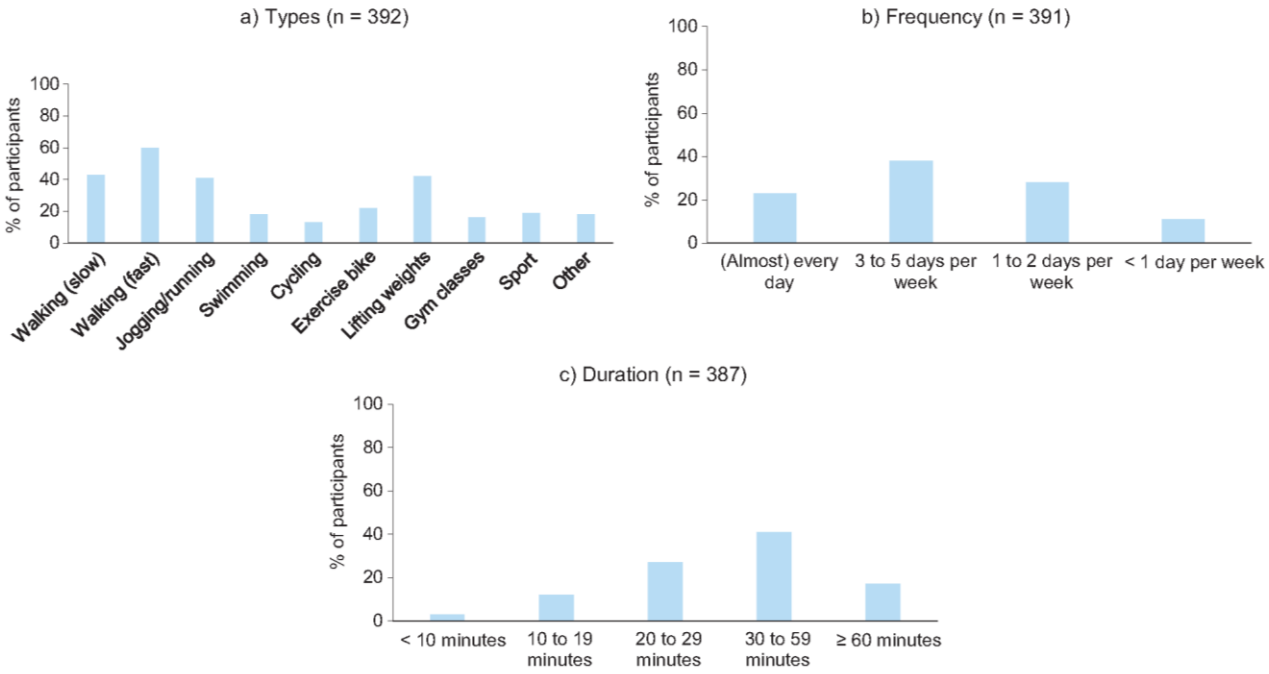

Figure 8. Reported exercise routines when exercising to improve the effectiveness of traditional airway clearance techniques: a) types of exercise, b) frequency and c) duration of exercise sessions.

recruited patients from Australian CF centres, the international applicability of these results is unclear.

This is the first study to explore airway clearance techniques and exercise regimens adopted by adults with CF across Australia and their beliefs and practices in relation to the use of exercise as a substitute for traditional airway clearance techniques. Exercise was used as a substitute for traditional airway clearance techniques by 44% of participants. Given the high prevalence of exercise as a substitute for traditional airway clearance techniques in routine clinical care, further research must be undertaken as a priority to investigate the clinical efficacy of this practice.

Table 5
Shortness of breath and perceived exertion reported by participants who used exercise to improve the effectiveness of traditional airway clearance techniques.

Perceived exercise intensity	n (%)
Shortness of breath[a]	
very, very slight to slight	136 (35)
moderate to severe	229 (59)
very severe to maximal	21 (5)
Rating of perceived exertion[b]	
very, very weak to weak	28 (7)
moderate to strong	285 (74)
very strong to maximal	74 (19)

[a] n = 386.
[b] n = 387.

What was already known on this topic: Current international guidelines either recommend exercise as an adjunct to, but not a replacement for, traditional airway clearance techniques.
What this study adds: Almost half of adults with CF use exercise as a substitute for traditional airway clearance techniques, based on their personal experience. Physiotherapists should advise patients that whilst there is some research suggesting a possible mechanism for exercise as a form of airway clearance, there are currently no medium-term to long-term data supporting exercise as a stand-alone form of airway clearance. Physiotherapists should explore a patient's beliefs and personal experience as part of the process for prescribing new or modified exercise and airway clearance regimens.

Footnotes: [a] Excel 2013, Microsoft Corporation, WA, USA. [b] SPSS Version 24, IBM Corporation, NY, USA.

eAddenda: Appendices 1 and 2 can be found online at DOI: https://doi.org/10.1016/j.jphys.2018.11.006.

Ethics approval: The study was approved by the following ethics committees: Royal Adelaide Hospital Human Research Ethics Committee, La Trobe University Science, Health and Engineering College Human Ethics Sub-Committee, Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee, Human Research Ethics Committee (Tasmania) Network, and ACT Health Human Research Ethics Committee.

Competing interest: Nil.

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Correspondence: Nathan Ward, Cystic Fibrosis Service, Royal Adelaide Hospital, Australia. Email: nathan.ward2@sa.gov.au

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CHAPTER 5: ASSESSMENT OF RESPIRATORY SYMPTOMS IN CYSTIC FIBROSIS

Declaration of authorship – Chapter 5

The nature and extent of contributions to Chapter 5 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Study concept and protocol development, data collection and analysis, writing of manuscript and review	75%	
Kathy Stiller	Study concept and protocol development, review of manuscript	10%	
Hilary Rowe	Data collection, review of manuscript	5%	
Anne Holland	Study concept and protocol development, review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 5 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

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Original Article

The psychometric properties of the Leicester Cough Questionnaire and Respiratory Symptoms in CF tool in cystic fibrosis: A preliminary study☆,☆☆,★

Nathan Ward [a,b,*], Kathy Stiller [c], Hilary Rowe [a], Anne E Holland [b,d]

[a] Royal Adelaide Hospital, North Terrace, Adelaide 5000, Australia
[b] La Trobe University, Melbourne 3004, Australia
[c] Central Adelaide Local Health Network, Adelaide 5000, Australia
[d] Alfred Health, Commercial Road, Melbourne 3004, Australia

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Abstract

Background: There are few tools to quantify the impact of cough in cystic fibrosis (CF). The psychometric properties of the Leicester Cough Questionnaire (LCQ) and Respiratory Symptoms in CF (ReS-CF) tool were investigated in adults with CF.
Methods: Validity and reliability were assessed in clinically stable participants who completed the questionnaires twice, along with the Cystic Fibrosis Questionnaire – Revised (CFQ-R). Responsiveness was assessed by change in questionnaires following treatment for an acute respiratory exacerbation.
Results: Correlations between the LCQ and CFQ-R respiratory domain were moderate ($n = 59$, $r_s = 0.78$, $p < 0.001$). Correlations between ReS-CF and CFQ-R respiratory domain were fair ($r_s = -0.50$, $p < 0.001$). The LCQ total score was repeatable (ICC 0.92, 95%CI 0.87–0.96, $n = 50$). In those reporting improvement in symptoms following treatment ($n = 36$), LCQ total score had a mean change of 4.6 (SD 3.7) and effect size of 1.2.
Conclusions: The LCQ and ReS-CF appear to be valid, reliable and responsive in CF.
Trial Registration: www.anzctr.org.au: ACTRN12615000262505

Keywords: Cystic fibrosis; Leicester Cough Questionnaire; Cough; Surveys and questionnaires; Signs and symptoms, respiratory

Abbreviations: CF, Cystic Fibrosis; LCQ, Leicester Cough Questionnaire; CFQ-R, Cystic Fibrosis Questionnaire (Revised); HRQOL, Health-related quality of life; VAS, Visual analogue scales; COPD, Chronic obstructive pulmonary disease; ReS-CF, Respiratory Symptoms in cystic fibrosis tool; GRCS, Global rating of change scale

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* Corresponding author at: c/o Physiotherapy Department, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia.
E-mail addresses: nathan.ward2@sa.gov.au (N. Ward), kathy.stiller@sa.gov.au (K. Stiller), hilary.rowe@sa.gov.au (H. Rowe), a.holland@latrobe.edu.au (A.E. Holland).

1. Introduction

Cystic fibrosis (CF) is characterised by thickened respiratory secretions as a sequelae of the defective chloride transport in the respiratory epithelium. Inadequate clearance of respiratory secretions provides an environment conducive to a cycle of retained secretions, chronic infection and inflammation, resulting in progressive lung damage and eventual respiratory failure in the majority of sufferers.

Lung function testing, especially forced expiratory volume in 1 s (FEV_1), has historically been used as the primary outcome measure in studies investigating new therapies aimed at the respiratory system of people with CF. The occurrence and frequency of respiratory exacerbations are other frequently utilised

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outcomes in CF trials, although a universally accepted definition of a respiratory exacerbation is still lacking. As the rate of decline in lung function has slowed as a result of improvements in available therapies, the suitability of FEV_1 or the rate/frequency of respiratory exacerbations as primary outcome measures in short and medium duration studies involving participants with CF has been questioned [1]. At the same time, there has been increasing interest in patient-reported outcomes as primary endpoints in CF clinical trials [2,3]. These encompass a broad range of assessments that measure how a patient feels or functions and includes generic and disease-specific health-related quality of life (HRQOL) assessments and more specific symptom evaluation tools [2]. The Cystic Fibrosis Questionnaire-Revised (CFQ-R), a 50-item, 12-domain tool assessing HRQOL, is currently the best validated HRQOL questionnaire for use in CF populations [4,5]. However, as recommended by the European Medicines Agency, there is a need to develop briefer, more targeted patient-reported outcomes for use in CF trials [4].

Cough is one of the most frequently reported respiratory symptoms in CF, with changes in cough behaviour a primary symptom identified by patients as an indicator of a respiratory exacerbation, even in the setting of mild lung disease [6–11]. Sawicki et al. [10] found that 94% of their sample of adults with CF reported cough, with the majority reporting it as being of high frequency and severity, with these frequency and severity ratings much higher than for other symptoms, including shortness of breath. A variety of tools have been developed to assess the frequency and impact of cough. Visual analogue scales (VAS) are a widely used evaluation tool and have been used to measure the impact of cough and other respiratory symptoms in people with non-CF bronchiectasis [12]. However, there is a paucity of data to support their use compared to other tools that evaluate the frequency and impact of cough [13]. Smith et al. [14] demonstrated, in a small sample of CF subjects treated for a respiratory exacerbation, that a change in VAS score assessing day and night cough correlated with a change in objective cough counts.

The Leicester Cough Questionnaire (LCQ) is a 19-item tool that assesses cough-related HRQOL. Originally developed in those with chronic cough, its validity and responsiveness has been demonstrated in patients with non-CF bronchiectasis and chronic obstructive pulmonary disease (COPD) [13,15–17]. The LCQ is moderately correlated with the number of explosive coughs and cough-seconds [18,19]. The LCQ has been used as an outcome measure in non-CF bronchiectasis airway clearance trials and in a case-series of cough changes related to laparoscopic fundoplication for reflux in CF [20–22]. However, the LCQ is yet to be formally validated for use in the CF population.

Given the prevalence and severity of cough across the disease severity spectrum in CF, there may be value in utilising a tool that specifically assesses the impact of cough on HRQOL in CF. The purpose of this study was therefore to investigate the psychometric properties of the LCQ in a cohort of adults with CF. As well as evaluating the psychometric properties of the LCQ in a sample of patients with CF, we also purpose-designed and evaluated a brief questionnaire comprising four simple VASs that assessed respiratory symptoms (ReS-CF) to investigate if a briefer questionnaire may be useful as a screening tool.

2. Methods

2.1. Study design

All patients with a diagnosis of CF attending the Adult CF Service at the Royal Adelaide Hospital were eligible for inclusion. Patients unable to understand written English were excluded. The study was divided into two parts: one part investigating validity and reliability and the other investigating responsiveness. Recruitment for the two parts occurred concurrently between March and September 2015. Ethical approval was obtained from the Royal Adelaide Hospital Research Ethics Committee (HREC/15/RAH/2) and La Trobe University Human Ethics Committee. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000262505).

2.2. Questionnaires

The LCQ is a 19-item questionnaire that specifically assesses the impact of cough on HRQOL [16]. Each item requires a response using a 7-point Likert-like scale (e.g. 1 = all of the time, 7 = none of the time). These 19 items are divided into three domains that consider the physical impacts (e.g. effect of cough on chest and stomach pains, sputum production), psychological impacts (e.g. effect of cough on embarrassment/anxiety) and social impacts (e.g. cough interfering with job/daily life, enjoyment of life) of cough. Three domain scores and a total score are calculated, with domain scores ranging from 1 to 7 and total scores from 3 to 21, with higher scores indicating greater HRQOL [16].

The Respiratory Symptoms in CF (ReS-CF) tool was developed by the authors specifically for the purpose of this study as a means of briefly measuring patient's perceptions of their respiratory symptoms. It consists of four VASs assessing patient-perceived severity of their overall respiratory symptoms, cough, chest congestion and sputum production. Each VAS was scored separately, ranging from 0 (no symptoms) to 10 (extreme symptoms).

The CFQ-R is a 50-item, 12 domain, CF-specific HRQOL questionnaire and is currently the most widely used HRQOL questionnaire in the CF population [5]. The respiratory domain consists of seven questions, with the domain score being based on six of these questions. These questions assess cough, congestion, mucus expectoration, wheezing and trouble breathing and are scored on a 4-point Likert-like scale. The respiratory domain of the CFQ-R has been shown to have good internal consistency (Cronbach's alpha = 0.87), with a minimal clinically important difference of 4 points for clinically stable patients and 8.5 points in those receiving treatment for an acute exacerbation [23,24].

Participants were approached for inclusion in the study during outpatient appointments or on admission to hospital and given a package containing the full versions of all questionnaires to

self-complete. Whilst the questionnaires within the packages were in a set order, the order of completion was left to each participant. Participants in the reliability and responsiveness studies were given a second set of questionnaires to complete one week later (reliability) or four weeks later (responsiveness). Up to three reminders were provided to each participant to complete the repeat set of questionnaires that were given to the participant at the initial visit.

2.3. Validity and reliability study

Patients who were clinically stable were approached to participate in the validity and reliability component of the study. Validity was assessed by having participants complete the LCQ, ReS-CF and CFQ-R questionnaires on the same day, after undergoing any clinical assessments (e.g. spirometry). The following concepts of validity were assessed: concurrent validity and floor or ceiling effects. Internal consistency of the LCQ was also determined. Test–retest reliability was assessed by having the same participants complete the questionnaires again, one week after completing the initial set of questionnaires. Participants were excluded from the reliability analysis if they developed an acute respiratory exacerbation during the period separating the two assessment time points.

2.4. Responsiveness study

Patients diagnosed by their treating respiratory physician with an acute respiratory exacerbation, based on clinical assessment (e.g. drop in lung function [spirometry], increase in symptoms) and requiring treatment with new oral, inhaled or intravenous antibiotics were approached to participate. Participants completed the LCQ, ReS-CF and CFQ-R when commencing treatment and again four weeks later. A global rating of change scale (GRCS) was used at the four week point to determine participant-defined changes in respiratory symptoms, ranging from −7 (a very great deal worse) to +7 (a very great deal better). Participants were withdrawn if, during the assessment period, they developed a critical illness requiring intensive care unit admission, surgical intervention or had end of life care implemented.

2.5. Statistical analyses

Concurrent validity was assessed by calculating correlation coefficients using either Pearson's correlation coefficient or Spearman's rank correlation coefficient depending on the distribution of the data (determined by visual inspection and skewness and kurtosis statistics). Content validity was assessed by analysing for floor and ceiling effects, with < 15% of subjects achieving either the minimum or maximum scores considered acceptable.

Reliability was assessed using several methods. Internal consistency of the LCQ (domain and total scores) was determined using Cronbach's alpha coefficient. Cronbach's alpha scores of 0.7–0.9 were selected as representing acceptable internal consistency. Test–retest reliability of the LCQ (domain and total scores) and ReS-CF were determined using Intraclass Correlation Coefficients (ICC). An ICC of 0.7 was considered acceptable [25]. A Bland–Altman plot for the LCQ total score was constructed, with limits of agreement equalling 1.96 × SD of the mean difference in scores.

Responsiveness was determined by calculating the effect size for those reporting an improvement in symptoms (GRCS ≥ 2) four weeks after starting treatment for an acute respiratory exacerbation. Effect size was calculated as the difference in mean scores between the baseline and repeat assessments divided by the standard deviation (SD) of the baseline score. Anchor-based estimates of the minimum important difference (MID) were calculated using the change in LCQ total score for those reporting a small improvement in their symptom (GRCS 2–3). The sensitivity and specificity for the change in LCQ total score to discriminate between those who did and did not report an improvement in symptoms were calculated and a Receiver Operator Curve (ROC) obtained. The minimum important difference was determined as the data point closest to the upper left corner of the curve [26,27]. The distribution-based estimate of the MID was calculated as 0.5 SD of the mean change in LCQ total score.

Data analyses were conducted using SPSS version 23 (SSPS, Chicago, IL, US).

3. Results

3.1. Validity and reliability

3.1.1. Patients

Fifty-nine patients met the eligibility criteria and completed the initial questionnaires, with their descriptive characteristics and questionnaire scores summarised in Table 1. The LCQ, ReS-CF and CFQ-R respiratory domain results were not normally distributed.

3.1.2. Validity

3.1.2.1. Concurrent Validity. The physical, psychological and social domains of the LCQ were moderately correlated with the CFQ-R respiratory domain (r_s = 0.71–0.74, $p < 0.001$). The three domains of the LCQ were moderately correlated with each other (0.74–0.78, $p < 0.001$). The LCQ total score was moderately correlated with the CFQ-R respiratory domain ($r_s = 0.78$, $p < 0.001$). The ReS-CF overall domain had a fair negative correlation with the respiratory domain of the CFQ-R ($r_s = -0.50$, $p < 0.001$).

3.1.2.2. Floor and Ceiling Effects. Only two (3.4%) participants achieved the maximum score for the physical domain and total LCQ scores, with no participants achieving a minimum score for any of the domains or total score. However 14 (23.7%) and 18 (30.5%) participants achieved a maximum score on the LCQ psychological and social domains respectively, indicating a possible ceiling effect in these domains. For the ReS-CF, no participant achieved a maximum score and only five participants (8.5%) achieved the minimum value for any domain.

Table 1
Descriptive characteristics of the participants in the validity/reliability and responsiveness studies.

Characteristics	Validity and reliability study (n = 59)	Responsiveness study (n = 53)
Sex, male, n (%)	42 (71)	27 (51)
Age (yrs), mean ± SD (range)	29.0 ± 9.3 (17–59)	29.3 ± 7.4 (18–47)
FEV_1 (L), mean ± SD (range)	3.05 ± 1.12 (0.82–5.85)[a]	2.40 ± 1.00 (0.55–4.20)[b]
FEV_1 (% pred), mean ± SD (range)	75.3 ± 23.1 (20–118)[a]	63.0 ± 24.0 (16–102)[b]
FVC (L), mean ± SD (range)	4.21 ± 1.20 (1.71–6.82)[a]	3.68 ± 1.36 (1.06–7.29)[b]
FVC (% pred), mean ± SD (range)	86.2 ± 17.5 (41–126)[a]	80.1 ± 22.0 (27–117)[b]
BMI (kg/m^2), mean ± SD (range)	24.8 ± 4.8 (18.2–40.7)	22.3 ± 3.8 (15.7–38.8)
F508del homozygote	22 (37%)	28 (53%)
Pseudomonas aeruginosa colonisation (%)	36 (61%)	41 (77%)
Pancreatic insufficient (%)	44 (75%)	49 (92%)
CF-related diabetes (%)	7 (12%)	10 (19%)
LCQ, median (IQR)		
Physical	6.1 (5.4–6.5)	4.4 (3.4–5.0)
Psychological	6.7 (5.9–6.9)	4.1 (3.3–5.3)
Social	6.5 (5.8–7.0)	4.8 (3.3–5.5)
Total	19.2 (17.1–20.3)	13.3 (10.0–15.4)
ReS-CF, median (IQR)		
Overall	1.2 (0.4–2.3)	5.5 (4.4–6.8)
Cough	1.1 (0.3–2.3)	6.1 (4.4–7.9)
Congestion	1.0 (0.3–3.5)	6.2 (4.7–7.8)[c]
Sputum	1.7 (0.6–3.5)	6.4 (4.9–7.9)
CFQ-R, median (IQR)		
Respiratory	77.8 (66.7–88.9)	50.0 (38.9–61.1)

n = number of participants.
yrs = years.
SD = standard deviation.
%pred = percentage of predicted.
kg/m^2 = kilogrammes/m squared.
FEV_1 = forced expiratory volume in 1 s.
FVC = forced vital capacity.
L = litres.
BMI = body mass index.
LCQ = Leicester Cough Questionnaire.
IQR = interquartile range.
ReS-CF = Respiratory Symptoms in CF.
CRQ-R = Cystic Fibrosis Questionnaire – Revised.
[a] n = 58.
[b] n = 45.
[c] n = 52.

Fig. 1 presents the scores from the three LCQ domains and the total LCQ score according to severity of disease as categorised by lung function results (based on forced expiratory volume in 1 s). Multivariate analyses revealed that the only significant difference was between the severe and both the mild and normal groups for the physical domain of the LCQ ($p < 0.05$).

3.1.3. Reliability

3.1.3.1. Internal consistency. The Cronbach's alpha for the physical, psychological and social domains of the LCQ were 0.84, 0.92 and 0.90 respectively and, for the LCQ total score 0.95.

3.1.3.2. Test–retest reliability. Of the 59 patients completing the initial questionnaires, 50 were eligible for the test–retest reliability analysis. Two patients were withdrawn as they developed an acute respiratory exacerbation in the time period between the two assessments and seven failed to return the repeat questionnaires. The LCQ demonstrated good test–retest reliability, with all domains and the total score having an ICC > 0.7 (Table 2). The four ReS-CF VAS scores also achieved ICCs > 0.7 however the lower limit of the 95%CI for all except the sputum domain fell below 0.7 (Table 2). Repeatability of the LCQ total score over one week is shown in the Bland–Altman plot in Fig. 2. The mean (SD) difference in score was 0.2 (1.1) units, with the upper limit of agreement being 2.4 and the lower limit of agreement being −2.0.

3.2. Responsiveness

Fifty-three patients were recruited for the responsiveness part of the study. Table 1 summarises their baseline characteristics. Forty-eight (91%) participants completed and returned the repeat set of questionnaires. Thirty-six participants (75%) reported an improvement in respiratory symptoms post-treatment (GRCS ≥ 2).

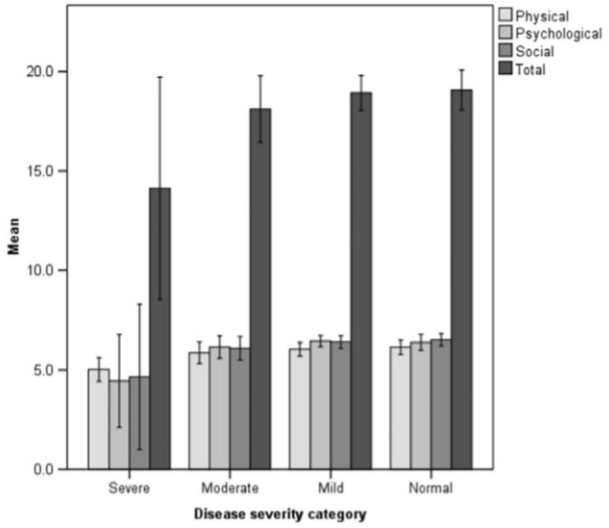

Fig. 1. LCQ domain and total scores by disease severity category. Data are mean and 95%CI. Disease severity category as measured by FEV_1 percentage of predicted: normal ≥ 90%, mild = 70–89%, moderate = 40–69%, severe < 40% predicted value.

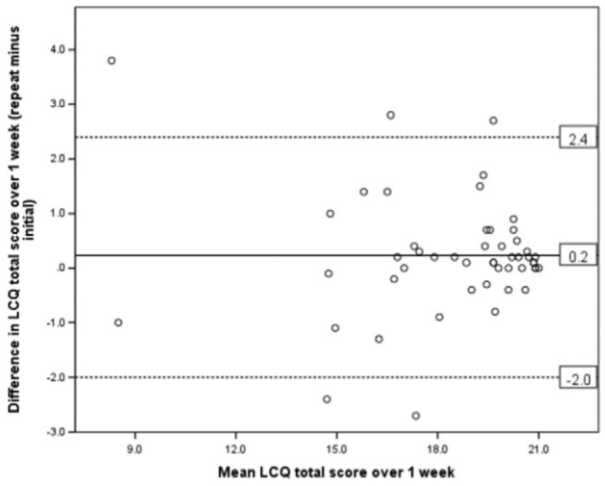

Fig. 2. Bland–Altman plot of the mean LCQ total score over one week. Difference in LCQ total score over 1 week equals repeat result minus initial result. The solid line represents the mean change in score and the dashed line represents the limits of agreement (1.96 × SD of the mean change in scores).

The LCQ total scores increased by a mean (SD) of 3.6 (3.9) for the 48 participants. The ReS-CF scores changed by a mean (SD) of −2.2 (2.7), −2.9 (2.9), −2.6 (3.3) and −2.7 (2.8) for the overall, cough, congestion and sputum domains respectively. Data from the 36 participants reporting an improvement in symptoms (GRCS ≥ 2) were further analysed, with the pre- and post-treatment results for these participants summarised in Table 3. For these participants reporting an improvement in symptoms, the LCQ total score increased by 4.6 (3.7) units, with an effect size of 1.2. The ReS-CF scores in participants reporting an improvement in their symptoms changed by a mean (SD) of −2.9 (2.6), −3.5 (2.7), −3.5 (3.1) and −3.1 (2.7) for the overall, cough, congestion and sputum domains respectively, with effect sizes ranging from 1.3–1.6. Thirty two participants exceeded the previously identified minimum important difference (MID) for the CFQ-R respiratory domain (8.5 units), with these participants reporting a mean (SD) increase in LCQ total score of 5.3 (3.4) which was significantly higher than the mean (SD) change of 0.2 (1.9) in those not exceeding the CFQ-R MID ($p < 0.001$) [23].

Using the anchor-based method for determining the MID of the LCQ total score, participants reporting a small improvement in their symptoms on the GRCS [2–3] had a mean (SD) increase of 2.0 (3.2) units in their LCQ total score. Fig. 3 shows the ROC for the LCQ total score. Visual inspection of the ROC indicated a threshold change of 1.9 units for the MID (area under the curve 0.80, 95%CI 0.65–0.94, sensitivity 75% and specificity 75%). This is in agreement with the distribution-based method for estimating the MID (0.5 SD of the mean change in LCQ total scores), which estimated an MID of 1.9 units.

Table 2
Test–retest reliability of the LCQ, ReS-CF and CFQ-R.

Questionnaire	ICC (95% CI)
LCQ	
Physical	0.85 (0.76–0.91)
Psychological	0.91 (0.85–0.95)
Social	0.86 (0.77–0.92)
Total	0.92 (0.87–0.96)
ReS-CF	
Overall	0.75 (0.60–0.85)
Cough	0.80 (0.67–0.88)
Congestion	0.78 (0.64–0.87)[a]
Sputum	0.82 (0.70–0.89)
CFQ-R	
Respiratory	0.84 (0.73–0.90)[b]

LCQ = Leicester Cough Questionnaire.
ReS-CF = Respiratory Symptoms in CF.
CRQ-R = Cystic Fibrosis Questionnaire – Revised.
[a] n = 48.
[b] n = 49.

Table 3
Results for responsiveness data when commencing treatment for a respiratory exacerbation and four weeks later for the 36 participants who reported an improvement in symptoms.

	Baseline mean (SD)	Reassessment mean (SD)	Effect size
LCQ			
Physical	4.3 (1.1)	5.7 (1.1)	1.3
Psychological	4.3 (1.4)	5.9 (1.2)	1.1
Social	4.5 (1.4)	6.0 (1.1)	1.1
Total	13.0 (3.8)	17.6 (3.1)	1.2
ReS-CF			
Overall	5.5 (2.1)	2.6 (2.1)[a]	1.4
Cough	6.0 (2.3)	2.4 (2.0)	1.6
Congestion	6.2 (2.4)[a]	2.7 (2.2)	1.5
Sputum	6.1 (2.3)	3.0 (2.1)	1.3
CFQ-R			
Respiratory	47.4 (17.1)	71.0 (18.0)	1.4

LCQ = Leicester Cough Questionnaire.
ReS-CF = Respiratory Symptoms in CF.
CRQ-R = Cystic Fibrosis Questionnaire – Revised.
[a] n = 35.

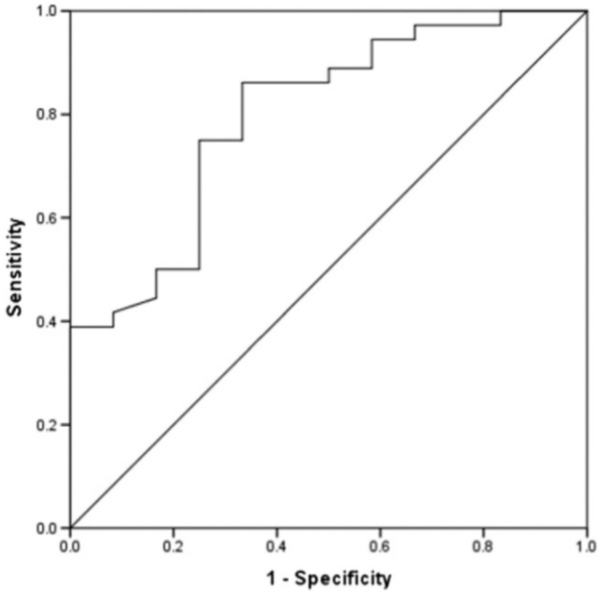

Fig. 3. Receiver Operator Curve for responsiveness of the LCQ total score. The area under the curve is 0.80 (95% CI 0.65–0.94).

4. Discussion

The current study found that the LCQ and ReS-CF were valid, reliable and responsive tools for the assessment of perceived respiratory symptoms in adults with CF. The LCQ total and domain scores were moderately correlated with the respiratory domain of the CFQ-R, currently the most widely used HRQOL in CF. The ReS-CF overall respiratory symptom domain had a fair correlation ($r_s = -0.5$) to the CFQ-R respiratory domain. The moderate correlation between the LCQ and CFQ-R respiratory domain suggests that the LCQ may have a complimentary role to the CFQ-R, with the cough-specific LCQ potentially having a place in the assessment of therapies where cough is a target.

Cough is a symptom that may have a significant social impact due to the stigma associated with coughing. It is therefore important to assess not only the physical symptom but also its psychological and social impact when determining HRQOL. Whilst the LCQ total score and physical domain, along with all domains of the ReS-CF, did not demonstrate a floor or ceiling effect, a ceiling effect was found for the psychological and social domains of the LCQ. The participants in this study generally had well preserved lung function which may have contributed to the ceiling effect demonstrated. Those achieving a maximum score for the two domains had a mean percent predicted FEV_1 of 82% for both domains respectively. For those not achieving the maximum score, it was 73% and 72% for the psychological and social domains respectively, suggesting, as expected, that those with milder respiratory disease may be more likely to achieve a maximum score. Given this potential ceiling effect, our recommendation would be that the LCQ total score be used as the primary outcome of interest when using the LCQ in people with CF, especially for those with mild respiratory disease pending larger, multi-centred investigations of the psychometric properties of the LCQ.

The LCQ demonstrated good internal consistency (Cronbach's alpha 0.84–0.95) with these results similar to those reported in the initial development study involving patients with chronic cough (Cronbach's alpha 0.79–0.92) and the Dutch-translation version (Cronbach's alpha 0.77–0.93) [16,28]. The internal consistency results in the current study are better than those seen in COPD (Cronbach's alpha 0.67–0.86) [15]. There is some debate about a suitable upper limit for Cronbach's alpha, with some suggesting 0.95 as opposed to 0.90 as the upper limit, therefore, the results of the current study with its values toward the upper limit of the commonly accepted range, indicate there may be some degree of redundancy in the LCQ when used to assess cough-related quality of life in CF [25,29,30].

Test–retest reliability was assessed by having participants complete the questionnaires one week apart which is within the repeat testing timeframes recommended by Deyo et al. [26]. We found that the LCQ and ReS-CF were both reliable, with ICCs greater than the recommended 0.7 cut-off [25]. Whilst the 95%CI for the LCQ domains and total score exceeded 0.7, it should be noted that only the sputum domain of the ReS-CF had the lower limit of the 95% CI above 0.7. The mean difference in the LCQ total score of 0.2 units between the initial and repeat testing is comparable with the −0.23 units reported by Murray et al. [17] in non-CF bronchiectasis and the 0.73 units reported by Berkhof et al. [15] in COPD.

The LCQ and ReS-CF were both responsive to change with effect sizes ranging from 1.1 to 1.3 for the LCQ and 1.3 to 1.6 for the ReS-CF. An effect size of >0.8 is generally considered to be large [31]. Our results are similar to those reported by Birring et al. [16] in the initial LCQ development study where they found effect sizes between 0.84 and 1.75. In the current study, the mean change in LCQ total score for those participants reporting an improvement in symptoms was 4.6, being consistent with the results reported by Murray et al. [17] in their cohort of patients with non-CF bronchiectasis undergoing treatment for an acute exacerbation. The anchor-based approach we used revealed 2.0 units as the mean change in LCQ score for those reporting a small improvement on the GRCS. Analysis of the ROC for the LCQ total score suggested a change of 1.9 units was able to detect those who reported an improvement in their symptoms, with an acceptable degree of sensitivity (75%) and specificity (75%). It must be noted however that the ROC had a wide confidence interval (0.65–0.94). The MID estimate of 2.0 is somewhat lower than the 3.0 suggested by Brokkaar et al. [32] in patients with chronic cough.

We developed the ReS-CF to see if a quick screening tool of respiratory symptoms consisting entirely of simple VASs might be useful in CF. The ReS-CF is very simple, taking less than 1 min to complete, whereas the LCQ takes around 5 min and the CFQ-R 10 min to complete. The ReS-CF seems well suited for use as a quick screening tool, particularly in the busy clinical setting where ease and speed of completion are important. The LCQ, with its higher test–retest repeatability and stronger correlation to the CFQ-R, may be a more robust and appropriate tool than the ReS-CF when considering outcome measures for clinical trials, particularly where cough is either a specific target or is likely to be affected by the intervention (e.g. airway

clearance trials) and where the time required to complete the questionnaire is less of an issue.

This study has several limitations. It only recruited a relatively small sample of patients attending a single adult CF service, so additional larger multi-centred trials would be of value. The participants in the validity and reliability analysis generally had well preserved lung function and therefore further evaluation of potential floor effects in those with more severe disease may be warranted. Our study recruited participants separately for the validity/reliability and responsiveness phases and we acknowledge that there may be value in evaluating the LCQ longitudinally and assessing LCQ in both stable and unstable disease states in the same participants. There were also some incomplete data due to several participants failing to answer all required questions, however there were less than 5% missing data for any individual analysis. Further research to evaluate the psychometric properties of the LCQ compared to more objective measures, such as genotype, Pseudomonas aeruginosa infection status and change in lung function, would also be of value. Another limitation is that we did not randomise the order of questionnaire completion, rather we left it to participant choice, so it is possible that there was an order effect. By chance, there were considerably more males than females (71% vs 29%) in the validity phase of our study. Further research with a more evenly mixed sample would be of value to determine if the gender bias in our cohort had any impact on the validity and reliability of the LCQ. It is important to note that, unlike the CFQ-R, the initial development of the LCQ did not include any participants with a diagnosis of CF. Nevertheless, our findings suggest that it may have psychometric properties that enable its use in the CF population, in keeping with those studies that found the LCQ useful for patients with COPD and non-CF bronchiectasis — populations that were also not included in the initial development of the LCQ [15,17]. Finally, it is acknowledged that, like previous research, the data from the questionnaires were treated as interval data, when it is possible that they are not truly interval (e.g. a 2 point change in score at the lower end of a scale may not mean the same as that seen at the upper end of a scale).

The results of this study indicate that further assessment into the role of the LCQ and ReS-CF in CF is warranted. The tools may have a role in the clinical assessment of patients when evaluating the impact of specific therapies added to a patient's regimen e.g. a change in airway clearance technique. Given that people with CF were not included in the initial development of the LCQ, further investigation into its structure and content in a CF-specific context is warranted prior to its potential use as a primary outcome measure in clinical trials.

5. Conclusion

The LCQ and ReS-CF appear to be valid, reliable and responsive tools for assessing the impact of cough in adult subjects with CF. The LCQ may be of use in evaluating clinical interventions that may impact upon cough, such as airway clearance techniques. Further assessment of these tools in multicentred studies and randomised controlled trials would be of benefit to clarify their role in assessing HRQOL in CF in clinical practice and clinical trials.

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CHAPTER 6: AIRWAY CLEARANCE BY EXERCISING IN MILD CYSTIC FIBROSIS (ACE-CF): A FEASIBILITY STUDY

Declaration of authorship – Chapter 6

The nature and extent of contributions to Chapter 6 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Study concept and protocol development, data collection and analysis, writing of manuscript and review	70%	
Kathy Stiller	Study concept and protocol development, review of manuscript	10%	
Hilary Rowe	Data collection, review of manuscript	2.5%	
Scott Morrow	Data collection, review of manuscript	2.5%	
Judith Morton	Medical consultancy, review of manuscript	2.5%	
Hugh Greville	Medical consultancy, review of manuscript	2.5%	
Anne Holland	Study concept and protocol development, review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 6 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

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Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study

Nathan Ward[a,b,*], Kathy Stiller[c], Hilary Rowe[a], Scott Morrow[a], Judith Morton[a], Hugh Greville[a], Anne E. Holland[b,d]

[a] Adult Cystic Fibrosis Service, Thoracic Medicine, Royal Adelaide Hospital, Chest Clinic, 275 North Terrace, Adelaide, SA, Australia
[b] La Trobe University, Melbourne, Australia
[c] Central Adelaide Local Health Network, Royal Adelaide Hospital, Port Road, Adelaide, SA, Australia
[d] Alfred Health, 99 Commerical Road, Prahran, Vic, Australia

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ABSTRACT

Background: People with cystic fibrosis (CF) are encouraged to perform airway clearance techniques on a daily basis. Whilst several short-term studies support a potential role for exercise as an airway clearance technique, to date no medium to longer term studies have investigated the use of exercise as a stand-alone airway clearance technique.

Objective: To determine the feasibility of a protocol investigating the use of exercise as a stand-alone form of airway clearance in adults with CF.

Methods: Adults with CF and a $FEV_1 \geq 70\%$ predicted were eligible. After a four week wash-in period of daily positive expiratory pressure (PEP) and exercise, adherent participants were randomised to either daily PEP plus exercise or exercise-only for three months. Pre-specified thresholds for feasibility for the primary outcomes were rates of recruitment ≥30%, randomisation ≥80% and completion ≥80%. Secondary outcomes included respiratory function tests, respiratory exacerbation rate and health-related quality of life.

Results: Of the 57 eligible patients identified, 17 were recruited (30%). After the wash-in period, 13 of the 17 participants (76%) were randomised and all 13 (100%) completed the final assessment. The median (IQR) change in FEV_1 (L) over the intervention period was 0.00 (−0.08 - 0.15) L for the PEP plus exercise group and −0.03 (−0.19 - 0.13) L for the exercise-only group.

Conclusion: The study achieved its a priori target feasibility rates for recruitment and completion but failed to meet the randomisation target rate. Changes in lung function and quality of life were similar between groups. Further refinement of the protocol may be required prior to expansion to a multi-centred trial.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive, life-shortening, genetic condition affecting over 3100 people in Australia [1]. Whilst historically considered a disease of childhood, survival has improved over the last few decades and over 40% of adults with CF in Australia now have normal or only mildly impaired respiratory function as a result of improved therapies [1].

One of the mainstays of treatment for CF is the use of airway clearance techniques (ACTs) to assist with the removal of the characteristic thickened and tenacious respiratory secretions. Most guidelines recommend that people with CF perform these ACTs on a daily basis [2–4]. Exercise is another important component of the therapeutic regimen for people with CF. In addition to its proven cardiovascular and musculoskeletal benefits, some authors have proposed that exercise combined with huffing and coughing may be sufficiently effective to be considered a stand-alone ACT, acting as a substitute for traditional ACTs [5]. Several cross-over studies, involving people with CF, found that exercising on a treadmill significantly reduced the mechanical impedance of respiratory secretions and improved ease of expectoration, probably due to increased ventilation and respiratory flow rates [6–8]. The reduction in mechanical impedance was not seen during stationary cycling, suggesting that the trunk movements seen during walking may be important to facilitate airway clearance. An

* Corresponding author. c/o Thoracic Medicine, 8E032, Royal Adelaide Hospital, Port Road, Adelaide, SA, 5000, Australia,
E-mail addresses: nathan.ward2@sa.gov.au (N. Ward), kathy.stiller@sa.gov.au (K. Stiller), hilary.rowe@sa.gov.au (H. Rowe), scott.morrow@sa.gov.au (S. Morrow), judith.morton@sa.gov.au (J. Morton), hugh.greville@sa.gov.au (H. Greville), a.holland@latrobe.edu.au (A.E. Holland).

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uncontrolled trial of 10 children with CF found that substituting a physical activity program for an ACT regimen (i.e. postural drainage, percussion and vibrations) over a 17 day period significantly improved respiratory function [9]. Cerny [10] in a small controlled trial found no differences in FVC and FEV_1 improvement between groups when exercise was used as a substitute for a proportion of traditional ACT sessions during treatment for an acute respiratory exacerbation. However, to date there are no medium to longer term randomised controlled trials evaluating the effectiveness of exercise as a stand-alone ACT. Most consensus guidelines regarding optimal management for people with CF recommend exercise as an adjunct to, but not a replacement for, specific ACTs or do not mention exercise as a form of airway clearance [4,11].

The increased number of treatment options available for people with CF has led to an increase in the complexity and time-burden associated with best practice care [12]. Furthermore, adherence to specific ACTs is lower than for other therapies for people with CF, with as few as 38% of patients doing ACTs as recommended [13]. There are many reasons for non-adherence with ACTs, including feeling well without doing ACTs, insufficient time and the perceived effort and energy required [14]. Of particular interest, previous studies have reported that many people with CF consider exercise as an alternative to specific ACTs, with up to 80% considering exercise as one of their ACTs [15]. In order to provide patient-centred care that minimises treatment burden, acknowledges each person's preferences and maximises treatment outcomes, the role of exercise as a stand-alone ACT needs to be examined in a well-designed clinical trial. The aims of the current study were, for adults with mild CF-related respiratory disease, to: 1) determine the feasibility of a protocol investigating the use of exercise-only versus exercise plus a specific ACT and 2) gather preliminary clinical data on the effect of exercise-only versus exercise plus a specific ACT.

2. Methods

2.1. Study design

This study was a randomised controlled trial comparing exercise-only to exercise plus a specific ACT. Due to variability in the ACT and exercise regimens in routine clinical care, a 4-week wash-in period was incorporated into the study design to ensure participants entered the intervention period after a standardised ACT and exercise routine. This wash-in period was also used to assess adherence with the study protocol, with non-adherent participants withdrawn prior to randomisation. For adherent participants, the wash-in period was followed by randomisation to a 3-month intervention period. Assessments were undertaken prior to the wash-in period (baseline), after the wash-in period (pre-) and after the 3-month intervention period (post-). Recruitment was open for 12 months. The study was approved by the Royal Adelaide Hospital Research Ethics Committee and the La Trobe University Human Ethics Committee and was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615001361594). Assessments were performed by assessors who were blinded to group allocation. A data safety management board was convened to review interim data at the midway point of the recruitment period.

2.2. Participants

Adults ($\geq$18 years of age) with a confirmed diagnosis of CF by either a positive sweat test (chloride $>$ 60 mmol/L) or identification of two CF-causing genetic mutations (www.cftr2.org) were recruited from the Royal Adelaide Hospital (RAH) Adult Cystc Fibrosis Service. Inclusion criteria were: mild respiratory disease (i.e. $FEV_1 \geq 70\%$ predicted at baseline assessment), an active patient of the RAH Adult CF Service (i.e. had attended at least 1 appointment in the last 12 months) and clinically stable at the time of baseline assessment (i.e. no new medications for $\geq$4 weeks prior to baseline assessment, FEV_1 (L) within 10% of most recent value at baseline assessment, no upper respiratory tract infection for $\geq$ 2 weeks). Patients were excluded if they were: post-lung transplantation, pregnant, unable to understand written English, had a pneumothorax in the last 6 months, haemoptysis $>$ 20 mls in the 4 weeks prior to the baseline assessment, positive culture for Burkholderia Cepacia within the last 12 months, undergoing treatment for non-Tuberculosis Mycobacteria infection or had a condition or abnormality that, in the opinion of the treating CF physician, compromised the patient's safety or would otherwise make them unsuitable for participation in the study.

2.3. Interventions

After completing the baseline assessment, participants underwent a 4 week wash-in period comprising a specific ACT and exercise regimen. Positive expiratory pressure (PEP) was chosen as the specific ACT as it is a commonly utilised ACT and has been shown to be as effective or more effective than other ACTs for clearing respiratory secretions, maintaining respiratory function and preventing respiratory exacerbations [16]. During each PEP session, participants were instructed to perform 6 cycles of 15 breaths per cycle [17]. Participants were also instructed to perform 30 min of moderate to strong intensity (Borg Rating of Perceived Exertion 3–5) exercise daily. Exercise consisted of walking or jogging or alternatively 6 cycles of 5 min of step-ups using an aerobic step, with the height and step rate adjusted to achieve the target exertion intensity. Participants were instructed to perform 2–3 huffs after each cycle of PEP and every 5 min during exercise. Participants' techniques were reviewed at the time of baseline and pre-randomisation appointments. Participants were provided with a Fitbit Charge HR© to promote adherence with the exercise regimen and were sent phone message reminders if the device had not been synchronised with the online platform within the preceding week.

After the 4 week wash-in period participants completed the pre-randomisation assessment where adherence was classified as good ($>$ 5 days/week), moderate (3–5 days/week) or poor ($<$ 3 days/week) based on their self-reported levels of adherence over the preceding week. To be counted as a treatment session, participants needed to report performing at least 4 $\times$ 10 breaths for the PEP and 20 min for the exercise components. Participants who reported at least moderate adherence with both the PEP and exercise regimens were then randomised to an intervention group using a computer-generated randomisation sequence to either continue daily PEP plus exercise (control group) or to cease PEP and only use exercise-alone (with huffing) for their ACT (intervention group). The randomisation sequence was concealed using opaque envelopes prepared by investigators not involved in participant recruitment. Participants were not aware of the minimum adherence level required to be randomised. Participants randomised to the intervention period then performed their allocated treatment regimen for three months, receiving a phone call one and two months into the intervention period from one of the investigators to assess and encourage adherence to their allocated treatment regimen and troubleshoot any problems. If a participant experienced a respiratory exacerbation during the intervention phase, participants in the exercise-only group were permitted to commence another form of airway clearance (e.g. PEP) if clinically indicated as determined by their treating physiotherapist for the duration of any additional treatments (e.g. intravenous antibiotics), reverting to their assigned intervention at the completion of the additional treatment.

2.4. Outcomes

Feasibility of the protocol was the primary outcome. Feasibility was defined a priori as: recruitment of at least 30% of eligible patients, randomisation of at least 80% of participants following the wash-in

period and that at least 80% of randomised participants completed the intervention period and completion assessments [18]. Secondary outcomes comprised respiratory function, number of respiratory exacerbations and health-related quality of life (HRQOL). HRQOL was measured using the Cystic Fibrosis Questionnaire (Revised) (CFQ-R) and Leicester Cough Questionnaire (LCQ) [19,20]. Spirometry was performed by a respiratory scientist using standard equipment according to American Thoracic Society/European Respiratory Society standards. A respiratory exacerbation was defined as any change in respiratory symptoms that resulted in the commencement of any oral, inhaled and/or intravenous antibiotics. At the completion of the study, participants were asked to indicate their future intentions regarding PEP and exercise based on the treatment regimen used in the study.

2.5. Data analysis

Analyses were performed using SPSS version 24 (SSPS, Chicago, IL, US). Feasibility rates were reported as percentages. Reasons for declining participation were thematically analysed by two of the investigators. Analyses of the secondary outcome measures were performed using the intention-to-treat principle. Results are presented as mean (SD) or median (IQR) unless otherwise specified. As this was a feasibility study, p values were not calculated.

3. Results

3.1. Feasibility

There were 159 patients registered with the RAH Adult CF Service during the 12 month recruitment period. Of these, 57 met the eligibility criteria and 17 (30%) provided informed consent (Fig. 1), thereby just achieving the a priori target rate of ≥30%. Reasons for declining participation are summarised in Table 1. Insufficient time and a belief that they would be non-adherent with study requirements were reported most frequently. After the 4 week wash-in period, four participants were withdrawn for non-adherence: two of these were non-adherent with the PEP regimen and two were non-adherent with both the PEP and exercise regimens. Thirteen (76%) participants were therefore randomised, falling just short of the a priori target rate of ≥80%.

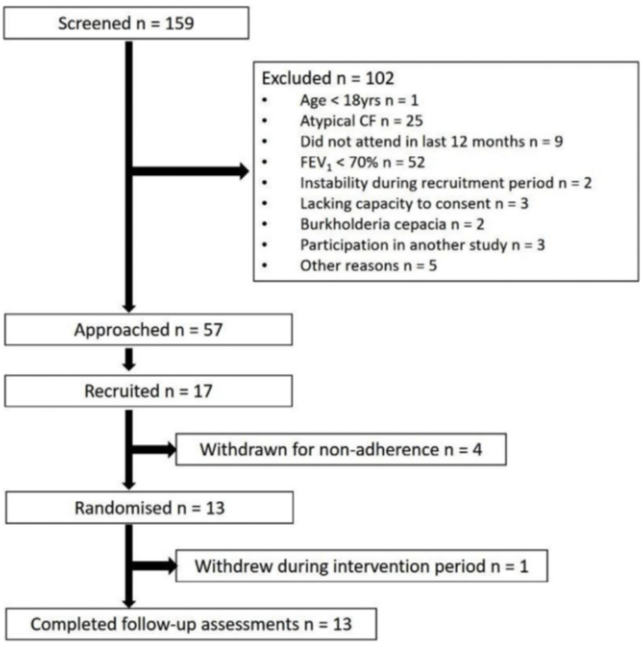

Fig. 1. Flow of participants through the study.

Table 1
Reasons for declining participation in the study (n = 40).

Reason	n (%)
Insufficient time	21 (53)
Belief they would be non-adherent with study requirements	14 (35)
Fear of interrupting usual treatment routine	4 (10)
Other	
A belief that medications are more effective than exercise	1 (3)
Patient didn't feel lung function was good enough	1 (3)
Gastrointestinal problemsmo	1 (3)
No interest	1 (3)
No reason given	5 (13)

Table 2
Demographic data at the baseline assessment for the 13 randomised participants and four withdrawn participants.

	PEP plus exercise (n = 6)	Exercise-only (n = 7)	Withdrawn (n = 4)
Age (yrs), mean (SD)	24.0 (3.0)	24.7 (5.0)	28.5 (5.4)
Male, n (%)	5 (83)	1 (14)	4 (100)
F508del homozygote, n (%)	2 (33)	4 (57)	1 (25)
FVC (L)	6.34 (5.09–6.59)	3.83 (3.61–4.03)	5.65 (4.44–6.06)
FVC (%pred)	109 (100–121)	105 (91–105)	105 (86–111)
FEV_1 (L)	4.48 (3.65–5.16)	2.94 (2.80–3.31)	4.00 (3.37–4.52)
FEV_1 (%pred)	100 (89–115)	86 (83–95)	90 (78–102)
FEF_{25-75} (L)	2.98 (2.74–5.58)	2.49 (2.15–3.07)	3.45 (2.37–4.33)
FEF_{25-75} (%pred)	75 (56–118)	65 (64–94)	74 (55–99)
BMI (kg/m^2)	23.7 (22.6–27.9)	22.0 (20.3–24.7)	23.8 (22.6–27.9)
CFQ-R respiratory domain	88.9 (83.3–90.3)	77.8 (72.2–88.9)	77.8 (65.3–77.8)
LCQ total score, mean (SD)	19.5 (0.9)	18.8 (1.5)	18.3 (1.1)

Median (IQR) unless otherwise stated; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; FEF_{25-75} = forced expiratory flow rate at 25–75% of FVC; BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire (Revised); LCQ = Leicester Cough Questionnaire.

Demographic data for the 13 randomised participants and four withdrawn participants are shown in Table 2. The participants in the PEP plus exercise group were taller than the exercise-only group (median [IQR] 178 cm [168–187 cm] to 163 cm [160–168 cm]) and had slightly better predicted FEV_1 (median [IQR] 100% [89–115%] to 86% [83–95%]) at baseline. During the intervention period, one participant withdrew from their allocated intervention group (exercise-only) after 2 months. All 13 (100%) randomised participants completed the final assessment in accordance with the intention-to-treat principle, thus exceeding the a priori target rate of ≥80%.

3.2. Clinical outcomes

Table 3 presents the clinical outcome measures at the three assessment times. The median (IQR) change in FEV_1 (L) over the intervention period was similar between groups, being 0.00 (−0.08-0.15) for the PEP plus exercise group and −0.03 (−0.19-0.13) for the exercise-only group. The change in FEV_1 percent predicted for each group is shown in Fig. 2. The median [IQR] changes in CFQ-R respiratory domain and LCQ total score were similar between groups over the intervention period (CFQ-R respiratory domain: 8.9 [4.1–11.1] for the PEP plus exercise group and 5.6 [0.0–22.2] for the exercise-only group; LCQ total score: 1.4 [-0.4-2.2] for the PEP plus exercise group and 0.5 [0.4–0.9] for the exercise-only group). During the wash-in period there were a total of four respiratory exacerbations in four different

Table 3
Clinical outcomes at baseline, and before and after the 3 month intervention period for the 13 randomised participants.

	PEP plus exercise (n = 6)			Exercise-only (n = 7)		
	Baseline	Pre-	Post-	Baseline	Pre-	Post-
FEV_1 (L)	4.48 (3.65–5.16)	4.37 (3.55–5.20)	4.36 (3.74–5.17)	2.94 (2.80–3.31)	2.84 (2.78–2.99)	2.86 (2.54–2.96)
FVC (L)	6.34 (5.09–6.59)	6.08 (5.01–6.79)	6.11 (5.09–6.72)	3.83 (3.61–4.03)	3.83 (3.60–4.04)	3.79 (3.22–4.09)
FEF_{25-75} (L)	2.98 (2.74–5.58)	3.26 (2.74–5.33)	3.15 (2.72–5.20)	2.49 (2.15–3.07)	2.56 (1.81–2.70)	2.54 (2.25–2.93)
CFQ-R (respiratory)	88.9 (83.3–90.3)	83.4 (66.7–93.6)	91.7 (76.4–100.0)	77.8 (72.2–88.9)	72.2 (61.1–77.8)	77.8 (72.2–83.3)
LCQ (total)	19.6 (18.6–20.5)	18.7 (17.1–20.1)	19.7 (18.0–20.7)	18.7 (17.9–20.1)	18.4 (17.7–20.0)	19.1 (18.8–20.5)

Data are median (IQR).
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; FEF_{25-75} = forced expiratory flow rate at 25–75% of FVC; CFQ-R = Cystic Fibrosis Questionnaire (Revised); LCQ = Leicester Cough Questionnaire.

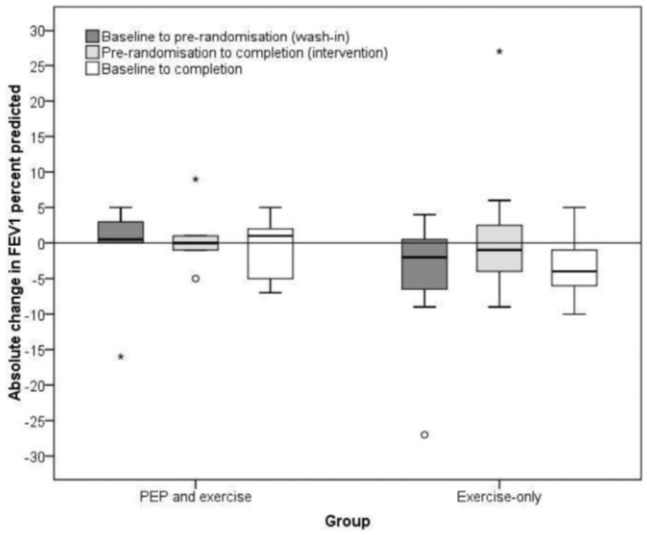

Fig. 2. Box plot of change in FEV_1 percent predicted for the 13 randomised participants. Box = interquartile range, middle line = median, ° = outlier, * = extreme outlier.

participants. All four participants were randomised as they met the adherence requirements. The participants with an acute respiratory exacerbation during the wash-in period represent all but one of the outliers/extreme outliers in Fig. 2. During the intervention period there were a total of seven respiratory exacerbations, three (three participants) in the PEP plus exercise group and four respiratory exacerbations (three participants) in the exercise-only group.

3.3. Participant adherence and future intentions

Table 4 summarises participants' self-reported adherence with their allocated intervention at each of the assessment times during the study. For the six participants in the PEP plus exercise group, four (67%) and five (83%) indicated that they planned to continue with the PEP and exercise routines respectively following the study. For the seven participants in exercise-only group, six (86%) reported that they intended to continue with the exercise routine after the study and four (57%) reported that they intended to resume using PEP.

4. Discussion

This is the first medium-term randomised controlled study to explore the use of exercise as a stand-alone form of airway clearance in CF. The primary purpose was to determine the feasibility of the protocol with regards to recruitment, randomisation and completion rates. The a priori recruitment target was just achieved (30% of eligible patients recruited), but the 80% randomisation target rate was just missed (76%). Once participants were randomised however, the majority completed the study, with only one participant withdrawing from their assigned group (exercise-only) two months into the intervention period and all randomised participants completed the final assessment in accordance with the intention-to-treat principle. Given the small sample size in this feasibility study, it should be noted that a change in outcome for a single participant may have affected achievement or not of the recruitment and randomisation target rates.

Exercise as a stand-alone form of ACT has the potential to reduce the treatment burden in people with mild CF by removing the requirement for a specific ACT session lasting ~15 min or so. Time requirements were still considered a significant barrier to participating in this trial, with the most common reasons for potential participants declining participation being centred around a perceived lack of time to meet the study requirements and a belief that they would be non-adherent with the airway clearance and/or exercise regimen [2–5]. There has been a large increase in the treatment options over the last two decades for people with CF, some of which are time-consuming [12]. The barriers identified by the non-participants in the current study further support

Table 4
Self-reported participant adherence the treatment interventions.

	Wash-in (n = 17)	1 month		2 months		Completion	
		PEP plus Exercise (n = 6)	Exercise- only (n = 7)	PEP plus Exercise (n = 6)	Exercise- only (n = 7)	PEP plus Exercise (n = 6)	Exercise- only (n = 7)
PEP							
Good	11 (65)	4 (67)	–	3 (50)	–	2 (33)	–
Moderate	2 (12)	2 (33)	–	3 (50)	–	4 (67)	–
Poor	4 (24)	0 (0)	–	0 (0)	–	0 (0)	–
Exercise							
Good	8 (47)	1 (17)	3 (43)	0 (0)	2 (29)	1 (17)	3 (43)
Moderate	7 (41)	4 (67)	3 (43)	5 (83)	5 (71)	4 (67)	3 (43)
Poor	2 (12)	1 (17)	1 (14)	1 (17)	0 (0)	1 (17)	1 (14)

Values in parenthese are percentages.

the equipoise behind the investigation into whether exercise may be considered as a substitute to traditional ACTs given its potential to reduce the overall treatment burden.

Previous studies involving people with CF have reported a wide range of ACT and exercise routines being utilised in routine clinical care, with some people undertaking no ACT or exercise at all and others performing both on a daily basis [14,15,21,22]. Given this substantial variability, we believed it was important to standardise ACT and exercise routines prior to participants entering the intervention phase. Therefore, a four week wash-in period was incorporated into our study design for two reasons. Firstly to standardise baseline ACT and exercise routines to ensure that participants were commencing the study intervention period from a common baseline treatment. Secondly to identify participants who were adherent with the ACT and exercise routines pre-randomisation and thus more likely to be adherent with their designated treatment regimen during the intervention period. Whilst our wash-in period achieved these aims, it introduced a complicating factor in deciding what to do with those participants who were adherent with the wash-in period ACT and exercise routines but developed an acute respiratory exacerbation during this time. We chose to retain these participants in our study as we believed that withdrawing them prior to randomisation (which is commonly reported in medication trials) could have biased our sample by selecting out 'non-responders', affecting interpretation of the exacerbation rate data [23]. In the current study, participants who had an exacerbation during the wash-in period (n = 4) were not withdrawn from this study and, by chance, these participants were allocated evenly between the two groups for the intervention period. However they also represented the outliers with regards to change in FEV_1 affecting the interpretation of this data (see Fig. 2). The implications of exacerbations during the wash-in period and subsequent timing of the pre-randomisation phase assessments needs to be further explored.

Given that the current study was a feasibility study, it was not powered to detect significant between-group differences in clinical outcomes. At baseline, the control group was taller and therefore had a higher percentage predicted FEV_1. However, the changes in lung function and HRQOL seemed to be similar for both groups across the assessment periods. The changes in LCQ total scores for both groups were below the previously identified minimum important difference (MID) (2.0) [24]. Both groups demonstrated an increase in the CFQ-R respiratory domain over the intervention period which just exceeded the previously reported lower estimate of the MID [25]. The respiratory exacerbation rates were also similar between groups. This study provides useful information regarding the variability in these measures that will be useful to power a definitive trial in the future.

The protocol used in this study only just achieved or just missed the recruitment and randomisation rates determined a priori and therefore the study protocol may require further refinement in order to increase these rates. Possible options include shortening the wash-in period to two weeks, which would still allow sufficient time to establish adherence and a consistent baseline treatment regimen whilst reducing the chances of respiratory exacerbations occurring. Regular and frequent support from a clinician (e.g. weekly telephone or email contact) during the wash-in and intervention periods may help improve adherence and therefore randomisation rates. It may also be appropriate to consider broadening the inclusion criterion with respect to respiratory function to increase the number of potential participants. We chose to limit recruitment to adults with well-preserved lung function ($FEV_1 \geq 70\%$) as we felt these people were the ones most likely to benefit from the use of exercise-alone as a form of airway clearance. Multi-centred trials should also be considered to ensure adequate participants can be recruited to achieve statistical power.

There were several limitations to this study. As it only included adults with mild respiratory disease, the applicability of these results should not be extrapolated to those with more severe respiratory disease. As participant recruitment was restricted to one site only, the recruitment rates reported may not be generalisable. Exercise capacity was not measured over the course of the study and there may be value in adding a formal evaluation of exercise capacity as a secondary outcome in any larger trial. Another limitation of our study was that it relied on participants' self-reporting adherence with their PEP and exercise interventions which may have led to an over-reporting of adherence levels. While Fitbit© data were recorded, these data were only used to assist participants with reporting of their exercise adherence rather than as a measure of adherence per se. The majority of participants informally reported that use of the Fitbit© and associated software increased their adherence with the exercise regimen. A similar method to promote and measure adherence with PEP would be of value.

5. Conclusion

This study found that, for adults with mild CF-related respiratory disease, a protocol to investigate the use of exercise-only versus exercise plus a specific ACT, just achieved the a priori rate set for recruitment, just missed the randomisation rate and achieved the a priori completion rate. Clinical outcomes appeared similar between treatment groups but given the small numbers involved, further investigation of the medium to longer term effectiveness of exercise as a stand-alone form of airway clearance is required. Modification of the protocol used in this study may enhance recruitment and randomisation rates in larger, adequately powered multi-centred trials in the future investigating the effectiveness of exercise as a stand-alone form of airway clearance in adults with mild CF-related respiratory disease.

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CHAPTER 7: DEVELOPMENT OF THE POSITIVE EXPIRATORY PRESSURE THERAPY RECORDER FOR ASSESSING ADHERENCE (PEPTRAC)

Declaration of authorship – Chapter 7

The nature and extent of contributions to Chapter 7 of this thesis are as follows:

Name	Nature of contribution	Extent of contribution	Signature
Nathan Ward	Study concept and protocol development, data collection and analysis, writing of manuscript and review	60%	
Bruce Ward	Study concept, device development, review of manuscript	17.5%	
Kathy Stiller	Study concept and protocol development, review of manuscript	10%	
Amanda Kenyon	Data collection, review of manuscript	2.5%	
Anne Holland	Study concept and protocol development, review of manuscript	10%	

Supervisor's declaration

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributors made toward Chapter 7 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

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CHAPTER 8: CONCLUSIONS AND FUTURE DIRECTIONS

Conclusions and future directions

8.1. Summary of main findings

The studies presented in this thesis aimed to advance our knowledge regarding the use of exercise as an alternative to traditional ACTs for people with CF. The main findings from the studies in this thesis were:

1. Exercise is a routinely recommended component of the therapeutic regimen in CF, having a multitude of potential respiratory and non-respiratory benefits. Exercise will likely remain a key component of the therapeutic regimen for people with CF into the future, even with the advent of effective disease modulators (Chapter 2).
2. Exercise is likely to be effective at increasing MCC when compared to rest. However, the efficacy of people with CF using exercise as an alternative to traditional ACTs is unclear, as the evidence is limited by short term, heterogeneous studies, often with important methodological limitations, and inconsistent results. There is a paucity of medium or longer term data upon which to base recommendations regarding the use of exercise as an alternative to traditional ACTs in clinical practice. It does however appear vital that if people with CF choose to use exercise as an alternative to traditional ACTs for improving secretion clearance, FET/huffing must be incorporated into the exercise regimen (Chapter 3).
3. In Australia, 43% of adults with CF reported that they believe that exercise can be used as alternative to traditional ACTs for improving secretion clearance, with 44% reporting having used exercise for this purpose in the previous three months. Jogging or running was most frequently identified by participants as the most effective type of exercise to use as an alternative to traditional ACTs. The most commonly performed traditional ACT was PEP (aside from huffing and coughing), with walking being the most commonly used type of exercise. Fifty eight percent of adults with CF reported performing a traditional ACT at least daily, whilst 72% reported exercising at least 3-5 days per week (Chapter 4).

4. The LCQ is a valid, reliable and responsive measure of cough-related HRQOL in CF and may have value as an outcome measure in CF clinical studies. The minimal important difference for the change in total LCQ score in people with CF is 2.0 units (Chapter 5).
5. It is feasible to recruit adults with mild CF respiratory disease to a study investigating the use of exercise as an alternative to traditional ACTs for improving secretion clearance. Adherence to the treatment interventions, particularly with the traditional ACT intervention, may represent a challenge to the success of any future studies. This was demonstrated by lower than expected adherence during the run-in period for the feasibility study, resulting in < 80% of participants being eligible for randomisation. Over the 3-month study duration, the changes in PFTs, HRQOL and respiratory exacerbation data were similar between groups, further adding to the equipoise for a larger, multi-centred, medium to long term study investigating exercise as an alternative to traditional ACTs (Chapter 6).
6. Objective measurement of adherence to positive pressure ACTs is possible, for both session attempts and within session quality. Use of a purpose-designed device, the PEPtrac, revealed variation in positive pressure ACT device technique over a period as short as one week. Objective review of technique and adherence with positive pressure ACT devices should be included in any future studies investigating traditional ACTs where positive pressure devices are used (Chapter 7).

8.2. Implications for clinical practice

There is clear evidence, from Chapter 4 and recent international data, that a large proportion of people with CF consider exercise to be a suitable alternative to traditional ACTs for improving airway secretion clearance.[90] It is unclear however if this is because they consider exercise to be at least as effective as traditional ACTs, or if they are prepared to sacrifice a degree of effectiveness in order to reduce treatment burden. Previous data have indicated that treatment adherence may be related to personal beliefs and that patients are willing to make compromises, including a potential reduction

in lifespan, when selecting which treatment options they prefer.[172, 173] Participants in the study presented in Chapter 4 overwhelmingly indicated that personal experience helped form the basis of their beliefs regarding the use of exercise as an alternative to traditional ACTs, with advice from health professionals or research evidence much less commonly reported. Clinicians should explore these beliefs with individual patients who consider using exercise as an alternative to traditional ACTs. An effort should be made to ensure that people with CF are fully educated on the evidence, or lack thereof, for the use of exercise as an alternative to traditional ACTs and people with CF should be encouraged to include this knowledge in their decision-making process.

Given the lack of clear evidence for exercise being a suitable alternative to traditional ACTs, as presented in Chapter 3 of this thesis, clinicians and people with CF should undertake a shared decision-making process when considering using exercise as an alternative to traditional ACTs. The positive (e.g. reduced treatment burden) and negative (e.g. potentially less effective airway secretion clearance) consequences for each individual patient should be considered in the context of that individual's clinical and social situation, including but not limited to: severity of respiratory disease based on PFT values, frequency of respiratory exacerbations, sputum load, adherence to other components of the treatment regimen, and family and work commitments. Patients should also be educated on the importance of performing the FET/huffing during exercise to promote MCC, particularly if exercise is used as an alternative to traditional ACTs, as the evidence suggests this may be of great importance.

There are currently a paucity of routinely collected clinical data with regards to the types of traditional ACTs and exercise used by people with CF in Australia. Whilst several national CF patient registries (e.g. United Kingdom, Canada) include the types of ACTs used by people with CF in their data sets, the Australian CF Data Registry does not currently collect these data. Efforts should be made to include the primary and secondary ACTs and exercise modalities used by people with CF in all CF data registries. By

collecting such data, clinicians will be able to compare the practices at their centre to other CF centres across Australia and internationally. Collection of these clinical data through national registries will also reduce the need for repeated, time-consuming, multisite studies which require multiple governance approvals in order to collect such clinical data.

The model of CF care delivery is shifting from regular face-to-face clinics to include a greater proportion of clinical reviews occurring via telehealth platforms. The shift to telehealth for service delivery, commenced prior to but accelerated by the current COVID-19 pandemic, means there is likely to be a greater need for home-based monitoring devices so that comprehensive clinical data can be obtained remotely.[174] Historically, physiotherapists have reviewed traditional ACTs at face-to-face clinic visits. These reviews, for example, may include the use of manual manometers to assess whether effective pressure profiles are generated by patients using positive pressure ACTs. However, arguably, the frequency of these well-established face-to-face assessments is unlikely to fully return to pre-COVID levels in the future. Whilst some patients will still be willing to attend onsite, it is anticipated that many will have adapted to the conveniences associated with telehealth and will prefer this method for at least some, if not all, of their clinic appointments. Devices such as the PEPtrac described in Chapter 7 of this thesis, may help to ensure that ACT techniques can still be thoroughly reviewed without the need for the patient to attend an onsite clinic.

Further refinement of the PEPtrac should be considered prior to adopting its use into routine clinical practice. In keeping with the feedback from people with CF, breath and set counts should be included in the device display. There is also potential value in providing an option for automated data upload to cloud-based solutions as well as real-time data streaming capabilities to allow timely review of adherence and technique. Whilst this data transfer could occur via a WiFi or Bluetooth connection with the patient's mobile or home internet device, there is value in exploring independent data upload (e.g.

via an inbuilt 4G transmitter in the adherence monitoring device) in order to minimise the setup requirements of the patient and to allow the device to be as portable as possible.

Another important clinical implication of the studies presented in this thesis is the ongoing need to optimise adherence with exercise and traditional ACTs in CF. As reported in Chapter 4 of this thesis, only 58% of adults with CF in Australia reported performing a traditional ACT on a daily basis. This is consistent with previous reports from the last 20-30 years, suggesting little has changed over this period despite considerable effort towards improving traditional ACT and exercise adherence in CF.[50] Even over a one week period, participants involved in the study described in Chapter 7 of this thesis, did not on average, perform one ACT session per day. There was also notable variability in technique over this one week period. Clinicians should consider whether technology, as presented in Chapter 7 of this thesis, may assist them in monitoring and improving a patient's adherence with positive pressure ACTs. The ongoing relatively poor rates of adherence over time also further highlights the question of whether or not rationalisation of the treatment regimen (e.g. using exercise as an alternative to traditional ACTs), particularly in the era of effective disease modulators, might improve adherence with the remaining components of the treatment regimen. The impact of rationalising components of the treatment regimen needs to be investigated in adequately powered, multi-centred, clinical studies.

8.3. Implications for future research

The findings from the chapters contained in this thesis provide the foundation for several areas of future research, which are discussed below.

8.3.1. Measurement of adherence

The measurement of adherence with exercise and traditional ACTs by people with CF is likely to remain important, particularly as the treatment options available to people with CF expands. However, standardisation of adherence data definitions and improved

adherence data collection methods are required. Whilst questionnaires are commonly used to assess adherence, different recall periods and heterogeneous response categories (e.g. '1-2 days per week' versus 'I often miss several days') are commonly used, making direct comparison of results between studies difficult. Ideally, efforts should be made to standardise both recall periods (e.g. 1 week, 3 months, etc) and response categories (e.g. twice or more per day, once per day, 3-5 times per week, etc) so that data from clinical trials can be directly compared and combined for meta-analysis.

Objective measurement of adherence with positive pressure ACTs is feasible, as shown in Chapter 7 of this thesis. The development of the PEPtrac and other similar devices contributes to the development of more robust methods for clinical trials investigating positive pressure ACTs, as the fidelity of intervention delivery can now be documented.[160, 163, 164, 175] Given the commonly reported discrepancies between self-report and objectively measured adherence, as discussed in Chapters 1 and 7 of this thesis, it is recommended that future clinical trials using positive pressure ACTs utilise devices such as the PEPtrac to objectively measure intervention adherence. Accurate assessment and reporting of adherence with the study protocols will aid in the interpretation of the results from such trials.

The optimal method for measuring adherence with exercise during clinical studies remains unclear. The feasibility study outlined in Chapter 6 of this thesis used a commercial device (Fitbit Charge HR®) in order to promote adherence with the exercise intervention and to guide adherence assessment, but was not relied upon as a sole measure of adherence. Whilst research-grade activity trackers are available, such as the ActiGraph®, their design and functionality may not be appealing to people with CF for use during a longer term study. Commercial activity trackers (e.g. Fitbit Charge HR®, Fitbit Flex®, Garmin Forerunner 45®, Apple iWatch®) report activity as well as provide additional functionality (e.g. show messages from a person's phone) and may be more aesthetically appealing. However, commercial activity trackers may not have the ability to

blind participants to their activity data and may not differentiate between specific types of exercise (e.g. walking/running versus step ups). This may be important if researchers require adherence data for each type of exercise used during a study and needs to be considered as part of the study design process. Further research is required to confirm if the accuracy of the activity data collected from these commercial devices is comparable to that collected by the research-grade devices and if commercial devices are suitable as an outcome measurement tool in clinical studies given the limitations discussed above.[157, 158, 176]

8.3.2. Optimisation of adherence

Whilst the PEPtrac, described in Chapter 7 of this thesis, may be used to objectively measure adherence in clinical trials, its design also means that it may have a potential role for improving adherence with positive pressure ACTs. Randomised controlled studies are required to confirm if devices such as the PEPtrac improve adherence (e.g. number of treatment sessions performed and/or quality of these sessions) with unsupervised ACT sessions and if their use is associated with improved clinical outcomes.[174] The modifications to the device suggested by people with CF, discussed in section 8.2, should be included in future device designs prior to undertaking these studies. The next phases of development of the PEPtrac, including independent data upload, real-time remote data transmission, updated user display and power supply modifications have already been commenced in preparation for these future clinical studies.

As noted earlier, whilst evidence from the general population indicates that the use of commercial activity trackers may improve physical activity levels, further research is required to determine if the use of such devices improves adherence with specific exercise regimens and if this leads to improved clinical outcomes in CF.[174, 177] The implications of using the activity tracker as a method to optimise adherence (which would

be unblinded) versus its use as an outcome measurement tool (which ideally would be blinded) needs to be considered during the study design process.

8.3.3. Specific recommendations for a multi-centred, medium to long term study investigating exercise as an alternative to traditional airway clearance techniques

This thesis provides the foundation for a future multi-centred study to establish whether exercise can be used as an alternative to traditional ACTs. The research studies presented here demonstrated the feasibility of a clinical trial protocol, as well as identifying potentially useful outcome tools. It is clear that there is sufficient equipoise for a medium to long term study investigating exercise as an alternative to traditional ACTs. A recent study found that 73% of health professionals working in CF care would support a trial where some or all traditional ACTs are replaced by exercise, with an additional 8% willing to consider supporting a trial in a carefully selected sub-group of patients.[90] These results indicate there is support from both people with CF and clinicians for the further investigation of the suitability of using exercise as an alternative to traditional ACTs.

There are some specific design considerations that should be taken into account in any future study comparing exercise to traditional ACTs. For example, whilst the aim of such a study will be to investigate the effectiveness of exercise as an alternative to traditional ACTs, it would be considered unethical to withhold exercise from the ACT group due to the non-respiratory benefits of exercise, as summarised in Chapter 2 of this thesis. In other words, it will not be possible to have an ACT-alone group. It would therefore be more appropriate to design the study as an ‘exercise’ versus ‘traditional ACT and exercise’ study. A study with this design could alternatively be thought of as a ‘withdrawal of traditional ACT’ study.

Another design consideration will be which patients with CF are appropriate to recruit for a study investigating exercise as an alternative to traditional ACTs. Historically there

have been concerns about such a study based on short term data supporting traditional ACTs. However these data come from studies conducted prior to the development of the majority of modern day pharmaceutical therapies (e.g. Dornase alfa, hypertonic saline, inhaled tobramycin).[55] People with CF are already commonly using exercise as an alternative to traditional ACTs, with those doing so having a higher mean FEV_1 and lower sputum load compared to those who do not (Chapter 4). Whilst the previous short term studies comparing exercise to traditional ACTs have recruited across the respiratory disease severity spectrum (Chapter 3), limiting recruitment in future medium to longer term studies to individuals with normal or only mildly impaired PFTs (as done in Chapter 6) may allay concerns around withdrawal of the traditional ACT and will ensure the study targets the cohort already most likely to be using exercise as an alternative to traditional ACTs in clinical practice.

Optimising recruitment and retention, a well-documented challenge in CF as discussed in Chapter 1 of this thesis, will be particularly important in the design of future clinical trials. The feasibility study presented in Chapter 6 of this thesis achieved its a priori target for recruitment (≥ 30%) but failed to meet its randomisation target (≥ 80%). All four participants withdrawn for non-adherence during the run-in period were withdrawn due to failure to meet the PEP adherence threshold. Two of these participants also failed to meet the exercise adherence threshold. As this study targeted those with normal or only mildly impaired FEV_1, it is not surprising that adherence with the traditional ACT, which may confer little symptom benefit in those with mild respiratory disease, was a challenge. It is also not surprising that some participants did not reach the exercise adherence threshold given the widely documented challenges with adherence to exercise in both the CF and general population. Detailed education, regular contact and support of participants in any future study will be important, as will objective measurement of adherence. Technology may be able to assist with treatment reminders, however there is some evidence that people with CF may consider support from the clinical (or research) team as being of greater value than technology in promoting adherence.[178] Whilst the

feasibility study described in Chapter 6 of this thesis used monthly calls to review and encourage adherence, more frequent contact (e.g. fortnightly) may be beneficial. In addition to regularly scheduled contact from a clinician or researcher, there may be value in contact with the participant being triggered by adherence monitoring methods alerting researchers to a decrease in adherence below a pre-specified threshold. For example, use of monitoring devices such as the PEPtrac (Chapter 7) or activity trackers which upload data to cloud-based platforms, may allow researchers to initiate contact with participants if adherence falls below a specific threshold over a pre-specified time period. However, the feasibility of translating this intensive support strategy to routine clinical care would require consideration. A combination of regular contact and remote adherence monitoring, for both exercise and ACT interventions, should be considered a core feature of the study design for any future studies investigating the effectiveness of exercise as an alternative to traditional ACTs.

Selection of intervention type will be crucial to the success of any future trial, as adherence with the different ACTs may not be equal. As previously discussed, there are a wide variety of types of traditional ACTs and exercise available for people with CF to use. Whilst there are many factors that may influence adherence, participant preference is one factor that has been linked to adherence to ACTs during clinical studies.[118, 179] Aside from huffing and coughing, PEP is one of the most commonly used traditional ACTs in clinical practice internationally (Chapter 4).[87, 180] Walking and/or running appears to be the most commonly used type of exercise in Australia, with short term physiological data indicating that walking/running may improve MCC (Chapters 3 and 4). These data therefore suggest that a study investigating exercise as an alternative to traditional ACTs should consider the use of PEP as the traditional ACT intervention and walking/running as the exercise intervention.

Selection of appropriate outcome measures will be an important consideration for a future multi-centred study investigating the effectiveness of exercise as an alternative to

traditional ACTs. Spirometry, particularly FEV_1, remains the PFT outcome of choice for measuring respiratory disease in CF and is likely to be the most robust choice as a primary outcome. The FEV_1 is feasible to measure, sensitive to change and strongly associated with long term clinical outcomes in CF.[119] It is also recommended that frequency of respiratory exacerbations be included as an outcome. Whilst there remains no clear consensus, a very specific respiratory exacerbation definition, such as those as used in studies investigating Dornase alfa or modulator therapies, should be used.[133, 134] Whilst having slight differences, these definitions specify that there needs to be new antibiotic therapy commenced as a result of a change in at least four signs or symptoms. If recruiting adults with mild respiratory disease, there may also be value in including a second, broader definition of a respiratory exacerbation. For example, a respiratory exacerbation may be defined as any physician-initiated, new antibiotic therapy, for any change in symptoms deemed clinically important. This will ensure that mild respiratory exacerbations, not just those resulting in a change of at least four signs or symptoms are identified. This may be particularly important for a study only recruiting people with minimal CF-related respiratory disease who may have less severe respiratory exacerbations. These different respiratory exacerbation definitions should be reported as separate outcomes in the study results. The measurement of HRQOL should also be considered an essential outcome measure. The CFQ-R is an obvious choice for measuring HRQOL due to its widespread use and multiple domains. As demonstrated in Chapter 5 of this thesis, there is also value in using the LCQ to assess for changes in cough-related HRQOL, as cough is one of the most common and bothersome symptoms in CF.[149, 181] It is also one of the symptoms most frequently reported by people with CF as being improved by exercise or traditional ACT (Chapter 4). The LCQ was found to be valid, reliable and responsive to change and has since been used in a study investigating different inhalation therapy and ACT regimens in CF.[182]

In addition to the outcome measures used successfully in the feasibility study described in Chapter 6 of this thesis, there is merit in future studies considering the use of newer

outcome measures, with LCI and impulse oscillometry the leading contenders. Whilst one small study has shown that a single session of exercise and airway clearance may not affect LCI measurement, current research is investigating the usefulness of both of these measures for assessing change associated with performance of ACTs.[183, 184] Until the usefulness of these measures in evaluating ACTs is clarified, it is recommended that these measures be included as secondary outcomes.

Table 8.1 provides a summary of the recommendations for the design features of a multi-centred study investigating exercise as an alternative to traditional ACTs, based on the findings of this thesis. Given that traditional ACTs are already a well-established component of the therapeutic regimen in CF, this study will need to be designed as a non-inferiority study, to address the hypothesis that exercise is not an inferior alternative to traditional ACTs. The duration of the study is also important to consider. It needs to be long enough to identify any differences in PFTs, respiratory exacerbations and HRQOL between the study groups whilst minimising the overall burden to the participants, as an excessively long study duration may adversely affect adherence with the study interventions. Based on other longer term studies comparing ACT options in CF, a 12-month intervention period is considered to be a reasonable compromise between these two competing elements.[117, 185]

Table 8.1: Summary of a proposed protocol of a multi-centred, medium to long term study investigating the use of exercise as an alternative to traditional ACTs.

Component	**Proposed**
Design	Prospective, randomised, controlled, non-inferiority trial 4 week run-in period 12 month intervention period
Participants	People with CF aged ≥ 18 years FEV_1 > 70% percent predicted
Intervention	Exercise: walking/running, step-ups as an alternative if circumstances prevent walking/running (e.g. inclement weather); FET/huffing every 4-5min during exercise Support/contact from a member of the research team every 2 weeks, with additional telephone calls triggered based on adherence data
Comparator	ACT: PEP therapy Exercise: walking/running, step-ups as an alternative if circumstances prevent walking/running (e.g. inclement weather); FET/huffing every 4-5min during exercise
Outcomes	Primary outcome: absolute change in FEV_1 percent predicted Secondary outcomes - PFTs: FVC, FEF_{25-75}, LCI, IOS - Respiratory exacerbations - HRQOL: CFQ-R, LCQ - Adherence: PEPtrac (or like device), activity tracker (?commercial device), questionnaire

CF: cystic fibrosis; FEV1: forced expiratory volume in one second; FET: forced expiratory technique; ACT: airway clearance technique; PEP: positive expiratory pressure; FVC: forced vital capacity; FEF25-75: forced expiratory flow at 25-75% of vital capacity; LCI: lung clearance index; IOS: impulse oscillometry; HRQOL: health-related quality of life;

CFQ-R: cystic fibrosis questionnaire (revised); LCQ: Leicester cough questionnaire; PEPtrac: positive expiratory pressure therapy recorder for assessing adherence

8.4. Conclusions

Exercise is commonly used by adults with CF as an alternative to traditional ACTs for improving airway secretion clearance. Whilst short term evidence suggests exercise improves MCC compared to rest and may be a suitable alternative to traditional ACTs, there are a paucity of medium to long term data to support or refute this practice. The research findings presented in this thesis provide the foundation for a multi-centred, medium to long term study investigating the effectiveness of exercise as an alternative to traditional ACTs for people with CF. This study needs to be considered a high priority for the CF community.

APPENDICES

Appendix A.1 - Ethics approval certificates for Chapter 4

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 21 June 2016

Mr Nathan Ward
Department of Physiotherapy
ROYAL ADELAIDE HOSPITAL

Dear Mr Ward,

Project Title: "Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice."

HREC reference number: HREC/16/RAH/173

CALHN Reference number: R20160501

Thank you for submitting the above project for ethical and scientific review. This project was first considered by the Royal Adelaide Hospital Human Research Ethics Committee at its meeting held on 25 May 2016.
I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research, incorporating all updates*. The documents reviewed and approved include:

- NEAF Application: AU/1/E2B5213. Site/s covered by this approval:
  - Royal Adelaide Hospital: CPI – Mr Nathan Ward
  - John Hunter Hospital, NSW: AI – Ms Tara Smith
  - Gold Coast University Hospital, QLD: AI – Mr Andrew Shaw
  - Mater Hospital Brisbane, QLD: AI – Ms Danielle Shortall
  - Royal Prince Alfred Hospital, NSW: AI – Dr Ruth Dentice
  - The Prince Charles Hospital, QLD: AI – Ms Kathleen Hall
  - The Alfred Hospital, VIC: AI – A/Prof Brenda Button
  - Westmead Hospital, NSW: AI – Ms Jennifer Bishop
  - Monash Medical Centre, VIC: AI – Ms Jennifer Corda
  - Gosford Hospital, NSW: AI – Ms Clare Chung
- Cover letter/investigators statement, dated 26 April 2016
- Protocol:, Version 1, dated 27 April 2016
- Participant Information Sheet, Version 2, dated 09 June 2016
- Questionnaire: Exercise and airway clearance in cystic fibrosis
- Response to request for further information letter, dated 20 June 2016
- Victorian-Specific Module, signed by Nathan Ward, Dept of Physiotherapy, dated 26 April 2016.
  - *Note that Section 3 involves information about 'Collection of information' in relation to Victorian Privacy Laws, and should be reviewed through the Governance Processes at Victorian sites.*

HREC approval is valid for **5 years** from **21 June 2016 to 21 June 2021.**

Please quote the **HREC Reference number, HREC/16/RAH/173** and the **CALHN Reference number, R20160501** and allocated to your study on all future correspondence.

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- For all clinical trials, the study must be registered in a publicly accessible trials registry prior to enrolment of the first participant.
- This HREC is certified with the NHMRC for National Mutual Acceptance of Single Ethical and Scientific Review of Multi-centre Clinical Trials. This HREC will act as a 'lead HREC' for the purpose of this ethics approval. Any study sites that are not listed on this letter are not covered by this ethics approval. Any study-sites that wish to be added must contact the CPI, who must write formally to this HREC requesting the additional study site.
- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.

- Researchers must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
  (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
  (b) changes to the protocol,
  (c) premature termination of the study
- The Committee must be notified within 72 hours of any serious adverse event occurring at each approved site.
- Confidentiality of the research subjects shall be maintained at all times as required by law.
- Approval is valid for **5 years** from the date of this letter, after which an extension must be applied for.
- Annual review reports must be submitted to the HREC, every 12 months on the anniversary of the above approval date. Each site covered by this HREC must submit a report, and it is the responsibility of the Coordinating Principal Investigator to ensure this is provided to the RAH HREC Executive Officer, within 10 working days on each anniversary of the approval date, using the Annual Review Form available at: https://www.rahresearchfund.com.au/rah-research-institute/for-researchers/human-research-ethics/
- The REC must be advised with a final report or in writing, and a copy of any published material, within 30 days of completion.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at any site until separate authorisation from the Chief Executive or delegate of that site has been obtained. For any queries, please contact the CALHN Governance Office: Health.CALHNResearchGovernanceIP&Contracts@sa.gov.au

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research (2007)* incorporating all updates.

Should you have any queries about the HREC's consideration of your project, please contact Mrs Heather O'Dea, Executive Officer on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

The HREC wishes you every success in your research.

Yours sincerely,

[redacted]

Digitally signed on behalf of the
Research Ethics Committee
Royal Adelaide Hospital
Time: 2016.07.05 17:50:05 CST

A/Prof A Thornton
CHAIRMAN
RAH HUMAN RESEARCH ETHICS COMMITTEE

LA TROBE UNIVERSITY

COLLEGE OF SCIENCE, HEALTH & ENGINEERING

MEMORANDUM

To: **Professor Anne Holland**

Student: **Nathan Ward**

From: **Secretariat, SHE College Human Ethics Sub-Committee (SHE CHESC)**

Reference: **SHE CHESC acceptance of Royal Adelaide Hospital HREC approved project – HREC/16/RAH173.**

Title: **Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice.**

Date: **25 July, 2016**

Thank you for submitting the above protocol to the SHE College Human Ethics Sub-Committee (SHE CHESC). Your material was forwarded to the SHE CHESC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Royal Adelaide Hospital HREC**, the SHE CHESC 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 Royal Adelaide Hospital HREC.

Limit of Approval. La Trobe SHE CHESC endorsement is limited strictly to the research protocol as approved by The Royal Adelaide Hospital HREC.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by The Royal Adelaide Hospital HREC for the project should be notified formally to the SHE CHESC

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

Final Report. A copy of the final report is to be forwarded to the CHESC within one month of it being submitted by The Royal Adelaide Hospital HREC.

If you have any queries related to the information above or require further clarifications, please contact chesc.she@latrobe.edu.au. Please quote reference number **HREC/16/RAH173 – Holland/Ward**.

On behalf of the College Human Ethics Sub-Committee, best wishes with your research!

Ms Kate Ferris
Human Ethics Officer
Secretariat – SHE College Human Ethics Sub-Committee
Ethics and Integrity / Research Office
La Trobe University Bundoora, Victoria 3086
E: chesc.she@latrobe.edu.au
[redacted]
http://www.latrobe.edu.au/researchers/ethics/human-ethics

ACT Government
Health

ACT Health
Research Ethics and Governance Office
Human Research Ethics Committee

Ms Margot Green
Physiotherapy Department
Canberra Hospital
Garran ACT 2605

Dear Ms Green,

Re: ETH.1.17.009E

Thank you for your letter of 12 December 2016 submitting the following study for site governance review:

Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice

ACT Health recognises the ethical and scientific review and approval of certified Human Research Ethics Committees (HREC). In this case I note the ethical review and approval from Royal Adelaide Hospital HREC, dated 21 June 2016.

The above named study is approved to commence at ACT Health sites as per the submissions approved by the lead reviewing HREC:

- Royal Adelaide Hospital HREC Letter of Approval 19 September 2016 - Protocol v2, dated 12 September 2016 and Participant Information Sheet v3, dated 11 September 2016

The following site specific documents have also been approved:

- Participant Information Sheet: Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice (Canberra) version 1 dated 6 October 2016

Please see conditions of approval on the following page.

This correspondence will be reported to the ACT Health HREC meeting of 6 February 2017.

Yours sincerely,

[redacted]

August Marchesi
Director
Research Ethics and Governance

13 December 2016

Outcome of Consideration of Protocol

Submission No: ETH.1.17.009E Date of Approval: 13 December 2016

Project Title: Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice

Submitted by: Ms Margot Green

Approval Period: 5 years from 13 December 2016 to 13 December 2021

First Annual Review due: 1 December 2017

Conditions of Approval

The following items are required for noting:

- All items submitted to and approved by the lead reviewing HREC to be notified to Health Research Ethics and Governance Office, including but not limited to:
    - Protocol amendments
    - Investigator brochure updates
    - Patient recruitment and retention materials intended for use at ACT Health sites
- All safety monitoring reports submitted to the lead reviewing HREC to be notified to ACT Health Research Ethics and Governance Office, including but not limited to:
    - Data Safety and Monitoring Board reports
    - unforeseen events that may affect the continued ethical acceptability of the project

The following items are required for review:

- Annual project progress report on the conduct of the study at ACT Health sites
- Current insurance certificate, annually or as required
- Any items or reports required by regulation or ACT Health policy

[redacted]

August Marchesi
Director
Research Ethics and Governance
13 December 2016

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

05 September 2016

Ms Hauser
C/- Physiotherapy Department
Royal Hobart Hospital
GPO Box 1061
Hobart Tas 7001

Sent via email

Dear Ms Hauser

REF NO: H0015945
TITLE: Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice

Document	***Version***	***Date***
PROTOCOL	Version 1	27/4/2016
Participant Information Sheet (Tas)	Version 3	19/7/2016
Questionnaire - Exercise and airway clearance in cystic fibrosis	Version 1	26/4/2016
Prior approval application form	-	-

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **30 August 2016** to be conducted at the following site(s):

Royal Hobart Hospital
Launceston General Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 30 August 2017. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

[redacted]

Lauren Black
Acting Research Integrity Coordinator & Executive Officer, Health and Medical Human Research Ethics Committee
Research Integrity and Ethics Unit
Office of Research Services
University of Tasmania
Private Bag 01
Hobart Tas 7001
[redacted]

Government of **Western Australia**
North Metropolitan Health Service
Sir Charles Gairdner Osborne Park Health Care Group

Our Ref: 2016-110 - letter – HREC approval -

Sir Charles
Gairdner Hospital

3 August 2016

Mr Nathan Ward
Physiotherapy Department
Royal Adelaide Hospital
NEDLANDS WA 6009

Dear Mr Ward

HREC No: 2016-110
Project Title: Exercise and airway clearance practices of adults with cystic fibrosis: current Australian practice

The ethics application for the above study was reviewed by the Sir Charles Gairdner and Osborne Park Health Care Group (SCGOPHCG) Human Research Ethics Committee (HREC) through its low risk review process. The study has been approved and the following documents have been approved for use in this project.

Documents
Protocol, version 1 dated 27 April 2016
Questionnaire, version 1 dated 26 April 2016
Participant Information Sheet and Consent Form, version 2.1 dated 29 July 2016

Approval of this project from the Sir Charles Gairdner Group HREC EC00271 is valid until 3 August 2021 and is valid on the basis of compliance with the *Conditions of HREC Approval for a Research Project*.

The nominated participating site/s in this project is/are:

Sir Charles Gairdner Hospital

A copy of this ethical approval letter must be submitted by all site Principal Investigators to the Research Governance Office, or equivalent body or individual, at each participating institution in a timely manner to enable the institution to authorise the commencement of the project at its site/s.

This letter constitutes ethical approval only. Site authorisation is required prior to commencing the study.

The SCGOPHCG HREC is registered with the National Health and Medical Research Council and operates according to its *National Statement on Ethical Conduct in Human Research (2000)*.

Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee,
Level 2 A Block, Hospital Ave, Nedlands, WA 6009
Telephone (08) 6457 2999 Fax (08) 6457 3307 ABN: 13 993 250 709
Email HREC.SCGH@health.wa.gov.au Website www.scgh.health.wa.gov.au

Should you have any queries about the HREC's consideration of this project, please do not hesitate to contact the HREC Office. In addition, the HREC's *Terms of Reference*, *Standard Operating Procedures 2016*, membership list and standard forms are available online.

Yours sincerely

[redacted]

Selina Metternick-Jones
Delegate of the Chair
Human Research Ethics Committee
Sir Charles Gairdner and Osborne Park Health Care Group
03/08/2016 11:09

Appendix A.2 - Ethics approval certificates for Chapter 5

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 3, Hanson Institute, IMVS Building
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Fax: +61 8 8222 3035
Email: rah.ethics@health.sa.gov.au

Approval Date: 2 January 2015

Mr Nathan Ward
Physiotherapy Department
Royal Adelaide Hospital

Dear Mr Ward,

HREC reference number: **HREC/15/RAH/2**

Project Title: **"Assessment of respiratory symptoms in cystic fibrosis."**

RAH Protocol No: 150101.

Thank you for submitting the above project for ethical review. This project was considered by the Chairman of the Royal Adelaide Hospital Human Research Ethics Committee. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*. The documents reviewed and approved include:

- **Protocol, Version 1**
- **Participant Information Sheet, Version 1, November 2014**
- **Consent Form, Version 1, 14 November 2014**
- **Cystic Fibrosis Questionnaire, Revised 2002**
- **Leicester Cough Questionnaire**
- **Respiratory Symptoms in CF (ReS-CF) Questionnaire**
- **Global Rating of Change Score**
- **Demographic Data**
- **Advertisement**

Please quote the RAH Protocol Number allocated to your study on all future correspondence.

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.
- You must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
  (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
  (b) changes to the protocol,
  (c) premature termination of the study.
- The Committee must be notified within 72 hours of any serious adverse event occurring at this site.
- Approval is valid for **5 years** from the date of this letter, after which an extension must be applied for. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the above approval date, within 10 workings days, using the Annual Review Form available at: http://www.rah.sa.gov.au/rec/index.php
- The REC must be advised with a report or in writing within 30 days of completion.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on [redacted] or rah.ethics@health.sa.gov.au .

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research* (2007). The HREC wishes you every success in your research.

Yours sincerely,

[redacted]

for
A/Prof A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

LA TROBE UNIVERSITY

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Dr Anne Holland, Physiotherapy, College of SHE**

From: **Executive Officer, La Trobe University Human Ethics Committee**

Subject: **UHEC acceptance of RAH HREC approved project - HREC/15/RAH/2**

Title: **Assessment of respiratory symptoms in cystic fibrosis**

Date: **11 March 2015**

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 **RAH 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 **RAH HREC.**

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

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

Annual Progress Reports. Copies of all progress reports submitted to **RAH 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 **RAH HREC.**

If you have any queries on the information above please e-mail: **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
[redacted]
http://www.latrobe.edu.au/researchers/ethics/human-ethics

Appendix A.3 - Ethics approval certificates for Chapter 6

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 30 December 2015

Mr Nathan Ward
Department of Physiotherapy
ROYAL ADELAIDE HOSPITAL

Dear Mr Ward

HREC reference number: HREC/15/RAH/518
CALHN Reference number: R20151132
Project Title: "Airway Clearance by Exercising in mild Cystic Fibrosis (ACE-CF): a feasibility study."

Thank you for submitting the above project for ethical and scientific review. This project was first considered by the Royal Adelaide Hospital Human Research Ethics Committee at its meeting held on 17 December 2015. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*. The documents reviewed and approved include:

- **NEAF Submission: AU/1/C2E226 Sites covered by this approval:**
  - **Royal Adelaide Hospital: CPI – Mr Nathan Ward**
- **Protocol: Airway Clearance by Exercising in mild Cystic Fibrosis (ACE-CF): a feasibility study, Version 3.0 ACE-CF, dated 27 December 2015**
- **Supplementary Patient Information Sheet for Declining Participation, Version 1, dated 27 December 2015**
- **ACE-CF Participant Information Sheet, Version 2, dated 21 December 2015**
- **ACE-CF Consent Form, Version 2, dated 18 December 2015**
- **Participant Technique Information Sheet, Version 1, dated 27 November 2015**
- **Leicester Cough Questionnaire**
- **Cystic Fibrosis Questionnaire (Revised), Version 2 (CFQ-R)**
- **Assessment forms:**
  - **Baseline Assessment, Version 1, dated 27 November 2015**
  - **Pre-randomisation Assessment, Version 1, dated 27 November 2015**
  - **Completion Assessment, Version 1, dated 27 November 2015**
  - **Adherence Assessment Record, Version 1, dated 27 November 2015**
  - **Monthly Physiotherapy Review, Version 1, dated 27 November 2015**
- **Acute Respiratory Exacerbation Record, Version 1, dated 27 November 2015**
- **Additional ACT Record, Version 1, dated 27 November 2015**
- **Physiotherapy Contact Record, Version 1, dated 27 November 2015**
- **Medication Change and Protocol Violation Record, Version 1, dated 27 November 2015**
- **Adverse Event Record, Version 1, dated 27 November 2015**
- **Participant Withdrawal Record, Version 1, dated 27 November 2015**

Please quote both the **CALHN Reference number, R20151132** and the **HREC Reference number, HREC/15/RAH/518** allocated to your study on all future correspondence.

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- For all clinical trials, the study must be registered in a publicly accessible trials registry prior to enrolment of the first participant.
- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.
- You must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
  (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
  (b) changes to the protocol,
  (c) premature termination of the study
- The Committee must be notified within 72 hours of any serious adverse event occurring at each approved site.
- Confidentiality of the research subjects shall be maintained at all times as required by law.

- Approval is valid for **5 years** from the date of this letter, after which an extension must be applied for. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the above approval date, within 10 workings days, using the Annual Review Form available at: http://www.rah.sa.gov.au/rec/index.php
- The REC must be advised with a report or in writing within 30 days of completion.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at any site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research (2007)* incorporating all updates.

Should you have any queries about the HREC's consideration of your project, please contact Mrs Heather O'Dea, Executive Officer on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

The HREC wishes you every success in your research.

Yours sincerely,

[redacted]

Digitally signed on behalf of the
Research Ethics Committee
Royal Adelaide Hospital
Time: 2016.01.04 22:15:20 CST

A/Prof A Thornton
CHAIRMAN
RAH HUMAN RESEARCH ETHICS COMMITTEE

LA TROBE UNIVERSITY

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Dr Anne Holland, La Trobe University Clinical School, Alfred Health**
Nathan Ward, Department of Physiotherapy, College of SHE

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

Subject: **UHEC acceptance of RAH HREC approved project - HREC/15/RAH/518 (R20151132)**

Title: **Airway Clearance by Exercising in mild Cystic Fibrosis (ACE-CF): a feasibility study**

Date: **13 January 2016**

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 **RAH 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 **RAH HREC.**

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

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

Annual Progress Reports. Copies of all progress reports submitted to **RAH 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 **RAH HREC.**

If you have any queries on the information above please e-mail: **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
[redacted]
http://www.latrobe.edu.au/researchers/ethics/human-ethics

Appendix A.4 - Ethics approval certificates for Chapter 7

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 24 November 2017

HREC Reference number: HREC/17/RAH/270

CALHN Reference number: R20171121
please quote this number in all future correspondence

Mr Nathan Ward

Physiotherapy

ROYAL ADELAIDE HOSPITAL

Dear Mr Ward,

Project Title: "Positive Expiratory Pressure Therapy Recorder for Assessing Compliance (PEPtrac)- Initial Evaluation' (PEPtrac-1)."

Thank you for submitting the above project for ethical review. This project was considered by the Chairman of the Royal Adelaide Hospital Research Ethics Committee. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research* (2007) incorporating all updates. The documents reviewed and approved include:

Document	***Version***	***Date***
HREA Application	AU/1/8802310	09 November 2017
Cover Letter	-	09 November 2017
Investigator Statement		
PEPtrac-1 Protocol	1	09 November 2017
PEPtrac-1 Participant Information Sheet	1	02 November 2017
PEPtrac-1 Participant Consent Form	1	02 November 2017
PEPtrac-1 Treatment Diary	1	02 November 2017
PEPtrac-1 Participant Feedback	1	02 November 2017
PEPtrac-1 Demographics	1	02 November 2017
PEPtrac Product Manual	1	09 November 2017
PEPtrac-1 Quick Start Guide	1	09 November 2017
PEPtrac NATA calibration reports		
Pneu-edge Fittings [EBK-40-20 17170]		
Honeywell sensors ABP series		

Sites covered by this approval:

- Royal Adelaide Hospital, SA: Mr Nathan Ward

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

1. This HREC is the South Australian 'lead HREC' for the purpose of this ethics approval. Any study sites that are not listed on this letter are not covered by this ethics approval. For any SA study-sites within the public health system that are proposed to be added, the CPI must write formally to this HREC requesting the additional study site and a separate formal letter will be issued.
2. Adequate record-keeping must be maintained in accordance with GCP, NHMRC and state and national guidelines. The duration of record retention for all clinical research data is 15 years from the date of publication.
3. Researchers are required to immediately report to this HREC anything which might warrant review of ethical approval of the study, including:
   (a) adverse events which warrant protocol change or notification to research participants;
   (b) changes to the protocol;
   (c) changes to the safety or efficacy of the investigational product, device or method;
   (d) premature termination of the study.
4. The Committee must be notified within 72 hours of any Urgent Safety Measures (USMs) occurring at this or any approved sites.
5. Confidentiality of the research participants shall be maintained at all times as required by law.
6. Approval is valid for **5 years** from the date of this letter, after which an extension must be applied for.

7. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the above approval date, within 10 workings days, using the Annual Review Form available at: https://www.rahresearchfund.com.au/rah-research-institute/for-researchers/human-research-ethics/
8. The REC must be advised with a report or in writing within 30 days of completion.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

Please ensure that approval under the TGA CTN scheme is obtained prior to commencement of the study. Provide acknowledgement of this approval to the Research Governance Office Health.CALHNResearchGovernance@sa.gov.au

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until governance authorisation at that site has been obtained. Please contact the CALHN Research Office Health.CALHNResearchLNR@sa.gov.au

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research* (2007).

The HREC wishes you every success in your research.

Yours sincerely,

[redacted]

A/Prof A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Ward, Nathan (Health)

From: Anne Holland <A.Holland@latrobe.edu.au>
Sent: Tuesday, 19 December 2017 13:45
To: Ward, Nathan (Health)
Subject: Fwd: Externally approved project - A Holland N Ward - RAH - Nov 2017 - Acceptance notification

Professor Anne E Holland
Clinical Chair, Physiotherapy
La Trobe University and Alfred Health
Level 4, The Alfred Centre
99 Commercial Rd
Melbourne 3004 Australia
[redacted]

Begin forwarded message:

From: Human Ethics <humanethics@latrobe.edu.au>
Date: 19 December 2017 at 12:22:48 pm AEDT
To: Anne Holland <A.Holland@latrobe.edu.au>
Subject: Externally approved project - A Holland N Ward - RAH - Nov 2017 - Acceptance notification

LA TROBE UNIVERSITY

ETHICS, BIOSAFETY AND INTEGRITY UNIT – RESEARCH OFFICE

MEMORANDUM

To: Professor Anne Holland, School of Allied Health, College of SHE
From: Human Ethics Officer, University Human Ethics Committee (UHEC)
Reference: Acceptance of Royal Adelaide Hospital HREC approved project – Ref HREC/17/RAH/270
Title: Positive Expiratory Pressure Therapy Recorder for Assessing Compliance (PEPtrac) – Initial Evaluation
Date: 19 December, 2017

Thank you for submitting the above protocol to the University Human Ethics Committee (UHEC). Your material was forwarded to the Chair for consideration. Following evidence of a full review and subsequent final approval by the **Royal Adelaide Hospital HREC**, the 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 **Royal Adelaide Hospital HREC**.

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

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

Annual Progress Reports. Copies of all progress reports submitted to **Royal Adelaide Hospital HREC**, are to be forwarded to the UHEC. Failure to submit a progress report will mean that endorsement for your involvement in this project will be rescinded. An audit related of 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 by **Royal Adelaide Hospital HREC**.

If you have any queries related to the information above or require further clarifications, please contact humanethics@latrobe.edu.au.

On behalf of the UHEC best wishes with your research!

Michelle Selbie
On behalf of
Ms Sara Paradowski
Senior Human Ethics Officer
Executive Officer, University Human Ethics Committee
Ethics and Integrity | Research Office | La Trobe University | Victoria 3086 Australia
[redacted] | **E:** humanethics@latrobe.edu.au | **W:**
http://www.latrobe.edu.au/researchers/research-office/ethics/human-ethics
Research Office Reception +61 3 9479 1144

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From: Anne Holland
Sent: Tuesday, 12 December 2017 10:49 AM
To: Human Ethics <humanethics@latrobe.edu.au>
Subject: HPRM: Externally approved project - A Holland N Ward - RAH - Nov 2017

Hello,

Re: Positive Expiratory Pressure Therapy Recorder for Assessing Compliance (PEPtrac) – Initial Evaluation

Please find a request for review of a study that was recently approved by the Royal Adelaide Hospital HREC. I have attached all the documentation, approval certificate and La Trobe form. The study involves a La Trobe PhD student, Mr Nathan Ward. The RAH HREC approval is on page 82 of the attached PDF.

Best wishes,
Anne

Fw: 32307 Notification of Human Research Ethics Approval - accepted

Bruce Ward <bruce.ward@adelaide.edu.au>
Thu 14/12/2017 10:49 AM
To: Ward, Nathan (Health) <Nathan.Ward2@sa.gov.au>; nathan_ward43@hotmail.com <nathan_ward43@hotmail.com>

Nathan

Approval came through this morning. Copy of page from ResearchMaster is below.

Note that this is covered by AU's Public Liability Insurance.
- Is this acceptable to RAH (ie it is not listed as Professional Indemnity insurance)\
- I am expecting email with copy of insurance certificate

From: hrec_notification@adelaide.edu.au <hrec_notification@adelaide.edu.au>
Sent: Thursday, 14 December 2017 10:10 AM
To: Bruce Ward; a.holland@latrobe.edu.au; amanda.kenyon@sa.gov.au; kathy.stiller@sa.gov.au
Cc: hrec_notification@adelaide.edu.au
Subject: 32307 Notification of Human Research Ethics Approval - accepted

Application ID: 32307
Title: Positive Expiratory Pressure Therapy Recorder for Assessing Compliance (PEPtrac) - Initial Evaluation
Chief Investigator: Ward, Nathan
Primary University of Adelaide Contact: Professor Ward, Bruce
Other Investigators: Ward, Bruce, Ward, Nathan, Stiller, Kathy, Holland, Anne, Kenyon, Amanda

This human research ethics approval notification has been reviewed by the Human Research Ethics Secretariat and Legal and Risk Office and has been accepted.

Please Login to ResearchMaster (https://rme6.adelaide.edu.au/RME6/) and locate the notification form via Ethics Applications, Amendments and Notifications> All Applications tab, and search for the Application ID. Refer to the user guide 'Searching for Ethics Applications in ResearchMaster'.

ResearchMaster Enterprise Login

rme6.adelaide.edu.au

ResearchMaster Enterprise: Please Log In To Continue: User Name * Password * ResearchMaster Enterprise 6.14.0 (39296)

The Review Outcome page of the notification form will outline any conditions that apply to the acceptance of the notification and insurance details.

Office of Research Ethics, Compliance and Integrity
Research Services
The University of Adelaide

System Helpdesk: researchsystems@adelaide.edu.au
User guides: ResearchMaster Home Page or https://www.adelaide.edu.au/research-services/systems-reporting/research-master/#ethics

This email was generated automatically; please do not reply to this email as this email address is not monitored.

Research Master notification

Review Outcome

This page provides the outcome of the reviews by the Human Research Ethics Secretariat and Insurance Office.

Outcome of Review of Notification Form:

Accepted: The University of Adelaide has accepted this notification of Human Research Ethics Committee approval(s). The University of Adelaide's involvement will be indemnified by The University of Adelaide's insurance(s).

Project Title:

University of Adelaide Notification Reference Number:
32307

Date notification processed:
Open the calendar popup.

End date of the primary Human Research Ethics Committee's approval:
Open the calendar popup.

Notification of Human Research Ethics Approval Conditions:

Researchers are required to conduct this project in accordance with the ethics approval(s) received. They are also required to comply with the National Statement on Ethical Conduct in Human Research (2007), the Australian Code for the Responsible Conduct of Research, the University of Adelaide's Responsible Conduct of Research Policy. University of Adelaide researchers must notify the HREC Secretariat by email of any adverse events or changes to their project in accordance with the University of Adelaide's reporting requirements for notifications.

Project Specific Conditions of Acceptance:

Insurance Details:

The University of Adelaide's involvement will be indemnified by the University of Adelaide's insurance(s).

Insurance Comment(s) from Legal and Risk:

Provision of Insurance Certificates:

- [x] Public Liability Certificate of Insurance
- [ ] Professional Indemnity Certificate of Insurance
- [ ] Clinical Trial(s) Certificate of Insurance
- [ ] Medical Malpractice Certificate of Insurance

The Primary University of Adelaide contact will receive relevant Certificate(s) of Insurance by email. Insurance policies held by The University of Adelaide are renewed on a calendar year basis and at the beginning of each year the Primary University of Adelaide contact will be issued the renewed Certificate(s) of Insurance.

Duty of Disclosure:

In order to receive the benefit of insurance, the University must fulfil a "duty of disclosure" to its insurer. This duty requires the University to

notify the insurer of every known fact, circumstance or event (i.e. 'notifiable event') as and when it happens, so that at all times the information relied on by the insurer is correct and complete. Failure to immediately report a notifiable event to the insurer places the University at risk of not being covered by insurance. A notifiable event may be a consequence, fact, event, situation, omission, occurrence, activity or failure to do something that could result in a claim made against the University. It may be words in an email, something said to you or a misrepresentation in a brochure. These 'things' may require a formal or an informal resolution and they may end up in court. For further information about Notifiable Event reporting, please click on the following link:
http://www.adelaide.edu.au/legalandrisk/insurance/notifiableevents/

Appendix B.1 – Publishing agreement for Chapter 2

Exercise as a therapeutic intervention for people with cystic fibrosis

Author: Nathan Ward, , Kathy Stiller, et al

Publication: Expert Review of Respiratory Medicine

Publisher: Taylor & Francis

Date: May 4, 2019

Rights managed by Taylor & Francis

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BACK CLOSE

Appendix B.2 – Publishing agreement for Chapter 3

From: noreply@bmj.com
To: Ward, Nathan (Health)
Subject: Re: Right to include published article in PhD thesis
Date: Tuesday, 29 December 2020 13:49:21

Thank you for your email to bmj.permissions@bmj.com.

If you are an author and wish to use your own article in a thesis please note that this is permitted by your author licence and you do not require permission. Please see your author rights here - https://www.bmj.com/company/products-services/rights-and-licensing/author-self-archiving-and-permissions/.

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Please note that if your request can be put through RightsLink you will not receive a response. Requests that do require a response will be dealt with within 7 working days.

Best wishes,

BMJ Permissions Team

Appendix B.3 – Publishing agreement for Chapter 4

Authors' Rights
Help | Print

RIGHTS & ACCESS

Australian Physiotherapy Association

Article:	**Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis: Australian data.**
Corresponding author:	**Mr. Nathan Ward**
E-mail address:	[redacted]
Journal:	**Journal of Physiotherapy**
Our reference	**JPHYS477**
PII:	**S1836-9553(18)30149-8**
DOI:	**10.1016/j.jphys.2018.11.006**

YOUR STATUS

- I am one author signing on behalf of all co-authors of the manuscript
- We are all UK, Canadian or Australian Government employees and Crown Copyright is claimed

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"Supplemental Materials" shall mean materials published as a supplemental part of the Article, including but not limited to graphical, illustrative, video and audio material.

With respect to any Supplemental Materials that I submit, Australian Physiotherapy Association shall have a perpetual worldwide, non-exclusive right and license to publish, extract, reformat, adapt, build upon, index, redistribute, link to and otherwise use all or any part of the Supplemental Materials in all forms and media (whether now known or later developed), and to permit others to do so. The publisher shall apply the same end user license to the Supplemental Materials as to the Article where it publishes the Supplemental Materials with the Article in the journal on its online platforms on an Open Access basis.

RESEARCH DATA

"Research Data" shall mean the result of observations or experimentation that validate research findings and that are published separate to the Article, which can include but are not limited to raw data, processed data, software, algorithms, protocols, and methods.

With respect to any Research Data that I wish to make accessible on a site or through a service of Australian Physiotherapy Association, Australian Physiotherapy Association shall have a perpetual worldwide, non-exclusive right and license to publish, extract, reformat, adapt, build upon, index, redistribute, link to and otherwise use all or any part of the Research Data in all forms and media (whether now known or hereafter developed), and to permit others to do so. Where I have selected a specific end user license under which the Research Data is to be made available on a site or through a service, the publisher shall apply that end user license to the Research Data on that site or service.

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REVISIONS AND ADDENDA

I understand that no revisions, additional terms or addenda to this Journal Publishing Agreement can be accepted without Australian Physiotherapy Association's express written consent. I understand that this Journal Publishing Agreement supersedes any previous agreements I have entered into with Australian Physiotherapy Association in relation to the Article from the date hereof.

AUTHOR REPRESENTATIONS / ETHICS AND DISCLOSURE / SANCTIONS

I affirm the Author Representations noted below, and confirm that I have reviewed and complied with the relevant Instructions to Authors, Ethics in Publishing policy, Declarations of Interest disclosure and information for authors from countries affected by sanctions (Iran, Cuba, Sudan, Burma, Syria, or Crimea). Please note that some journals may require that all co-authors sign and submit Declarations of Interest disclosure forms. I am also aware of the publisher's policies with respect to retractions and withdrawal (https://www.elsevier.com/about/our-business/policies/article-withdrawal).
For further information see the publishing ethics page at https://www.elsevier.com/about/our-business/policies/publishing-ethics and the journal home page. For further information on sanctions, see https://www.elsevier.com/about/our-business/policies/trade-sanctions

Author representations

- The Article I have submitted to the journal for review is original, has been written by the stated authors and has not been previousl
- The Article was not submitted for review to another journal while under review by this journal and will not be submitted to any othe
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Journal:	**Respiratory Medicine**
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