Longitudinal effects of supervised exercise on lung function, exercise capacity and quality of life in children with cystic fibrosis

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DECLARATION

I, **Sean James Ledger**, confirm that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this has been identified and referenced within the thesis.

This work has not been accepted in any previous application for a degree.

Signed: **Date:** 31.03.2022

ACKNOWLEDGEMENTS

I have certainly been challenged, but I have achieved and learnt far more during my doctoral training than I could ever document in this thesis, for which I am indebted to the finest of supervisory teams. A massive thank you to Professor Eleanor Main for the humour, advice, mentorship, logicality, tenacity, passion, support, and great friendship throughout my time at UCL – you have been an incredible inspiration! To Dr Paul Aurora who provided candid advice, pragmatism, and cynicism that was hugely appreciated, and Professor Angie Wade who tried her hardest to introduce me to the wonders of statistical analysis, and almost succeeded – thank you!

Thank you to the A-team: Helen Douglas, Paul Rayner, Laura Sarria-Jaramillo, Ammani Prasad, Dr Alan Goldman, Sarah Rand, and Louisa Hill who committed their unwavering energy and enthusiasm to *Inspire-CF*. To Stephanie Rees, Emma Fettes, and Emma Raywood who meticulously carried out lung function tests, and to Dr Jane Kirby and Aidan Laverty who helped me extract raw lung function data for analysis, and Dr Alessandro Giardini, Clare Hanrahan, Sophie John, Annelyse Crozier, and Shila Taylor who advised on and assisted with cardiopulmonary exercise tests in an already very busy clinic – thank you all!

Thank you to Professor Emma Stokes and Professor Anand Pandyan, fantastic mentors, for their friendship and relentless curiosity to find answers to big challenges, and their deep integrity for student education and well-being, which has had a marked effect on my approach to academic life.

My hugest round of thanks goes to all the amazingly courageous children with cystic fibrosis who participated in *Inspire-CF*, and their parents and carers who championed the programme.

Thank you to my very fine group of friends who have supported me through the highs and the lows:
Nicky Haskins, *for simply being the finest of the finest;*
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Ryan Callan, *for creating hysterical laughter and filling my wine glass;*
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Sharon Mattiace, *for intense loyalty and laughter;*
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Kathryn Isemonger, *for your incredible grace and humour;*
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Sarah Whyte, *for the endless laughter and the craic;*
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Finally, I would not have been able to complete this journey without my awesome family and extended family who have encouraged me to pursue my dreams and follow my heart. To my extraordinary mum and dad, *Georgina and Peter*, and my brother and sister, *Mark and Simone* who have always been my greatest critics and staunchest of supporters - thank you! I am what I am because of who we all are.

For

JACK & TOM

Thank you to you, and your families, for sharing your amazing life stories with me.

Life is not measured by the number of breaths we take,
but by the moments that take our breath away.

MAYA ANGELOU

ABSTRACT

Longitudinal effects of supervised exercise on lung function, exercise capacity and quality of life in children with cystic fibrosis

Introduction: *Inspire-CF* was a randomised controlled trial that explored the effects of 24-months of supervised exercise on lung function, exercise capacity and quality of life in children aged 6-15 years with CF. A cost of care analysis was completed to understand differences, if any, between groups after 24-months.

Methods: Children were randomised into 2 groups: control and exercise. The control group continued to receive specialist CF care as delivered by the Cystic Fibrosis Unit at Great Ormond Street Hospital for Children. The exercise group continued to receive specialist care plus a once-weekly, individually supervised exercise training session at a local fitness facility. A MBW, spirometry, cycle ergometry-based CPET, 10m-MSWT and the CFQ-R were completed at baseline, 12- and 24-month assessment points. Cost of care, length of stay during hospital admissions, and IV-antibiotic requirements during exacerbations and routine admissions, were also recorded. The primary outcome measure was change in FEV_1 z-score at 24-month assessment.

Results: 71 children were recruited to *Inspire-CF* (control=34; exercise=37), of which 4 children dropped out at 12-months. There were no significant between-group differences in outcomes at baseline. At 24-month assessment, there were no significant between-group differences in FEV_1 z-score, however there was a significant ($p<0.05$) dose-related effect of exercise on FEV_1, FVC and FEF_{25-75}, which suggested exercise may help to maintain lung function. A 10m-MSWT showed that functional aerobic capacity significantly ($p<0.05$) improved in the exercise group. CPET markers of W_{peak} and VO_{2peak} also improved, but between-group differences were not significant. The perception of ability to cope with treatment burden significantly improved in the exercise group. There were significant differences in overall length of stay and IV-antibiotic requirement in favour of the exercise group, but cost of care was not significantly different.

Conclusion: *Inspire-CF* demonstrated that supervised exercise slowed the rate of deterioration in lung function, particularly in younger children, but this required a commitment to regular attendance to exercise.

Keywords: cystic fibrosis, paediatrics, lung function, exercise capacity, quality of life, cost-analysis

IMPACT STATEMENT

A dose of weekly supervised exercise helps to protect lung function in children with cystic fibrosis

Thirty years ago, exercise was considered harmful to children with cystic fibrosis (CF), the most common life limiting disease in Caucasian populations, and was not encouraged. However, in 1982 two landmark studies conducted in children and adolescents with CF, found that exercise was safe and provided health benefits. Since then, regular exercise has been actively promoted and is a core component of the physiotherapy management of children with CF. Much of what is understood about the physiological effects of exercise has been learnt through studies of relatively short duration. Supervised and partially supervised exercise programmes have shown that lung function, exercise capacity, breathlessness, muscle strength and quality of life could be improved. However, the improvements were not maintained when the programmes ended, as children were not motivated to continue exercising at the same intensity without supervision, or simply stopped exercising. Adherence to daily physiotherapy routines of airway clearance and exercise is poor in CF as the routines are time consuming and monotonous, and so the role of the paediatric physiotherapist is to find innovative ways to actively engage children in their self-care.

This research reflects the outcomes of 71 children and adolescents with CF (and their families) who volunteered to take part in *Inspire-CF*. The study was a 24-month randomised controlled trial that explored the effects of an individually supervised exercise programme in children aged 6-15 years with CF. The main finding was that a dose of once-weekly, moderate-to-high intensity exercise helped to slow the rate of deterioration in lung function in children who attended at least 52 weeks of exercise training. However, attendance levels varied between 16% and 91%, and so this positive effect was not realised in all children. Unfortunately, lung function declined at approximately 1.5% annually, which was the same rate as the control group. Nevertheless, the results of a modified-bleep test showed that there was a significant improvement in functional aerobic fitness, with children saying they felt more 'normal' because they could run further, and at the same level or even higher, than their healthy peers. Despite more regular contact with physiotherapists, children's perception of their ability to cope with their treatment burden improved, as did their overall quality of life.

The exercise prescription and training resources that were developed for *Inspire-CF*, may be useful to physiotherapists and researchers in global CF clinical units. The results of the study were presented at numerous international respiratory and physiotherapy conferences, and was the first to identify a dose-related effect of exercise in children with CF. This provides a new direction for future research into minimum levels of exercise required to maintain or improve lung function. Longitudinal supervised exercise programmes are challenging and expensive to implement, so the cost-analyses may help to inform healthcare policy makers decisions, when considering the costs of rolling out similar programmes into clinical practice.

ROLES AND RESPONSIBILITIES

I was co-lead investigator and grant holder with Professor Eleanor Main for the *Inspire-CF* randomised controlled trial, as well as the Team Lead and Lead Physiotherapist and Personal Trainer.

My primary roles and responsibilities included the design of the randomised controlled trial and writing the related protocols; writing the grant application; responding to reviewers; writing the application for ethical approval; recruitment of staff to the study; design of patient information sheets and recruitment strategies; design of the exercise prescription and training protocols; design of all data recording sheets and development of all databases; primary liaison with children and parents/carers; primary liaison with the Great Ormond Street Hospital CF Unit, CF Specialist physiotherapists, administrative teams, lung function testing team and clinical exercise testing team; secured free access to a network of ~46 fitness facilities; day-to-day general management of the team and the study; and dissemination of the results of *Inspire-CF* in academic journals, and conference posters and oral presentations.

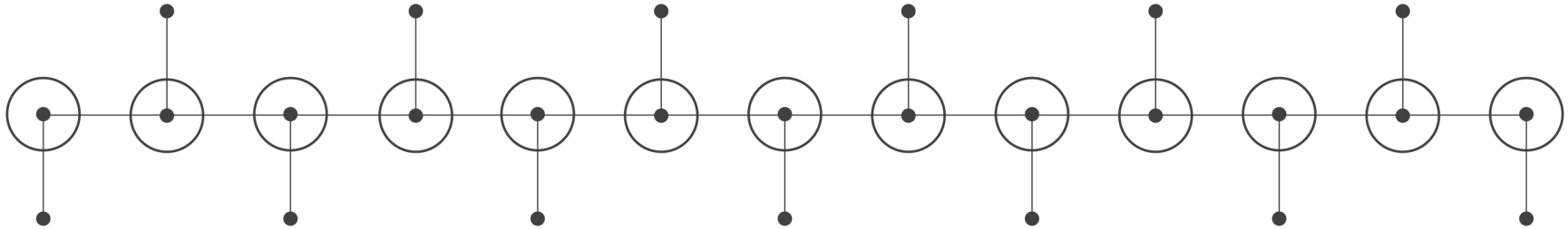
I provided pre-data collection training on the protocols related to lung function, exercise testing, quality of life, finances and admissions data to the *Inspire-CF* research team to ensure standardisation of data collection and testing. Additionally, I provided a 2-week exercise-related training programme to the *Inspire-CF* personal training team, to ensure safety and standardisation of testing and training methods and adherence to protocols throughout the study.

Professor Angie Wade advised on the power calculation for *Inspire-CF* and provided statistical support, advice and guidance on the interpretation of the statistical modelling and results. She also conducted randomisation by minimisation for the study using the customised software package, SiMin (Wade et al., 2006). Based on her advice, I have conducted all the statistical analysis related to lung function, exercise capacity, quality of life, cost of health care and admissions data in this thesis. Additionally, I created all tables and figures shown in this thesis.

Multiple inert gas washout tests and spirometry were conducted by Specialist Respiratory Physiologists Stephanie Rees, Emma Fettes, and Emma Raywood. Dr Jane Kirby and Aidan Laverty helped me extract raw spirometry and growth data, which I independently transformed for analysis using the GLI-2012 Desktop Software for Large Data Sets (Quanjer et al., 2013) and LMSgrowth (Ver 2.74), a Microsoft Excel add-in to access growth references based on the LMS method (Pan and Cole, 2011). I calculated lung clearance indices using raw data provided by the lung function unit. Exercise Physiologists Clare Hanrahan, Sophie John, Annelyse Crozier, and Shila Taylor calibrated the cycle ergometers and gas-analysis equipment and monitored the cardiac outcomes of children during cardiopulmonary exercise tests. Of the ~210 cardiopulmonary exercise tests, I conducted ~175 of these tests, with the remaining tests conducted by Helen Douglas or Paul Raynor. Similarly, of the ~284 10 metre modified shuttle walk tests and ~210 Cystic Fibrosis Questionnaire's completed, I conducted ~200 and ~175 of each of these tests respectively, with the remaining tests conducted by Helen Douglas, Paul Raynor or Laura Sarria-Jaramillo.

The Great Ormond Street Hospital for Children finance department provided a Microsoft Excel spreadsheet, after auditing, of each child's individual costs incurred during the previous financial year, which I then merged and compiled these databases for statistical analysis. I created the database of digitally extracted data on admissions and reasons for admission to hospital from the Patient Information System, and this data was cross referenced for accuracy by Helen Douglas and Laura Sarria-Jaramillo using data provided by the Cystic Fibrosis Unit.

PHD TIMELINE (UCL PART-TIME PATHWAY)



May 2012

Great Ormond Street Hospital Children's Charity research grant of £414,000 awarded to Sean Ledger and Professor Eleanor Main (co-lead investigators) for Inspire-CF.

Nov 2012

Enrolled into MPhil to PhD part-time pathway at the UCL GOS Institute of Child Health.

Inspire-CF research team recruited.

Training of Inspire-CF research team starts and is completed by 1st Feb 2013.

Aug 2012

Ethical approval granted by South-East Kent Research Ethics Committee (#REC 107522/338653/1/748) and UCL GOS Institute of Child Health (#11AR13). Inspire-CF registered as a clinical trial at the U.S. National Institutes of Health, ClinicalTrials.gov (#NCT01889927)

Feb 2013

Enrollment of first participant into Inspire-CF.

Baseline assessments begin.

Rolling recruitment of participants continues until June 2014.

Oct 2013 – May 2015

Approved interruption of studies (19-months).

Research team member takes maternity leave and my personal workload on Inspire-CF is increased, such that an interruption of studies is considered appropriate.

Jun 2014

All 71 participants randomised, enrolled and completed baseline assessments of multiple breath inert gas washout test, spirometry, cardiopulmonary exercise test, 10-meter modified shuttle walk test, Cystic Fibrosis Questionnaire.

May 2015

Re-enrolled into MPhil to PhD part-time pathway at the UCL GOS Institute of Child Health.

Submission of Chapter's 1, 2 and 3 for review.

Jun 2015

All 71 participants completed 12-month assessments of multiple breath inert gas washout test, spirometry, cardiopulmonary exercise test, 10-meter modified shuttle walk test, Cystic Fibrosis Questionnaire, and pre-enrolment health economic data collated.

June 2015

Chapter 4 and Chapter 5 submitted for review.

Data and Safety Monitoring Committee determined that protocols were being maintained, no adverse events had been detected, and that the trial could continue.

Jun 2016

All 71 participants completed 24-month assessments of multiple breath inert gas washout test, spirometry, cardiopulmonary exercise test, 10-meter modified shuttle walk test, Cystic Fibrosis Questionnaire, and 12-month health economic data collated.

Sep 2016 - Jun 2019

Databases checked and prepared for statistical analysis. 24-month health economic data collated in May 2017.

Professor Angie Wade advises on statistical analysis for Inspire-CF.

Analysis of data for Chapter's 6, 7, 8, 9.

Write up of Chapter's 6, 7, 8, 9.

Jul 2019 – Mar 2022

Continuing Research Status (CRS) approved.

COVID-19 impacts CRS (Apr 2020 – Sep 2021).

Chapter's 6, 7, 8, 9, 10 submitted for review.

March 2022

PhD submitted for viva examination on 30th March 2022.

Viva completed on 7th September 2022.

Minor corrections submitted 14th December 2022.

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10m-MSWT	10 metre modified shuttle walk test
95%CI	95% confidence interval
beats·min^{-1}	beats per minute
BMI	body mass index
BP	blood pressure
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire, Revised version
CFTR	cystic fibrosis trans-membrane conductance regulator
cm	centimetre
CO_2	carbon dioxide
CPET	cardiopulmonary exercise test
ECG	echocardiogram
FEF_{25-75}	forced expiratory flow that occurred in the middle 50% of exhaled volume
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
GET	gas exchange threshold
GOSH	Great Ormond Street Hospital for Children NHS Foundation Trust
GP	General Medical Practitioner
Helium	He
HIIT	high intensity interval training
hr·week^{-1}	hours per week
HR	heart rate
HRR	heart rate reserve
HR_{max}	maximum heart rate
HR_{peak}	peak heart rate
HR_{rest}	heart rate at rest
$HR_{recovery}$	heart at rate recovery
Hz	Hertz (events per second)
IV	intravenous
kg	kilograms
L	litres
L·min^{-1}	litres per minute
LCI	lung clearance index
MBW	multiple breath inert gas washout test
MET	metabolic equivalents
min	minutes
min·day^{-1}	minutes per day

$min \cdot week^{-1}$	minutes per week
ml	millilitre
ml·kg	millilitre per kilogram
$ml \cdot kg \cdot min^{-1}$	millilitre per kilogram per minute
mmHg	millilitre of mercury
$mmol \cdot L^{-1}$	millimoles per litre
ms	millisecond
NHS	National Health Service
N_2	nitrogen
Nm	Newton metre as a unit of torque
O_2	oxygen
PI_{max}	maximum peak inspiratory pressure
%pred.	percentage predicted
RER	respiratory exchange rate
$rev \cdot min^{-1}$	revolutions per minute
RPE	rating of perceived exertion
RR	respiratory rate
SD	standard deviation
SF_6	sulphur hexafluoride
SpO_2	peripheral oxygen saturation (as measured by pulse oximetry)
THRR	target heart rate training range
UK	United Kingdom
V_E	minute ventilation
V_E/VO_2	ratio of minute ventilation to rate of oxygen uptake
V_E/VCO_2	ratio minute ventilation to rate of carbon dioxide uptake
VO_2	rate of oxygen uptake
VO_2 at GET	rate of oxygen uptake at the gas exchange threshold
VO_{2peak}	rate of peak oxygen uptake
V_T	tidal volume
W	work rate measured in Watts
W_{GET}	work rate at the gas exchange threshold
$W \cdot kg^{-1}$	work rate adjusted for body mass in kilograms
W_{peak}	peak work rate measured in Watts

LIST OF GRANTS, PUBLICATIONS, CONFERENCE PROCEEDINGS & CASE STUDIES

Research Grant Awards

Ledger SJ*, Goldman A, Giardini A and Main E*. £414,000. Great Ormond Street Hospital Children's Charity Grant. *Inspire-CF*: A randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis. Funded from 1st May 2012 to 30th June 2016. (* co-Lead Investigators).

Peer Reviewed Publications

Ledger SJ, Owen E, Prasad SA, Goldman A, Williams J and Aurora P. (2013) A pilot outreach physiotherapy and dietetic quality improvement initiative reduces IV-antibiotic requirements in children with moderate-severe Cystic Fibrosis. *Journal of Cystic Fibrosis*, 12:766-772.

Editorial

Ledger SJ and Aurora P. Are exercise programs an effective treatment for children with cystic fibrosis? *Clinical Practice*, Sept 2013, Vol. 10, No. 5, Pages 547-550

Conference Abstracts

Ledger, SJ, Douglas H, Main E. (2022) A dose of weekly supervised exercise helps protect lung function in children and young people with cystic fibrosis. *Journal of Cystic Fibrosis*, 21, 2: S270.

Ledger SJ, Douglas H, Sarria-Jaramillo L, Rayner P, Goldman A, Giardini A, Prasad SA, Wade A, Aurora P and Main E. (2017) *Inspire-CF*: a randomised trial evaluating the longitudinal effects of a weekly supervised exercise programme on children with cystic fibrosis. State of the Art Platform Presentation, WCPT Congress 2017, 2-4 July 2017, Cape Town, South Africa.

Douglas H, Bryon M, **Ledger SJ**, and Main E. (2017) My quality of life or yours? The discrepancies between parent and child reported quality of life scores. *Journal of Cystic Fibrosis*, 392, 16: S162.

Ledger SJ, Wade A, Douglas H, Sarria-Jaramillo L, Rayner P, Goldman A, Giardini A, Prasad SA, Aurora P and Main E. (2016) Interim results of *Inspire-CF*: a 24-month RCT evaluating effects of weekly supervised exercise in children with CF. *European Respiratory Journal*, 48: Suppl. 60, OA1493.

Ledger SJ, Wade A, Douglas H, Sarria-Jaramillo L, Rayner P, Goldman A, Giardini A, Prasad SA, Aurora P and Main E. (2016) Interim results for *Inspire-CF*: a 24-month randomised trial evaluating effects of a weekly exercise intervention for children with cystic fibrosis. *Journal of Cystic Fibrosis*, 144, 15: S88.

Ledger SJ, Douglas H, Sarria-Jaramillo L, Rayner P, Aurora P and Main E. (2016) *Inspire-CF*: Levels of participation of children with cystic fibrosis randomised to a 24-month weekly supervised exercise intervention. *Journal of Cystic Fibrosis*, ePS04.5, 15: S44.

Douglas H, Ahlquist A, **Ledger SJ**, Prasad SA, Hill L, Dudley J and Rand S. (2016) 5-year milestone reached in collaborative partnership between CF Unit and UK fitness provider. *Journal of Cystic Fibrosis*, 145, 15: S88.

Ledger SJ, Douglas H, Sarria-Jaramillo L, Rayner P, Aurora P and Main E. (2015) *Inspire-CF*: An interim review of participation of children with cystic fibrosis randomised to a weekly supervised exercise intervention. *Journal of Cystic Fibrosis*, 14, S97.

Douglas H, Main E, Rand S, Giardini A, Aurora P and **Ledger SJ**. (2015) A case of asymptomatic exercise and Wolff–Parkinson–White syndrome: Physio's be aware! *Journal of Cystic Fibrosis*, 14, S141.

Douglas H, Main E, Rand S, Giardini A, Aurora P and **Ledger SJ**. (2015) Routine ECG monitoring for patients with cystic fibrosis: physiotherapists be aware! *Physiotherapy*, Volume 101, Supplement 1 eS932.

Physiotherapy Case-Presentations

Douglas H, Main E, Bryon M, Rand S, Aurora P and **Ledger SJ**. "A case of exercise, weight-loss, body image and a feisty teenage attitude!", 38th Annual European Cystic Fibrosis Conference, Basel, Switzerland; June 2016.

Douglas H, Main E, Rand S, Goldman A, Giardini A, Aurora P and **Ledger SJ**. "Wolff-Parkinson White: a dangerous wave to surf!" Presented at the 37th Annual European Cystic Fibrosis Conference, Belgium, June 2015

Douglas H, Main E, Rand S, Goldman A, Giardini A, Aurora P and **Ledger SJ**. "A case of asymptomatic exercise and Wolff-Parkinson White Syndrome: Physio's be aware!" WCPT Congress, Singapore, 2015.

PREFACE

Childhood should be an energetic and a fun-filled time of life, spent with friends and teammates on playgrounds and sport fields. For children with moderate-to-severe cystic fibrosis (CF) lung disease, childhood can follow a very different and challenging pathway. Impaired lung function caused by inflammation and frequent lung (Bradley et al., 2001, van de Weert-van Leeuwen et al., 2012, van de Weert-van Leeuwen et al., 2013, van de Weert-van Leeuwen et al., 2014) poor nutritional status (Marcotte et al., 1986), peripheral muscle weakness (de Meer et al., 1999), reduced skeletal muscle oxidative capacity (Erickson et al., 2015), genotype (Selvadurai et al., 2002b), gender (Selvadurai et al., 2004), and repeated admissions to hospital (Britto et al., 2002) can all contribute to reduced exercise tolerance. Historically, the view was that exercise was detrimental to health, and was not advocated for children with CF (Dodd and Prasad, 2005). However, the safety of exercise in CF was confirmed in two exercise studies conducted in children and adolescents by Cerny et al. (1982) and Cropp et al. (1982), and since then exercise has formed an integral component of physiotherapy in CF (Wilkes et al., 2009, van Doorn, 2010).

Increased exercise capacity has been demonstrated to lower mortality risk (Nixon et al., 1992, Pianosi et al., 2005a), to improve and/or maintain lung function (Hebestreit et al., 2010, Paranjape et al., 2012, Kriemler et al., 2013), reduce breathlessness (O'Neill et al., 1987), increase aerobic and anaerobic capacity (Selvadurai et al., 2002a, Orenstein et al., 2004, Santana-Sosa et al., 2012) and improve quality of life (Schmidt et al., 2011, Hebestreit et al., 2014). Regular exercise may also lower the risk for hospitalisation for treatment of respiratory exacerbations (Perez et al., 2014) and reduce cost of healthcare (Ledger et al., 2013). Whilst exercise has been acknowledged to be safe and is actively encouraged in all severities of lung disease (Wilkes et al., 2009), the available evidence on the benefits of exercise has been primarily demonstrated through short-term randomised controlled trials (Radtke et al., 2015). Supervised exercise programmes have produced better outcomes than partially supervised and unsupervised programmes, but supervised exercise programmes are expensive and complex to implement (Gulmans et al., 1999). Although longitudinal trials have been suggested (Bradley and Moran, 2008, Radtke et al., 2015), they may not have been prioritised by CF research groups because of these reasons.

Observational 12-month studies conducted in the sickest, and typically least adherent group of children who require frequent admissions to hospital, have shown that weekly supervised exercise could slow the rate of decline in lung function and improve exercise capacity and quality of life (Urquhart et al., 2012, Ledger et al., 2013). Children who participated in these studies also reported that they were able to perform exercise at the same level as their peers, and sometimes even higher (Ledger et al., 2013). However, motivating children to undertake moderate-to-high intensity exercise is highly dependent on the child's willingness to exercise (Prasad and Cerny, 2002), which has made evaluating maximal exercise capacity challenging.

There have been determined efforts to define the most appropriate exercise test to measure exercise capacity in children with CF (Godfrey, 1970, McKone et al., 1999, Karila et al., 2001, Werkman et al., 2011, Hulzebos et al., 2012, Saynor et al., 2013a), and the Godfrey (1970) cycle ergometer based cardiopulmonary exercise test (CPET) is currently advocated as the gold standard test (Hebestreit et al., 2015). Limitations to exercise are similar in both CF and healthy children, with optimal exercise performance determined by 3 key mechanisms: (1) ventilatory ability to supply oxygen (O_2), (2) circulatory capacity to deliver O_2 to, and remove carbon dioxide (CO_2) from muscles, or (3) muscular consumption of O_2 for energy conversion (Urquhart, 2011). However, increased alveolar dead space, caused by CF lung disease, may also limit a child's ability to increase alveolar ventilation during exercise (Thin et al., 2004). Consequently, the two key indicators of level of exercise capacity, peak oxygen consumption (VO_{2peak}) and peak work rate (W_{peak}), are ostensibly lower in children with CF than in healthy children (Groen et al., 2010).

Exercise programmes by nature of design should include 3 core components: exercise testing, exercise prescription and exercise training. Exercise guidelines for testing, prescription and training of healthy children are well documented (Behm et al., 2008, Faigenbaum and Myer, 2010a, Thompson, 2010). However, whilst exercise testing in CF has seen significant development and resulted in a consensus statement (Hebestreit et al., 2015), disease specific exercise prescription and training guidelines are less well defined. The primary reason for this is that previous studies have not clearly described their exercise prescriptions and/or published their exercise training protocols.

RESEARCH QUESTIONS

This thesis addresses the following 2 research questions:

1. Does a weekly supervised, individually tailored exercise training programme, provided in addition to current specialist CF care, produce significant improvements in lung function, exercise capacity, and quality of life, in children aged 6-15 years, with a wide range of lung disease severity?
2. Is there a health-economic benefit associated with the provision of a weekly supervised, individually tailored exercise training programme in children aged 6-15 years with CF, and a wide range of lung disease severity?

AIMS AND OBJECTIVES

The aim of this thesis was to address these questions by undertaking *Inspire-CF*, an entirely funded, 24-month, fully powered, single centre, randomised controlled trial focused on supervised exercise in children with CF, who were treated at Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) in the United Kingdom (UK). A healthcare economic analysis was completed, as it may help healthcare policy decision makers when considering the length of stay, impact of IV-antibiotics requirements, and cost of healthcare when considering the implementation of a similar programme into clinical practice.

The broad objectives of this thesis were to:

- Design and implement a 24-month, structured programme of exercise testing, prescription, and training.
- Understand between-group differences, if any, after a 24-month exercise intervention in:
    - lung function;
    - exercise capacity;
    - quality of life; and
    - cost of healthcare.
- Determine the dose-related effect of exercise, if any, on lung function.

STRUCTURE OF THE THESIS

This thesis is comprised of 10-chapters: **Chapter 1** describes the pathophysiology of CF, the trajectory of lung function, and the medical and physiotherapy management of the disease. **Chapter 2** provides a comprehensive review of the published literature prior to the start of *Inspire-CF*, related to exercise focused randomised controlled trials conducted in children with CF. **Chapter 3** describes the general methodology employed in the research. The design of the *Inspire-CF* exercise programme is described in **Chapter 4**, and **Chapter 5** provides an overview of the study population. The effects of the exercise programme on lung function, exercise capacity and quality of life are documented in **Chapter's 6–**, **7–**, and **8** respectively. **Chapter 9** provides a comprehensive analysis of health economic outcomes. **Chapter 10** provides a summary and synthesis of the findings from *Inspire-CF* and considers the potential impact of the findings on the general population of children with CF. The chapter also provides an update on evidence published after *Inspire-CF* was completed in June 2016, primarily related to trajectory of lung function, updated exercise testing protocols, the effects of exercise on lung function and exercise capacity, a reflection on the impact of CFTR modulator therapies on exercise, recommendations for future research, and the conclusion.

The terms *'child'* and *'children'* are used in this thesis to describe children and young people aged 6-17 years.

The terms '*physical activity*' and '*exercise*' are used in this thesis, and are based on Caspersen et al. (1985) definitions. '*Physical activity'* is defined as: "any bodily movement produced by skeletal muscles that results in energy expenditure. The energy expenditure can be measured in kilocalories. Physical activity in daily life can be categorised into occupational, sports, conditioning, household, or other activities." **Chapter 5, Table 5–3, pg.124** outlines the types of general physical activities children participated in at baseline and may have continued throughout the study. *'Exercise'* is defined as: "a specific type of physical activity that is planned, structured and repeatedly done to improve or maintain physical fitness". The children enrolled in the *Inspire-CF* exercise group undertook a structured, supervised and individually prescribed exercise programme that is explained in **Chapter 4, Subheading 4.7, pg.107**

1.

CHAPTER 1. INTRODUCTION

1.1. Pathophysiology of cystic fibrosis

CF is the most common genetically inherited autosomal recessive disease in Caucasian populations, with a current carrier rate of 1:25 and an incidence of 1:2500 live births, and there are 200-300 new diagnoses in the UK each year (O'Sullivan and Freedman, 2009). In 2013, there were 10,338 adults and children registered with the disease in the UK CF Registry, with a median predicted survival age of 36.6 years (Cystic Fibrosis Trust, 2014). The life-limiting disease is caused by a mutation in the gene coding protein, the cystic fibrosis trans-membrane conductance regulator (CFTR) on the long arm of chromosome-7 (Riordan et al., 1989). Abnormal CFTR function affects the transportation of sodium ions across chloride channels that are required for epithelial cell functioning, which results in depletion of airway surface liquid and an increase in viscosity of mucociliary secretions (Collins, 1992). As a consequence of this defect, multiple organs, but primarily the lungs, pancreas, liver and digestive system become congested with thick sticky mucous, that triggers recurrent bacterial infections and inflammation (Ratjen and Doring, 2003). More than 85% of CF-related deaths are caused by lung disease, therefore regular monitoring to preserve or slow the rate of decline in lung function is the core focus of CF medical management (Gibson et al., 2003)

Diagnosis of CF in most countries with high prevalence levels, including the UK, is through a new-born screening process (Mayell et al., 2009). Infants that show markedly high-concentrations of immuno-reactive trypsinogen extracted during a heel-prick blood test taken in the first week of life, are typically referred to a specialist CF centre for a diagnostic sweat test. A sweat chloride concentration of ≥ 60 mmol$\cdot L^{-1}$ on repeated analysis is suggestive of CF, however, 5% of these tests produce false negatives (Rosenstein and Cutting, 1998), therefore a diagnosis is typically only confirmed after CFTR genotyping (De Boeck et al., 2006).

Globally, of the more than 1,500 CFTR mutations identified, phenylalanine on position 508 (*p.Phe508del,* legacy name *F508del*) accounts for approximately 67% of mutated alleles, whilst no other single mutation accounts for more than 6% of the remaining CFTR mutations (Lao et al., 2003, Mehta et al., 2010). In the UK, 90.8% of individuals with CF have at least one *p.Phe508del* mutation, with the next most common genotype being the *p.Gly551Asp* (legacy name *G551D*), which accounts for 5.8% of mutations (Cystic Fibrosis Trust, 2014). The more defective the CFTR, the more negative the impact on the function of the mucociliary tract and pancreas, such that gene mutation likely plays a significant role in lowered resistance to bacterial infection (Lyczak et al., 2002).

1.2. Lung disease in cystic fibrosis

Repeated colonisation of the lungs with bacterium such as *Pseudomonas aeruginosa* (the most common isolate), *Staphylococcus aureus*, *Haemophilus influenza*, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* (Rowe et al., 2005), ultimately leads to irreversible bronchiectatic changes in the lungs (Zemanick et al., 2010). Eradication of bacterium such as *Pseudomonas aeruginosa* has been shown to improve life expectancy, whilst regular control and treatment of chronic infection and exacerbation of symptoms improves prognosis (Doring et al., 2004). Therefore, oral and intravenous (IV) antibiotics, corticosteroids, and nebulised mucolytic medications are commonly prescribed as prophylaxis against infection, for eradication of early infection, suppression of chronic bacterial infection, and the treatment of infective exacerbations (Doring et al., 2012). However, colonisation with *Methicillin-resistant Staphylococcus aureus*, *Nontuberculous mycobacterium*, and *Mycobacterium abscesses* are increasingly more prevalent and difficult to treat because they are highly resistant to antibiotics (Sherrard et al., 2014), whilst colonisation with *Burkholderia cepacia* is associated with increased mortality rates (Parkins and Floto, 2015).

Respiratory exacerbations are a significant clinical event in individuals with CF, and the primary cause of morbidity and mortality is worsening lung disease, hence early intervention and prevention of exacerbations is important (Doring et al., 2004). Frequent exacerbations have a significant negative effect on lung function in children with CF (Konstan et al., 2007, Sanders et al., 2011, Konstan et al., 2012), with 50% of decline associated with severe exacerbations that require

hospitalisation for IV-antibiotics (Waters et al., 2012). Treatment with oral and/or IV-antibiotics, coupled with intensive airway clearance and inhaled mucolytic therapy has been shown to improve lung function in those admitted to hospital (Sanders et al., 2010, Wagener et al., 2013); however in more than a quarter of cases, baseline lung function does not recover and children are likely to have a repeat exacerbation within 3, 6 or 12-months post-discharge from hospital (Sanders et al., 2010).

Children who exhibit persistent or recurring colonisation with pathogens such as *Pseudomonas aeruginosa* may be prescribed a protocol of regularly timed (3 or 4 monthly) elective hospital admissions for intensive IV-antibiotic eradication therapy (Doring et al., 2012). This approach has been shown to slow the decline in lung function (Doring et al., 2004), however this is at the cost of less time at school, socialising with peers, and spending time with family and friends. In some cases, parents may be taught to provide outpatient parenteral antibiotic therapy (Rucker and Harrison, 1974, Patel et al., 2015), such that they can administer their child's IV-antibiotic treatment at home. Typically, a child will be admitted to hospital for 1 to 2 days so that the course can be started. During this time children are monitored for any adverse reaction to the drugs, and if none are identified they are discharged to complete the remainder of the course at home.

1.3. Monitoring of lung function

Spirometry, plethysmography and chest x-ray, are the most common lung health assessment measures, used both clinically and in research (Corey, 2007), to monitor lung function during periods of stability and exacerbation (Waters et al., 2012). The purpose of lung function tests are to assist with diagnosis and prognosis of CF, whilst also monitoring for disease progression and the effect of therapeutic interventions (Amin et al., 2011). Lung function may be variable throughout childhood, with some children experiencing recurrent pulmonary exacerbations and a resultant decline in lung function, and this may be accelerated through adolescence and into adulthood with concurrent bacterial infections and malnutrition (Waters et al., 2012). Serial measurements and tracking of changes in lung function from soon after birth (Hoo et al., 2012, Nguyen et al., 2014), through childhood, adolescence and adulthood is a staple component of CF outpatient and inpatient reviews (Merkus et al., 2002, Liou et al., 2010, Vandenbranden et al., 2012).

Forced expiratory lung volume in one second (FEV_1) and forced vital capacity (FVC) are considered the two most important outcomes measured by spirometry (Miller et al., 2005). For prognosis, FEV_1 compared to a healthy reference population, is generally regarded as the primary measure for assessing and monitoring CF lung disease (VanDevanter et al., 2010), and is typically used to define disease stage, identify change in lung function, and to make decisions on treatment (Kerem et al., 2014). However, reliable forced expiratory manoeuvres are often difficult to achieve, particularly in younger children, and most school age children with CF have an FEV_1 within normal ranges of 80-100% (Aurora et al., 2004). Spirometry is also insensitive to changes in the smaller peripheral airways as the large total cross-sectional area in the peripheries limits airflow, especially in the presence of lung disease (Aurora, 2010).

A multiple breath inert gas washout test (MBW) (Gustafsson et al., 2003) has been shown to be a sensitive method of determining early airways disease in infants as young as 3-months (Lum et al., 2007, Hoo et al., 2012), in pre-schoolers aged 3-6 years (Aurora et al., 2005a), and school-children aged 6-16 years (Aurora et al., 2004). The data is used to calculate an individual's lung clearance index (LCI), which is an indicator of ventilation inhomogeneity and abnormalities in the smaller peripheral airways. MBW has mostly been the focus of research and has not been fully integrated into the clinical environment (Fuchs and Gappa, 2011, Kent et al., 2014) due to gaps in knowledge about the reliability and validity of devices, differences in inert gas choice, and standardisation of the MBW protocol (Subbarao et al., 2015).

FEV_1 remains the primary outcome measure for assessing CF lung disease and is recommended as the primary end-point for evaluating the effectiveness of interventions on lung function in CF clinical trials, and in regulatory approval of respiratory therapies (European Medicines Agency Committee for Medicinal Products for Human Use, 2009). Consequently, FEV_1 has been widely reported as a common primary outcome in exercise-based trials (Bradley and Moran, 2008, Radtke et al., 2015).

1.4. Prediction models for rate of change in lung function

Prior to 2009, there were several reference equations used to predict an individual's lung function (Rosenthal et al., 1993, Wang et al., 1993, Quanjer et al., 1995, Hankinson et al., 1999). Prediction models for determining rate of change in lung function in both adults (Liou et al., 2010, Taylor-Robinson et al., 2012) and children (Corey et al., 1976, Dankert-Roelse and te Meerman, 1995, Merkus et al., 2002, Schneiderman-Walker et al., 2005, Que et al., 2006, Konstan et al., 2007, Vandenbranden et al., 2012, Waters et al., 2012) between the ages of 5-70 years have been published. The range of reference equations has reflected the widespread recognition of the limitations of existing equations (Stanojevic et al., 2010).

Each reference equation model accounted for a range of unmodifiable risk factors i.e., gender, ethnicity, CFTR mutation, early diagnosis, meconium ileus, pancreatic status; and/or modifiable risk factors such as chronic lung infection with *Pseudomonas aeruginosa* or other microbiology, repeated respiratory exacerbations, nutritional status, CF-related diabetes mellitus, liver status, and exercise or physical activity levels (Stanojevic et al., 2009). These models have allowed for better understanding of disease progression and identified key factors that might slow, modify, or accelerate the rate of decline in lung function (Konstan et al., 2007). However all the reference equations had limitations, particularly in relation to arbitrary break points between pre-school and school age groups (pubertal growth) and ethnicity (Stanojevic et al., 2010). Lung function may have been underestimated or overestimated depending on the reference equation used, which has biased lung function data and resulted in erroneous diagnoses of severity of lung disease, particularly in non-Caucasian populations (Quanjer et al., 2012a).

Standardisation of spirometry measurement (Miller et al., 2005), and a significant effort to collate multiple countries existing lung function data, first in children aged 3-7 years (Stanojevic et al., 2009) and then in ages 3-95 years, have resulted in globally accepted, multi-ethnic reference equations to determine upper and lower limits of normal lung function (Quanjer et al., 2012b). Conversion of raw data from litres (L) to percentage predicted (%pred.) and z-scores using the Global Lung Initiative reference equations, accounts for age, gender, height and ethnicity related variability;

and also allows for lung function comparisons against other local, national and international CF cohorts (Stanojevic et al., 2010).

1.5. Trajectory of lung function in children with cystic fibrosis up to 2014

The variable ranges in lung function have been described in 9 studies that reported annual changes in FEV_1 %pred. in individuals aged 3-22 years with CF, and are presented in **Table 1-1**, and reflect the years 1970–2013 (Corey et al., 1976, Dankert-Roelse and te Meerman, 1995, Merkus et al., 2002, Schneiderman-Walker et al., 2005, Konstan et al., 2007, Vandenbranden et al., 2012, Waters et al., 2012, Schneiderman et al., 2014, Cogen et al., 2015). Rates of decline in lung function in the 1970's (Corey et al., 1976) were between 3.5%-6.7% annually, however, predictions from a 2013 cohort suggested that deterioration of between 0.86%-1.5% could be expected (Cogen et al., 2015). These changes were echoed by two large international epidemiological studies: (1) a Canadian study (Xu et al., 2004) tracked birth cohorts between 1960-1989, and reported a significant deceleration in the rate of decline in FEV_1 from 2.1% (1960-1964) to 1.88% (1975-1980) to 0.8% per year (1985-1989); and (2) a UK based study (Que et al., 2006) that showed that rate of decline in FEV_1 changed from 2.5% (1960-1964) to 1.65% (1975-1980) to 0.65% annually (1985-1989).

The UK Cystic Fibrosis Registry (Cystic Fibrosis Trust, 2014) reported median FEV_1%pred. for male and female children and adolescents with CF aged 6-19 years are presented in **Table 1-2**, and show that lung function declined with age, and that females had slightly lower lung function than males. In **Table 1-3** the mean FEV_1%pred. calculated in 2008 was compared to 2013 data and showed that rate of deterioration had slowed in children. This deceleration was likely due to earlier diagnosis and improved medical and therapeutic interventions (Que et al., 2006), however, risk factors such as repeated respiratory exacerbations were linked to steeper declines in lung function, especially in children (Waters et al., 2012). An update on number of individuals affected by CF, survival and trajectory of lung function since 2014 is provided in **Chapter 10, Subheading 10.2.1, pg. 227.**

Table 1-1: Studies reporting rate of decline in FEV_1 %pred. in children and young adults aged 3-20 years

Author	n	Age in years	Country	Group	Annual change in FEV_1 %pred.	Risk factors
Corey et al. (1976)	132	5-18	Canada	Males	-2.47% to -3.15%	Age, gender, FEV_1
				Females	-3.54% to -6.01%	
Dankert-Roelse and te Meerman (1995)	412	5-15	Netherlands	New-born screened	-0.36% to -0.84%	New-born screening
				Non-screened	-2.7% to -3.7%	
				Late diagnosis	-1.1% to -4.7%	
Merkus et al. (2002)	52	5-20	Netherlands	Males and Females	-5.6% to 1.3%	Lung function
Schneiderman-Walker et al. (2005)	109	7-17	Canada	Males vs. Females	-2.66% to 2.66% vs. 1.17% to -3.05%	Gender, physical activity
				(Mean for group)	(-1.77%)	
Konstan et al. (2007)	4866	6-17	USA	Age group 6-8 yr.	-1.12%	Age, gender, *Pseudomonas aeruginosa*, exacerbations
				Age group 9-12 yr.	-2.39%	
				Age group 13-17 yr.	-2.34%	
Vandenbranden et al. (2012)	4680	14-17	USA	Age group 14-17 yr.	-1.59%	Lung function + risk factors
Waters et al. (2012)	851	3-10	Canada	≥1 exacerbation in 1-year	-2.1% to -2.8%	Exacerbations
				No exacerbation in 1-year	-1.0% to -1.5%	
Schneiderman et al. (2014)	212	7-17	Canada	9-year longitudinal tracking of children aged 7-17 years	-0.13% to -1.55%	Habitual physical activity
Cogen et al. (2015)	946	6-12	USA	Pseudomonas aeruginosa negative	-0.85% to -1.17%	Female, exacerbations, Methicillin-resistant Staphylococcus aureus

Table 1-2: Median FEV_1%pred. for male and female children aged 6-19 years based in the UK in 2013

	Overall			Females			Males		
Age	N	Median	IQR	N	Median	IQR	N	Median	IQR
6-7 yr.	421	91.0	78.3-99.9	201	90.6	78.2-100.1	220	91.4	77.7-99.6
8-11 yr.	858	88.0	77.1-98.0	441	87.5	75.6-97.0	417	89.3	78.1-99.7
12-15 yr.	919	79.8	67.1-91.3	447	80.0	66.5-91.0	472	79.5	67.3-91.4
16-19 yr.	952	74.3	56.4-88.4	480	72.2	53.0-86.3	472	77.3	60.6-90.5

FEV_1 %pred. based on Global Lung Initiative equations (Quanjer et al., 2012b) as reported in the UK Cystic Fibrosis Registry Annual Data Report 2013 (Cystic Fibrosis Trust, 2014).

Table 1-3: Comparison of mean FEV_1%pred. for male and female children aged 6-19 years based in the UK between 2008 and 2013

	Age groups			
Year	6-7 yr.	8-11 yr.	12-15 yr.	16-19 yr.
2008 mean FEV_1%pred.	88.2	85.5	78.3	69.7
2013 mean FEV_1%pred.	91.0	88.0	79.8	74.3
Difference (2013-2008)	2.8	2.5	1.5	4.6

FEV_1 %pred. based on Global Lung Initiative equations (Quanjer et al., 2012b) as reported in the UK Cystic Fibrosis Registry Annual Data Report 2013 (Cystic Fibrosis Trust, 2014).

1.6. Medical management of cystic fibrosis

There is no known cure for CF, and medical management of respiratory exacerbations are complex and burdensome, and 90% of individuals with CF are required to ingest supplementary pancreatic enzymes to improve fat absorption, that is secondary to CFTR dysfunction and pancreatic insufficiency (Kerem et al., 2005). A wide range of national and international consensus adopted guidelines have defined the standards of care to optimise clinical and health outcomes in individuals with CF (Kerem et al., 2005, Cystic Fibrosis Trust, 2009, Flume et al., 2009a, Cystic Fibrosis Trust, 2011b, Cystic Fibrosis Trust, 2011a, Farrell et al., 2017). These guidelines have advocated intensive prophylactic treatment as a response to acute exacerbations, which may lead to decreased hospital admissions, and improved survival rates and quality of life (Kerem et al., 2005, Elborn et al., 2016). Variations in the level of care between centres have been identified as being inevitable due to differences in infrastructure of CF centres, experience of staff in evaluation and assessment of patients, documentation of results in a standardised database, and management of exacerbations (Kerem et al., 2005). In the UK, specialist CF centres most likely demonstrate adoption of the Cystic Fibrosis Trust (2011a) guidelines for CF medical care, with physiotherapy care also provided in accordance with the Cystic Fibrosis Trust (2013) guidelines. As an example, the specialist model of care delivered by GOSH, the host site for *Inspire-CF* is outlined below.

1.7. Specialist cystic fibrosis care at Great Ormond Street Hospital for Children

At GOSH, a highly specialist multidisciplinary team (MDT) that included respiratory consultants and doctors, physiotherapists, nurses, pharmacists, dietitians, psychologists, respiratory and sleep physiologists, radiographers and play specialists, were all responsible for care and treatment of children, which was provided at clinics and during admissions to hospital. Children were typically assessed, and treatment escalated, when necessary, at two to three monthly outpatient clinics, at annual review, or as a response to acute exacerbation of CF-related symptoms.

There were a number of reasons an individual with CF could be admitted to hospital and included: (1) the child had been recently diagnosed with CF and family education was required; (2) a bronchoscopy and oesophageal pH impedance study in newly diagnosed patients was required; (3) a

deterioration in clinical status that had not responded to oral antibiotics or other dispensed medications e.g. exacerbation of respiratory symptoms, distal intestinal obstruction syndrome, CF-related diabetes; (4) elective 3-, 4-, 6- or 12-month admissions for IV-antibiotics (typically of 14-day duration); (5) elective 1-month admission for IV-immunoglobulin (typically delivered overnight); (6) elective admission for IV delivered methylprednisolone (typically admitted for 3 nights to start a 1-month dose); (7) elective surgery e.g. Portacath (implanted venous access device) insertion; gastrostomy insertion; bronchoscopy; ear, nose and throat or dental surgery; (8) a lung transplant (Cystic Fibrosis Trust, 2011a).

Outside of admissions and clinics, parents or guardians typically reported any CF-related changes in health to the CF Unit telephonically, and these were logged on the Central Document Database, and disseminated to the relevant member of the multidisciplinary team. Members of the CF outreach (community) clinical team could also be contacted directly. For all other health concerns (i.e., childhood diseases, cold, flu etc.) parents/carers were advised to contact their local General Medical Practitioner (GP).

At outpatient clinics, the physiotherapy team reviewed and reinforced the importance of home physiotherapy regimens of airway clearance and inhaled mucolytic therapies, and adaptations to therapy techniques were made where necessary. Participation in regular exercise and physical activity was actively encouraged. At annual review, a functional field-based exercise test such as the 10 metre modified shuttle walk test (10m-MSWT) (Selvadurai et al., 2003) or the newly validated iStep test (Rand et al., 2015) were planned, but not always performed due to the physiotherapists time pressures. Performance of cycle ergometer cardiopulmonary exercise test (CPET) was not routinely undertaken at GOSH.

During admissions, the physiotherapy team ensured that airway clearance and nebulised therapy were optimised, and home regimens reinforced during twice daily airway clearance sessions. Where time permitted, a daily 15-30 minute, moderate-to-intensive exercise session was undertaken. For additional guidance for children and their parents or carers, the physiotherapy area of the CF Unit's

web space on the GOSH website provided downloadable leaflets on the appropriate use and cleaning guidelines for the variety of types of airway clearance devices.

At home, children maintained a prescribed medication regimen, which may have included oral and/or nebulised antibiotics, vitamins, and pancreatic enzymes (Creon™). Independently or with parental assistance, children also maintained a daily home physiotherapy regimen, and may have participated in school physical education (PE) classes, as well as sport at school and/or clubs. Some children may have availed of a Nuffield membership and attended weekly exercise training sessions. This initiative is explained in more detail in **Chapter 4, Subheading 4.4, pg.104.**

Home or school visits may have been scheduled on an ad-hoc basis with either the outreach specialist CF physiotherapist or clinical nurse specialist to provide support, education and guidance for families, carers, or teaching staff, regarding diagnosis, physiotherapy regimens, treatment escalation, portable lung function assessment, sputum sample collection, medication and IV-antibiotic therapy, transition to adult services and liaison with community care workers. Additionally, the clinical nurse specialist may have monitored drug levels, flushed a child's implanted Portacath, or removed needles after a course of IV-antibiotics that had been completed at home. During these visits, either the outreach physiotherapist or nurse usually checked that both nebulised and airway clearance equipment were in good working condition and were being maintained and cleaned regularly in accordance with manufacturer and hospital protocols.

1.8. Shared care agreements with local hospitals and care centres

Shared care agreements were used by GOSH as an approach to seamless prescribing and monitoring of medications, which enabled children to receive care in an integrated and convenient manner at their local hospital. Shared care was a transfer of clinical responsibility from a specialist CF hospital like GOSH, to a general practice or local general hospital, such that prescribing of medications by the GP, or other primary care prescriber, was supported by the shared care agreement. When a Respiratory Consultant considered a child's condition to be stable or predictable, they would seek to share patient care and would advise on prescription and review of medications, with ongoing

monitoring of actions to be taken in the event of deterioration in clinical status. Shared care clinic appointments, admissions and treatment were co-ordinated and managed by the GOSH CF MDT. Additionally, on-going support was provided locally by the child's GP, community nurse, pharmacist, and other allied health professionals through the shared care network.

1.9. Advances in pharmaceutical therapeutics

Prior to the start of *Inspire-CF*, there was an active and significant pipeline of pharmacological therapeutics that were undergoing research trials that targeted the CFTR mutation classes, and corrected the basic molecular and cellular defects (Ashlock et al., 2009). Results from these trials suggested the drugs significantly improved lung function and growth outcomes (Davies et al., 2014). *Ivacaftor*® (trade name *Kalydeco*®, Vertex Pharmaceuticals, USA) was a drug that targeted the *p.Gly551Asp* mutation, and in Stage 4 trials was demonstrated to improve FEV_1 by between 4.9%-10.5% in adults and 10%-12.5% in children (Kotha and Clancy, 2013). Another randomised, double-blinded, placebo-controlled trial investigated a combination of *Lumacaftor*® and *Ivacaftor*® (trade name *Orkambi*®, Vertex Pharmaceuticals, USA) in patients that were homozygous for *p.Phe508del* mutation and showed significant improvements of 2.6%-4% in FEV_1 (Wainwright et al., 2015).

These high-cost drugs were expensive and not available on the National Health Service (NHS) in the UK[1] when enrolment in *Inspire-CF* had started. Whiting et al. (2014) undertook a cost-effectiveness analysis of *Ivacaftor*®, anticipated to cost >£150,000 a year per patient. *Orkambi*® was the next drug to undergo a cost effectiveness analysis. These significant pharmaceutical breakthroughs presented a substantial practical and financial challenge to the NHS and the drugs were not available to all patients because of the cost. This meant that until these new drugs were made available, CF MDT's had a considerable task to manage the expectations of children and their parents and carers, and had to continue to maintain, and further optimise, clinical and health outcomes, and ensure that life expectancy predictions continued to increase (Bryon and Wallis, 2011). The impact of CFTR

[1] Ivacaftor® was first prescribed on the NHS in December 2016, and Orkambi® was first prescribed in October 2019. LOPES-PACHECO, M. 2016. CFTR Modulators: Shedding light on precision medicine for cystic fibrosis. *Front. Pharmacol.*, 7, 275-275.

modulator drugs on exercise capacity since *Inspire-CF* was completed is discussed in **Chapter 10, Subheading 10.3, pg. 233**.

1.10. The role of the paediatric specialist cystic fibrosis physiotherapist

The role of physiotherapy in CF care in the UK was primarily concentrated on education, provision of regular airway clearance and inhaled mucolytic therapies, and exercise, as well as the management of secondary complications such as musculoskeletal and postural problems, bone health and continence issues (Cystic Fibrosis Trust, 2013). Airway clearance regimens were initiated in the infant years and were then individually tailored to reflect the needs of the person as they aged and required optimisation of their mucociliary clearance routine (Rand et al., 2013). The rationale being that if a regular routine were established, ideally in early childhood, this might be maintained through adolescence and into adulthood.

Physiotherapists employ a wide range of airway clearance strategies to maintain airway patency and to help clear mucociliary secretions, which may include a combination of low, medium and high-volume forced expiratory manoeuvres (huffing and coughing), manual chest physiotherapy (percussion and chest-wall vibrations), positive end expiratory pressure, oscillation of the airways, autogenic drainage, high frequency chest wall oscillations, non-invasive ventilation, intrapulmonary percussive ventilation and intermittent positive pressure breathing (Chatham et al., 2004, Elkins et al., 2005, Kendrick, 2006, McCool and Rosen, 2006, Flume et al., 2009b, Lester and Flume, 2009, Rand et al., 2013). Nebulised mucolytics such as hypertonic saline (concentrations of 3% and 7%) and recombinant human DNase (*Dornase alfa* or *Pulmozyme*®, Genentech, Roche, USA) may also be incorporated into airway clearance regimens to reduce viscosity, improve the rheology of mucous, and aid mucociliary clearance rate (Ballmann and von der Hardt, 2002, Elkins et al., 2005, Donaldson et al., 2006, van der Giessen et al., 2007, Heijerman et al., 2009).

Regular airway clearance and inhaled mucolytic therapy have been shown to have a short-term effect on increasing mucociliary clearance when compared to no chest physiotherapy (van der Schans et al., 2000). However, a combination of exercise and regular airway clearance was

reportedly more effective at enhancing sputum clearance (Salh et al., 1989, Baldwin et al., 1994). The rationale was that shearing forces generated in the airways through increased work of breathing and body movement during exercise, may reduce the viscosity of mucous (Kim et al., 1986, Kim et al., 1987). This, coupled with an increased peak expiratory flow bias generated during exercise, may facilitate the movement of mucous from the periphery of the lungs to the oropharynx, which could then be cleared by coughing (Dwyer et al., 2011). Several studies have reported that some patients (4%-85%) considered exercise as an optimal form of airway clearance and did not perform traditional airway clearance techniques (Abbott et al., 2011, Dwyer et al., 2011). Evidence on the use of exercise as an alternative to airway clearance therapy since *Inspire-CF* concluded is provided in **Chapter 10, Subheading 10.2.2, pg. 229.**

Exercise has been promoted to children by physiotherapists as a fun and interactive way to help build self-confidence, keep-up with their peers, and potentially reduce treatment burden (Rand and Prasad, 2012), however adherence and motivation to exercise is variable (Prasad and Cerny, 2002), therefore this view may not be universally accepted by children. The time required to complete all of the components of medical regimens (O'Donohoe and Fullen, 2014), coupled with pathophysiological limitations, could have a negative influence on willingness to participate in any form of exercise or physical activity (Moorcroft et al., 1998).

1.11. Summary

Chapter 1 has described the pathophysiology of CF and the impact the disease has on lung function in children. Improvements in CF medical care have meant that children in the UK have recorded improvements in FEV_1 of between 1.5 to 4.6% between 2008-2013. The trajectories of FEV_1 in international cohorts of CF patients have also improved from an average deterioration of between 2.5% to 6% annually in 1976, to an average of 0.85% to 1.17% in 2015. Medical management remains focused on preserving lung function and reducing the risk of admission to hospital for exacerbation of symptoms. The role of the paediatric physiotherapist is to actively promote exercise and airway clearance therapy to all children with CF, irrespective of lung disease severity. *Inspire-CF* aimed to improve lung function by increasing exercise capacity.

2.

CHAPTER 2. LITERATURE REVIEW

2.1. Introduction

The primary difference in ventilatory response during exercise between healthy individuals and those with CF, is that those with CF may have bronchiectatic changes in the lungs that results in increased dead space (Thin et al., 2004). Dead space is wasted ventilation and may be greater in those with more severe lung disease and may therefore limit a person's ability to maintain or increase alveolar ventilation during exercise. For example, in a healthy person inhaling a tidal volume (V_T), or normal breath, of 500 millilitres (ml), 70% (350 ml), contributes to alveolar ventilation; however, at the same given V_T in a person with dead space caused by CF lung disease, only 50% (250 ml) may contribute to alveolar ventilation (Urquhart, 2011). Therefore, to meet the increased ventilatory demands of exercise at any given level of oxygen uptake (VO_2), respiratory rate (RR) and/or V_T must be increased. A child with CF may have increased metabolic requirements during exercise compared to a healthy child at the same workload, therefore the child will have to increase their minute ventilation (V_E) to meet the demands of maintaining normal alveolar ventilation. Gas trapping, obstruction caused by thick secretions, and airway hyper-reactivity may also contribute to ventilatory limitations during exercise (Urquhart, 2011).

Exercise induced hypoxemia has been shown in individuals with CF who completed an incremental exercise test to self-determined exhaustion, with associated drop in peripheral oxygen saturations (SpO_2) (Ruf and Hebestreit, 2009). Reduced $VO_{2peak,}$ deficient O_2 delivery and altered VO_2 kinetics during exercise suggest that cardiac dysfunction may also have an adverse effect on exercise capacity in CF (Williams et al., 2014). Using tissue Doppler electrocardiography, Ionescu et al. (2001) demonstrated that the individuals with CF may have right ventricular dysfunction, and systematic review by Labombarda et al. (2016) concluded that there was specific myocardial involvement in CF,

that may affect systolic and diastolic function at rest and during exercise. Cardiac arrythmias are rarely reported in CF (Chéron et al., 1984, Sullivan et al., 1986), however Ruf and Hebestreit (2009) reported exercise induced cardiac arrythmias in 5-7% pf participants, during an incremental exercise test. These reports demonstrate the important of cardiac monitoring in CF and help to justify the inclusion of CPET as the primary exercise test in CF (Hebestreit et al., 2015).

Lean muscle mass is a major determinant of VO_{2peak} and children with CF have less lean muscle mass than healthy children, consequently children with CF have decreased peripheral muscle strength when compared to healthy children (de Meer et al., 1999, Hussey et al., 2002). This deficit is prevalent irrespective of reduced pulmonary or nutritional status, such that children with CF are typically unable to replicate the intensity of work generated during aerobic (de Meer et al., 1999) and muscle strength exercises (Hussey et al., 2002). Near-infrared spectroscopy has shown that skeletal muscle oxidative capacity is also reduced in children with CF, and that this deficiency may accelerate with age, and contribute to further decline in exercise tolerance (Erickson et al., 2015, Werkman et al., 2016).

Despite these ventilatory and metabolic limitations, ability to perform exercise to peak exertion when health status is stable have been recorded in children with CF (Moorcroft et al., 1997, Pianosi et al., 2005b); however, tolerance for exercise at any given intensity in CF may also be limited by nutritional status (Marcotte et al., 1986, Milla, 2004). Exocrine pancreatic insufficiency affects 85-90% of individuals with CF (Mehta et al., 2010), and causes malabsorption of fats, vitamins and minerals, which contributes to an inability to meet increased energy demands caused by bronchial infections (Wilschanski and Durie, 1998). There is an inverse correlation between energy expenditure and lung function (Bowler et al., 1993), and a correlation between nutritional status and lung function (Peterson et al., 2003) therefore optimisation of growth and nutritional status in conjunction with management of lung function is essential (Sinaasappel et al., 2002). Energy expenditure is higher during rest and exercise in individuals with CF, which may increase metabolic demand following exercise (Stevens et al., 2011), and elevated levels of pro-inflammatory markers following exercise may also impact on exercise metabolism (Stevens et al., 2011, van de Weert-van

Leeuwen et al., 2013). It is therefore important to carefully monitor growth outcomes in those who exercise regularly, particularly at higher intensities (Ledger et al., 2013), and in children with malnutrition where muscle wasting may occur as a result of protein deficiency and decreased fat storage (Marcotte et al., 1986). Consequently, high-calorie nutritional supplementation or hormonal treatment to help children who regularly exercise should be considered to meet metabolic requirements and to help increase peripheral muscle development should be considered (Gruet et al., 2017).

2.2. Aims and objectives

It is evident that exercise capacity may be limited in CF because of the myriad of adverse physiological effects caused by abnormal CFTR function on the airways, pancreas and gastrointestinal tract (Quinton, 1999). The aim of **Chapter 2** was to conduct a literature review that employed a systematic search strategy to identify exercise-based randomised controlled trials conducted in children with CF and then to synthesise the results of these studies. The objectives were to identify the effects that the exercise interventions had on lung function, exercise capacity and quality of life. This will help to clearly explain the defined gaps in knowledge that this thesis aimed to address.

2.3. Methodology

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.3.1. Search strategy

A systematic search strategy was conducted using 4 databases, PubMed, Medline, CINAHL Complete, and Embase, with the aim of identifying peer review journal articles related to exercise training in children with CF. Search terms included ‘cystic fibrosis’ OR ‘CF’ AND ‘children’ OR ‘paediatric’ OR ‘pediatric’ AND ‘spirometry’ OR ‘lung function test’ AND ‘exercise’ OR ‘aerobic training’, OR ‘anaerobic training’ OR ‘strength training’ OR ‘resistance training’ AND ‘quality of life’ OR ‘health-related quality of life’ OR ‘Cystic Fibrosis Questionnaire’.

2.3.2. Search criteria

Inclusion criteria for article selection included: 1) randomised control trials; 2) participants aged 6-18 years with a confirmed diagnosis of CF; 3) peer-reviewed articles published as full manuscripts; 4) written in the English language; 5) studies that reported endpoint measurements of FEV_1 and VO_{2peak} and/or W_{peak}; and 6) published between January 1982 and December 2014. Articles were excluded if they were related to adults, chest physiotherapy techniques, lung transplantation, asthma, bronchiectasis, non-cystic fibrosis bronchiectasis, inspiratory or expiratory muscle training, videogames, and animal-studies. Abstracts, narrative and systematic reviews, observational studies and validation studies were all excluded.

2.3.3. Selection process

Results were exported into EndNote 8 (Clarivate Analytics, Philadelphia, USA), and then screened for duplicates. A systematic process of screening was undertaken based on title and abstract with articles excluded if irrelevant. Full texts of eligible articles were then read to identify the final included studies. Citation tracking and a search of the grey literature was conducted using Google search to identify any additional studies.

2.3.4. Data extraction

Participant characteristics, study design and sessions, methodology, defined outcome measures, and results of statistical analysis were extracted. Where available, mean difference, standard deviation (SD), and 95% confidence intervals (95%CI) were recorded to allow for comparisons between studies.

2.3.5. Risk of bias and quality of assessment

The Critical Appraisal Skills Programme UK (2014) quality appraisal tool for randomised controlled studies was used to screen for risk of bias. The appraisal tool consisted of four sections (A, B, C and D) with a total of 11 multi-choice questions, with the answer options being 'Yes', 'No', and 'Can't tell'. Section A was composed of screening questions related to the validity of the study as a randomised controlled trial. If all questions in Section A were answered with a 'Yes', then appraisal was continued.

2.4. Results

2.4.1. Database search

A total of 2359 studies were extracted from the databases, of which 1547 duplicates were identified. The remaining 812 titles were individually screened with 441 articles excluded as they were not relevant. The abstracts of the remaining 371 articles were read, and a further 289 articles were excluded as they were also not relevant. A total of 82 abstracts were identified as being related to exercise.

The full texts of 82 articles were downloaded into EndNote 8 (Clarivate Analytics, Philadelphia, USA) and screened for eligibility. Of these articles, 27 included both adults and children as participants, and were excluded. The remaining 55 articles were individually read and categorised into supervised, unsupervised, or partially supervised exercise programmes, and a list of outcomes generated, with articles that included FEV_1 and W_{peak} and/or VO_{2peak} selected. A further 47 articles were excluded as FEV_1 and/or W_{peak} and/or VO_{2peak} data was not reported.

Eight (n=8) peer reviewed and full-text published randomised controlled trials, with an exercise training protocol conducted in children and adolescents aged 5 to 18 years with CF, were included in the final review (Braggion et al., 1989, Cerny, 1989, Schneiderman-Walker et al., 2000, Selvadurai et al., 2002a, Klijn et al., 2004, Orenstein et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014). All 8 studies were included in the qualitative analysis. It was not possible to undertake a meta-analysis as mean±SD data for FEV_1 and/or W_{peak} and/or VO_{2peak} were inconsistently reported, and only the studies by Santana-Sosa et al. (2012) and Santana-Sosa et al. (2014) reported mean and 95%CI. **Figure 2-1** illustrates the selection process for inclusion of studies.

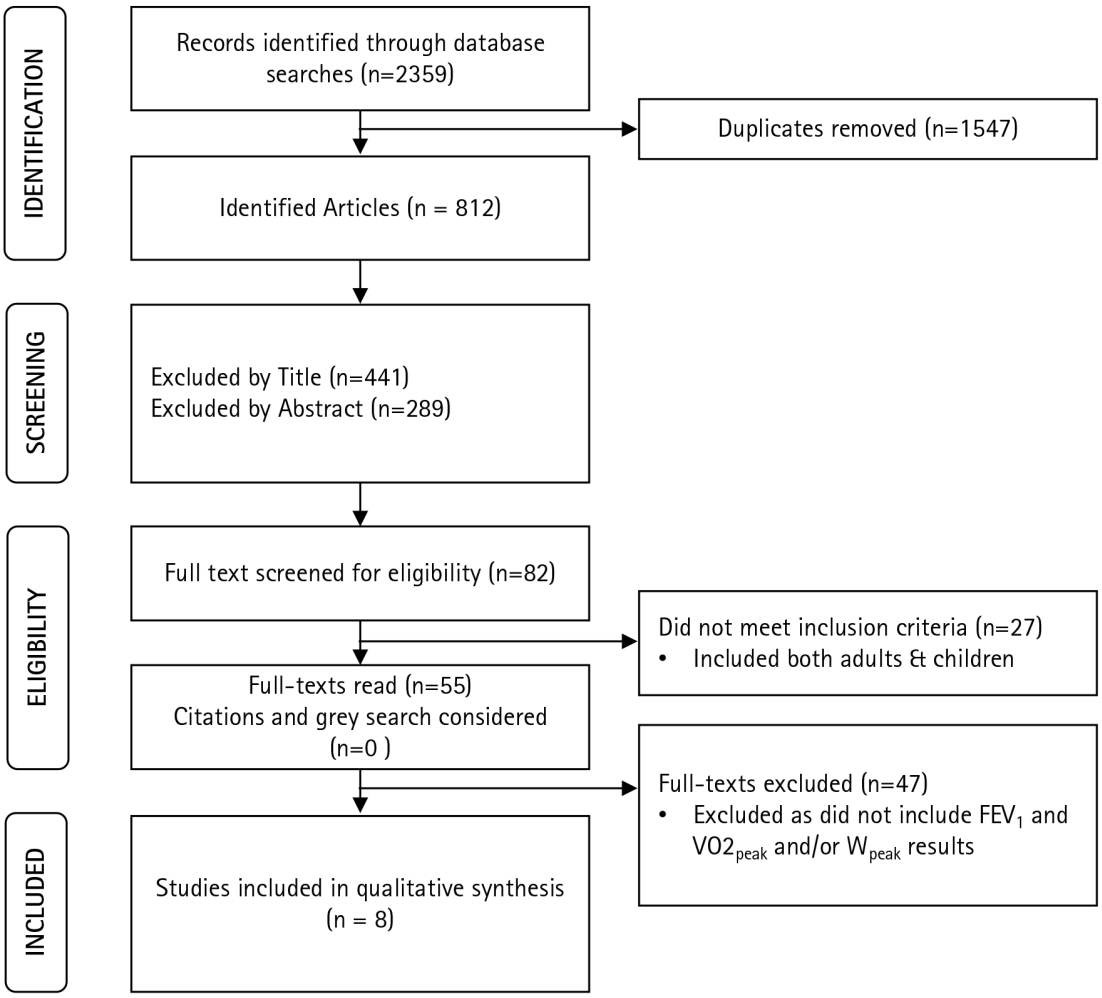

Figure 2-1: Prisma flow diagram for the selection process of included randomised controlled trials

2.4.2. Study design and characteristics

The heterogeneity of study populations, variation in reporting of study design, outcomes, and intervention protocols, as well as omission of data, made synthesis of these articles challenging. Braggion et al. (1989) compared exercise training in healthy children versus children with CF; Cerny (1989) and Selvadurai et al. (2002a) conducted supervised, hospital-based training in children admitted for exacerbation of respiratory symptoms; Schneiderman-Walker et al. (2000) and Orenstein et al. (2004) considered the effects of partially-supervised, home-based exercise training; Klijn et al. (2004) studied the effects of anaerobic exercise training; and the two studies by Santana-Sosa et al. (2012) and Santana-Sosa et al. (2014) evaluated the effects of a combination of aerobic and strength training in children enrolled in a supervised out-patient gym setting.

2.4.3. Risk of bias and quality assessment

All 8 studies were of low-to-moderate quality, primarily as the methodologies were limited in their descriptions of exercise prescription and training protocols, which would make repeating of the studies difficult. There was wide variation of reporting of outcomes, with some studies only showing change since baseline in graphical format (Braggion et al., 1989, Cerny, 1989), which made precision identification of change difficult, whilst others did not report change in some outcomes beyond baseline results (Braggion et al., 1989, Klijn et al., 2004). This selective reporting made comparison of results between groups difficult and would likely impact on comparison with *Inspire-CF* results.

There were no adverse events reported in any of the studies, and as exercise is generally considered relatively low risk, the positive effects described were likely of health and possibly clinical benefit to the participants. However, generalisability to the wider CF population was more difficult as not all exercise interventions were carried out during periods of stable clinical status (Cerny, 1989, Selvadurai et al., 2002a), which meant that outcomes were measured when participants were admitted to hospital and on IV-antibiotics treatment. As such, the conclusions on the effectiveness of the exercise programmes were likely masked by the therapeutic effects of IV-antibiotic treatment.

All the studies were classified as randomised controlled trials and stated and addressed a clearly defined research question. The risk of bias was relatively high in all the studies as none of the participants were blinded to their treatment, and assessors were not blinded to each groups intervention, outcomes, and analysis of results. One study (Braggion et al., 1989) did not randomise participants as the trial compared healthy children to children with CF. In all other 7 studies, allocation of participants to group's was described as performed by blinded randomisation, which meant that neither participant nor researcher would be likely to guess the group they would be allocated to. However, as is common in physiotherapy research (Opara et al., 2013), it was not impossible for participants to be blinded from knowing which intervention they were allocated to. All, except 2 studies (Braggion et al., 1989, Santana-Sosa et al., 2012) showed that there were no significant between group differences in FEV_1 at baseline. Braggion et al. (1989) showed significant between-group differences in healthy children when compared to children with CF, however, these differences were accounted for in the analysis. Santana-Sosa et al. (2012) showed that there was a significant difference in VO_{2peak} at baseline but accounted for these differences in analyses.

The results of these 8 randomised controlled trials were relevant to children recruited to *Inspire-CF*, primarily due to age and outcome measures reported, however the exercise prescription and training programmes were poorly described, therefore drawing comparisons to *Inspire-CF* would likely be difficult. **Table 2–1** shows the assessment of bias identified by the Critical Appraisal Skills Programme UK (2014) tool, **Table 2–2** summarises the general characteristics of each of the studies exercise testing, prescription, and training protocols, and **Table 2–3** shows the changes from baseline for FEV_1, W_{peak} and/or VO_{2peak} as were reported.

Table 2-1: CASP appraisal of the methodological quality and risk of bias for randomised controlled trials

	CASP Question	Braggion et al. (1989)	Cerny (1989)	Schneiderman -Walker et al. (2000)	Selvaduri et al. (2002)	Klijn et al. (2004)	Orenstein et al. (2014)	Santana Sosa et al. (2012)	Santana Sosa et al. (2014)
1.	Did the trial address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y
2.	Was the assignment of participants to treatments randomised?	N	Y	Y	Y	Y	Y	Y	Y
3.	Were all of the participants who entered the trial properly accounted for at its conclusion?	Y	Y	Y	Y	Y	Y	Y	Y
4.	a. Were the participants 'blind' to intervention they were given?	N	N	N	N	N	N	N	N
	b. Were the investigators 'blind' to the intervention they were giving to participants?	N	N	N	N	N	N	N	N
	c. Were the people assessing/analysing outcome/s 'blinded'?	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell
5.	Were the groups similar at the start of the randomised controlled trial?	N	Y	Y	Y	Y	Y	N	Y
6.	Aside from the experimental intervention, were the groups treated equally?	Y	Y	Y	Y	Y	Y	Y	Y
7.	Were the effects of intervention reported comprehensively?	N	N	Y	Y	Y	Y	Y	Y
8.	Was the precision of the estimate of the intervention or treatment effect reported?	N	N	Y	Y	Y	Y	Y	Y
9.	Do the benefits of the experimental intervention outweigh the harms and costs?	Y	Y	Y	Y	Y	Y	Y	Y
10.	Can the results be applied to your local population/in your context?	N	N	N	N	N	Y	Y	Y
11.	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	N	N	N	N	N	N	N	N

Critical Appraisal Skills Programme (2017). CASP Randomised Controlled Trial Checklist. [online] Available at: https://casp-uk.net/casp-tools-checklists/

Table 2-2: Summary characteristics of exercise training study protocols for children with cystic fibrosis

Authors	N	Study duration	Groups	Intervention	Outcomes	Frequency	Intensity	Time	Type	Adherence
Braggion et al. (1989)	20	16-weeks 8-weeks normal activity + 8-weeks intervention	2: Healthy controls vs. CF	Aerobic and strength training	FEV_1 FVC VO_{2peak} W_{peak}	3 x per week	165-175 beats·min^{-1}	60 min·day^{-1}	Running, circuits, motor-skills and flexibility	75%
Cerny (1989)	17	14-days (admission) mean±SD; 13±3 days	2: CF Control vs. CF	Postural drainage vs. Aerobic training	FEV_1 FVC VO_{2peak} W_{peak}	3 x per day	10-65% heart rate reserve	5-10 min·day^{-1} progressed to 15-20 min·day^{-1}	Cycle ergometer	96%
Schneiderman -Walker et al. (2000	72	36-months	2: CF control vs. CF	Control vs. home-based aerobic exercise	FEV_1 FVC VO_{2peak} Quality of life	2 x per week + 1 airway clearance session	70-80% HR_{peak} or 150 beats·min^{-1}	20 min·day^{-1}	Aerobic activities: swimming, cycling, running, football	>60%
Selvaduri et al. (2002)	66	14-days (admission) mean 18 days [range 14-36]	3: CF vs. CF vs. CF	Control vs. Aerobic training vs. strength training	FEV_1 FVC VO_{2peak} Quality of life	5 x per week	70% HR_{peak} 5 x 10 sets at 70% subjective maximum exertion	30 min·day^{-1} 30-45 min·day^{-1}	Treadmill or cycle Non-isokinetic resistance circuit training	>90%

Authors	N	Study duration	Groups	Intervention	Outcomes	Frequency	Intensity	Time	Type	Adherence
Klijn et al. (2004)	20	12-weeks	2: CF control vs. CF	CF control vs. Anaerobic training	FEV_1 FVC VO_{2peak} Quality of life	2 x per week	Near maximum	30-45 $min{\cdot}day^{-1}$	Short distance multi-directional sprints and stop-start heavy ballgames	98%
Orenstein et al. (2004)	67	12-months	2: CF vs. CF	CF Aerobic vs. CF Strength	FEV_1 VO_{2peak} Quality of life	3 x per week	70% HR_{peak} <55% HR_{peak}	30-60 $min{\cdot}day^{-1}$	Stair-stepping machine Nordic Power resistance machine	Not reported
Santana Sosa et al. (2012)	22	12-weeks (8-week intervention; 4-week detraining)	2: CF control vs. CF	CF control vs. aerobic + upper & lower body strength	FEV_1 VO_{2peak} W_{peak} Quality of life	3 x per week	HR at GET and 40-60% 5 $rev{\cdot}min^{-1}$	60 $min{\cdot}day^{-1}$	Cycle ergometer + 11 strength exercises (1 set x 12-15 repetitions)	95.1%
Santana Sosa et al. (2014)	20	12-weeks (8-week intervention; 4-week detraining)	2: CF control vs. CF	CF control vs. aerobic + upper & lower body strength exercise + inspiratory muscle training	FEV_1 VO_{2peak} Quality of life	3 x per week	HR at GET and 40-60% 5 $rev{\cdot}min^{-1}$ + inspiratory muscle training at 40-50% PI_{max} (5-min x 30 inspirations)	60 $min{\cdot}day^{-1}$	Cycle ergometer + 11 strength exercises (1 set x 12-15 repetitions)	97.5%

Key: W_{peak} = peak work rate; VO_{2peak} = peak oxygen uptake; HR = heart rate; HR_{peak} = peak heart rate; GET = gas exchange threshold; RM = repetition maximum.

Table 2-3: Summary of change in FEV_1, W_{peak} and VO_{2peak} outcomes

				FEV_1		Work rate		VO_{2peak}	
Author	Groups	Interventions	n	ΔMean	*p*-value	ΔMean	*p*-value	ΔMean	*p*-value
Braggion et al. (1989)	Healthy controls	Aerobic & strength	10	No change	NR	0.2 W·kg^{-1}	>0.05	2.1 ml·kg·min^{-1}	>0.05
	CF	Aerobic & strength	10	No change	NR	0.3 W·kg^{-1}	>0.05	2.1 ml·kg·min^{-1}	>0.05
Cerny (1989)	CF Control	Postural drainage	8	11.3 %pred.	<0.01*	0.26 W·kg^{-1}	<0.01*	-	-
	CF	Aerobic	9	18.4 %pred.	<0.01*	0.44 W·kg^{-1}	<0.02*	-	-
Schneiderman-Walker et al. (2000)	CF control	Control	36	-3.5 %pred.	NR	-2.5 W_{peak} %pred.	0.56	-1.9 ml·kg·min^{-1}	NR
	CF	Aerobic	36	-1.5 %pred.	NR	-1.68 W_{peak} %pred.	0.56	-1.8 ml·kg·min^{-1}	
Selvaduri et al. (2002)	CF Control	Control	21	-4.5 %pred.	<0.05*	-	-	-1.2 ml·kg·min^{-1}	>0.05
	CF	Aerobic	21	6.5 %pred.	<0.05*	-	-	7.3 ml·kg·min^{-1}	<0.01*
	CF	Strength	22	10.1 %pred.	<0.01*	-	-	0.7 ml·kg·min^{-1}	>0.05
Klijn et al. (2004)	CF control	Control	9	No change	NR	-0.3 W·kg^{-1}	>0.05	-0.6 ml·kg·min^{-1}	>0.05
	CF	Anaerobic	11	No change	NR	1.4 W·kg^{-1}	<0.001*	1.5 ml·kg·min^{-1}	>0.05
Orenstein et al. (2004)	CF	Aerobic (at 6-months)	26	-2.8 %pred.	>0.05	-	-	-1.9 ml·kg·min^{-1}	>0.05
	CF	Strength (at 6-months)	30	-1.3 %pred.	>0.05	-	-	-2.2 ml·kg·min^{-1}	<0.01*
	CF	Aerobic (at 12-months)	25	-4.7 %pred.	>0.05	-	-	-0.9 ml·kg·min^{-1}	>0.05
	CF	Strength (at 12-months)	28	-1.0 %pred.	>0.05	-	-	-1.7 ml·kg·min^{-1}	>0.05
Santana Sosa et al. (2012)	CF control	Control	11	0.1 L	>0.05	-	-	2.2 ml·kg·min^{-1}	>0.05
	CF	Aerobic + upper & lower body strength	11	0.07 L	>0.05	-	-	3.9 ml·kg·min^{-1}	0.002*
Santana Sosa et al. (2012)	CF control	Control	10	0.002 L	>0.05	-	-	-0.6 ml·kg·min^{-1}	>0.05
	CF	Aerobic + upper & lower body strength exercise + inspiratory muscle training	10	0.01 L	>0.05	-	-	6.9 ml·kg·min^{-1}	<0.001*

NR = Not reported; A dash (-) indicates that this outcome was not recorded as an outcome; *statistically significant

2.5. Discussion

This discussion will focus on the synthesis of study designs, interventions, and comparisons of results of the 8 randomised controlled trials

2.5.1. Exercise training in healthy children vs. children with cystic fibrosis

The Italian study by Braggion et al. (1989) compared the effects of exercise training in previously non-exercising children with moderate CF lung disease (n=10; age 12.9±1.3 years) and healthy controls (n=10; 13.0±0.8 years). Two consecutive periods, each of 8-weeks duration were compared. During the first 8-weeks, all children were asked to maintain their usual daily activity, whilst during the second 8-weeks children took part in a supervised exercise programme. The 3 x 60 min·week^{-1} exercise training sessions consisted of 3-phases: (1) 10-15 minute warm-up; (2) self-paced running at a heart rate (HR) ≤150 beats·min^{-1} for 10 min·day^{-1} during the first week, and then progressively lengthened to 25-30 min·day^{-1} by the final week; and (3) circuit-training of progressively increasing duration and repetition of upper and lower body strength and flexibility exercises, motor-skills games and a sprint run at a HR of 165-175 beats·min^{-1}.

Spirometry measurements of FEV_1 %pred. and FVC %pred. was recorded at baseline, 8-weeks, and 16-weeks, as were two cycle ergometer exercise tests. The first was a 6-minute submaximal cycle test at a fixed work rate adjusted for weight in kilograms (W·kg^{-1}) of 1.7 W·kg^{-1} followed by 30-minutes rest, and then an incremental cycle test (Godfrey, 1970) to voluntary exhaustion with VO_{2peak}, W_{peak}, ventilatory equivalent of oxygen or ratio of minute ventilation to rate of oxygen uptake (V_E/VO_2) and peak heart rate (HR_{peak}) all recorded. At baseline there was a significant between-group difference in FEV_1 %pred. (106±8 vs. 77±22; p<0.05) and FVC %pred. (109±8 vs. 89±19; p<0.01), and this difference remained throughout the study. p≤

There were no significant between-group differences in VO_{2peak} between baseline, 8-week and 16-week measurements for both control (42.7±4.4 vs. 44.6±5.9 vs 44.8±6.3 ml·kg·min^{-1}) and CF groups (41.9±6.1 vs. 42.8±6.3 vs. 44.0±6.3 ml·kg·min^{-1}). However, W_{peak} improved slightly but non-

significantly, between each assessment point for both control (3.9±0.5 vs. 4.0±0.5 vs 4.1±0.5 $W \cdot kg^{-1}$) and CF groups (3.9±0.3 vs. 4.0±0.6 vs. 4.2±0.6 $W \cdot kg^{-1}$).

2.5.2. Exercise training in children admitted to hospital for exacerbations

Cerny (1989) conducted a trial in 17 children who were admitted to hospital for 2-weeks (range of 10-14 days) of IV-antibiotic treatment due to acute exacerbation of respiratory symptoms. The effects of a postural-drainage regimen (n=8; aged 15.9±4.9 years) was compared to a cycling plus postural drainage regimen (n=9; aged 15.4±4.9 years). Baseline spirometry measurements of FEV_1 %pred. and FVC %pred. was recorded 2-hours after the first airway clearance session on day of admission. A cycle ergometer-based exercise test was then performed at an initial load of 0.3 $W \cdot kg^{-1}$, with the load increased by 0.3 $W \cdot kg^{-1}$ every 2-minutes until volitional exhaustion, or SpO_2 decreased by more than 15% (or dropped below 75% of resting SpO_2), to determine W_{peak} and HR_{peak}.

Each day, the postural-drainage group undertook 3 x 20-40 $min \cdot day^{-1}$ of airway clearance therapy combined with chest percussion and vibration. The supervised exercise group performed 5-10 $min \cdot day^{-1}$ of cycling between days 1-4, at an intensity of 25-40% of heart rate reserve (HRR) and progressed to a minimum of 15-20 $min \cdot day^{-1}$ of cycling of least 40% HRR from day 5 onward, with all participants having achieved an intensity of 45%-65% HRR by discharge.

FEV_1 %pred. was significantly ($p<0.05$) lower in the postural drainage group at baseline. At final assessment, there were no significant between-group differences in lung function, however there was a significant within-group change in FEV_1 %pred. for both postural-drainage and exercise groups (18.4%; $p<0.01$ vs. 11.3%; $p<0.01$), as well as in FVC %pred. (22.4%; $p<0.01$ vs. 14.6%; $p<0.01$). Comparison of cycle test results showed no significant between group difference in W_{peak} and HR_{peak}, however there were significant within-group changes in W_{peak} (0.26 $W \cdot kg^{-1}$; $p<0.01$ vs. 0.44 $W \cdot kg^{-1}$; $p<0.02$) and in HR_{peak} (9 $beats \cdot min^{-1}$; $p<0.02$ vs. 13 $beats \cdot min^{-1}$; $p<0.05$).

For the first time, Cerny (1989) proposed that exercise was safe and could be used to supplement airway clearance sessions without adversely affecting lung function. However, the results of this

study should be interpreted with caution as severity of lung disease was not controlled for, and all the children were being treated with IV-antibiotics throughout the duration of the study. It is therefore difficult to distinguish the level of influence the exercise may have had on lung function because IV-antibiotics are known to have a significant positive effect on lung function (Gibson et al., 2003); furthermore, 2-weeks of exercise training may be too short a time for the true physiological benefits of exercise to be determined.

Selvadurai et al. (2002a) conducted a study in 66 children (range 14-22 days) admitted to hospital with for IV-antibiotic treatment of respiratory exacerbation and compared the effects of aerobic exercise to strength training. Children were randomised at baseline to one of 3 groups: control group (n= 22; aged 13.2±2.0 years), aerobic training group (n= 22; aged 13.2±2.0 years) or resistance training group (n= 22; aged 13.1±2.1 years). Spirometry measurements of FEV_1 %pred. and FVC %pred. was recorded, as well as skinfold thickness measurements (biceps, triceps, scapular, iliac crest) to calculate fat-free mass. A treadmill based CPET (Bruce et al., 1949) was performed to determine VO_{2peak}, and dominant quadriceps femoris and hamstring muscle strength were calculated using an isokinetic dynamometer. Quality of life was evaluated using the Quality of Well Being Scale (Kaplan et al., 1989). All outcomes were recorded at baseline, on the day of discharge and 4-weeks after discharge.

The control group received a standardised protocol of regular chest physiotherapy but did not attend exercise sessions. Supervised aerobic training consisted of either running on a treadmill or stationary cycling at a 70% HR_{peak} during 1 x 30 min·day^{-1} session for 5 days. Progressive recalculation of HR_{peak} was completed every 5 days when children performed a maximal treadmill test without gas analysis. The recalculated 70% HR_{peak} were then used for the next 5-days of training. Supervised resistance training comprised of 1 x 30-45 min·day^{-1} session for 5 days, with 5 sets x 10 repetitions of an unspecified number of upper and lower limb exercises completed, using a non-isokinetic resistance machine. Resistance for each exercise was calculated as 70% of maximal subjective resistance.

FEV_1 %pred. significantly improved between baseline and discharge for control (57.4%±17.4%; Δ4.5%±6.9%; $p<0.05$), aerobic (56.8%±17.9%; Δ6.54%±7.76%; $p<0.05$) and resistance groups (58.0%±16.8%; Δ10.1%±7.4%; $p<0.01$) and these improvements were maintained 4-weeks post discharge (Δ4.7%±7.2% vs. Δ6.3%±7.9% vs. Δ9.8%±7.1%; $p<0.05$). There were no significant changes in FVC %pred. for any of the groups. VO_{2peak} did not improve between baseline and discharge for control (34.0±17.7; Δ-1.22±6.2 ml·kg·min^{-1}) and resistance training groups (34.0±17.7; Δ0.7±5.9 ml·kg·min^{-1}) but did significantly improve for the aerobic training group (33.8±17.0; Δ7.3±6.3 ml·kg·min^{-1}; $p<0.01$) and these changes were maintained 4-weeks post discharge (Δ7.6±6.8 ml·kg·min^{-1}; $p<0.01$).

The control group lost strength, as measured in a Newton metre (Nm) as a unit of torque, between baseline and discharge (155±20 Nm; Δ-6.3±6.1 Nm), the aerobic training group marginally increased strength (155±19; Δ1.8±6.2 Nm), whilst the resistance group significantly improved their strength (156±21; Δ18.3±7.0 Nm; $p<0.01$). The resistance group lost their strength gains 4-weeks post discharge (Δ15.0±7.2 Nm; $p<0.01$), but these results were slightly better than baseline measurements. Fat-free mass as an indicator of muscle growth, improved significantly in all three groups, but mostly in the resistance group, and these changes were maintained 4-weeks post-discharge. Quality of life outcomes were selectively reported but suggested a significant positive correlation (r=0.57; $p<0.05$) between improved VO_{2peak} and Quality of Well Being Scale scores.

FEV_1 %pred. was significantly increased in all groups, but without a significant change in FVC %pred., therefore it was more likely that the IV-antibiotics and airway clearance regimen were responsible for the improved lung function. Strength and fat free mass gains from resistance training were significantly different, despite the short period of training, and appeared to counteract the possible deconditioning that the control group had experienced. Cerny (1989) suggested that participation in exercise was potentially more beneficial than airway clearance alone, to maintain airway health and patency. Selvadurai et al. (2002a) proposed that a combination of aerobic and strength training may be an optimal method of exercise training for children with CF.

2.5.3. Partially supervised home-based exercise training

In the most recent longitudinal study, Schneiderman-Walker et al. (2000) evaluated the effects of 36-months of home-based exercise on 72 children with an FEV_1 %pred. ≥40%, who were randomised to a control group (n=36; aged 13.3±3.6) and an exercise group (n=36; aged 13.4±3.9). All children continued to receive specialist CF medical care for the duration of the study. The control group were also asked to maintain their usual activity level, and the exercise group were asked to self-select exercise from a range of physiologist suggested aerobic activities (e.g., swimming, cycling, running and football), and to exercise for 3 x 20 min·week^{-1} at 70-80% HR_{peak} or at a HR of 150 beats·min^{-1} using a self-monitoring technique. A telephone call to monitor and actively encourage children to maintain their activity levels was made every 4-6 weeks by the research team. Both groups recorded their activity levels in a diary that included date, type of activity, duration in minutes, and level of intensity denoted as: 1 (easy), 3 (easy conversation) and 5 (too difficult to talk).

At baseline, spirometry measurements of FEV_1 %pred. and FVC %pred. were recorded, and then serially measured every 12-16 weeks at scheduled clinic appointments. A cycle ergometer (Godfrey et al., 1971) test was completed at baseline, 12-months, 24-months and at 36-months, with VO_{2peak} and W_{peak} recorded. At baseline, FEV_1 %pred. (87.9±17.8 vs. 89.2±19.5) and FVC %pred. (90.1±12.9 vs. 92.6±15.7) were not significantly different. For each year of the study, there was a significantly steeper decline in FVC %pred. in the control group when compared to the exercise group (-2.4±4.2 vs. -0.25+2.8; p=0.02) and a similar trend was shown for FEV_1 %pred. (-3.5±4.9 vs. -1.5±3.6; p=0.7).

Control and exercise group measurements of VO_{2peak} (40.7±7.9 vs. 40.6±7.6 ml·kg·min^{-1}) and W_{peak} (93.5±17.5 vs. 94.8±15.0 W·kg^{-1}) were recorded at baseline, however Schneiderman-Walker et al. (2000) only stated that there were no significant differences between groups for any of the exercise parameters at the end of the study. This selective reporting makes independent comparisons to the other studies results impossible. The conclusion of the study was that 36-months of partially supervised exercise slowed the rate of decline in FEV_1, however the interpretation of the results should be treated with caution as the results were not statistically significant, and the researchers could not explain the significantly steeper decline in FVC.

In another home-based exercise study, Orenstein et al. (2004) compared the effects of upper-body strength training to aerobic exercise training in children with CF over the course of 12-months. A total of 143 children were invited to participate, but those who were already regularly exercising, or had a VO_{2peak} >45 ml·kg·min^{-1} and/or a W_{peak} >110% of predicted as measured during a Godfrey (1970) cycle protocol were excluded. A total of 67 children (mean age 11.5 years; range 8-18 years) were enrolled into the study, but only 62 data sets were analysed (1 set twin; 5 sets sibling data were excluded) from those randomised to strength (n=28) and aerobic (n=25) exercise groups.

For the first 8-weeks of the partially supervised study, exercise physiologists completed weekly home-visits, followed by once-a-month visits for the remainder of the 12-month to encourage adherence to exercise and progress the training programmes. The aerobic exercise group completed their programme on a stair-stepping machine, starting with 1 x 5-min·day^{-1} initially, and progressing to 1 x 30 min·day^{-1} over the course of the study at up to 70% HR_{peak}. The upper-body strength training group performed biceps curls, lateral pull-downs, and military and bench presses on a Nordic Power weight resistance machine at individually tailored weight, sets and repetition, at <55% HR_{peak}.

Participants completed assessment at baseline, 6- and 12-months, with all measurements completed at least 2-weeks post-discharge from hospital for IV antibiotic treatment. There were no significant differences baseline differences in FEV_1 %pred., VO_{2peak}, W_{peak}, and 1-repetition maximum (1RM) lifts of bicep curl, bench press and leg-extension exercises, and the Quality of Well-being scale domains of mobility, physical activity, and social activity.

FEV_1 %pred. decreased between baseline and 6-months in both aerobic (92.2±18.3 vs. 89.7±19.3; p=0.20) and strength (90.3±17.9 vs. 86.1±17.2; p=0.05) groups but increased in both groups between 6 and 12-month assessments. The increase was not significant for the aerobic group (89.7±19.3 vs. 90.3±17.9; p=0.36) but was significant in the strength group (86.0±17.7 vs. 90.3±15.8; p=0.05). Over the course of 12-months both groups maintained a mean FEV_1 %pred. >90% (aerobic group 91.5±18.2 vs 90.3±17.9, and strength group 91.2±18.1 vs. 90.3±15.8).

There were no significant differences in VO_{2peak} between baseline and 12-months for either aerobic (34.6±5.5 vs. 33.7±7.2; p=0.56) or strength (32.6±6.2 vs. 30.9±6.7; p=0.07) groups. However, there was a significant change in predicted W_{peak} between baseline and 12-months for the aerobic group (4.59%±0.3% vs 4.68%±0.3%; p=0.003) and strength group (4.56±0.4% vs. 4.64±0.4%). 1-repetition maximal strength measurements of bicep curl, bench press and leg-extension exercises were also significantly increased by 3-4% (p<0.001) per body-part and in both groups. Lower-limb strength was also increased in the group that only trained upper-limb strength. Upper limb strength gains for the aerobic group were attributed to use of the upper limbs for stability during stepping, and lower limb strength gains for the upper-limb strength group were attributed to the lower limb still bearing weight and being manoeuvred during exercise sessions. Quality of life reportedly did not significantly change for either group, but data were not presented.

There was a higher number of dropouts in the aerobic group, which was linked primarily to smaller children being unable to perform an optimal exercise technique on the stair-stepping machine. It may be that children also found using the same exercise single piece of equipment for the full 12-months boring, despite motivation by telephone.

2.5.4. The effects of anaerobic exercise training

Klijn et al. (2004) evaluated the effects of anaerobic training on lung function, aerobic and anaerobic capacity, and quality of life over a 12-week period, in 20 children randomised to control (n=9; aged 14.2±2.1) and anaerobic training groups (n=11; aged 13.6±1.3). All children completed spirometry to measure FEV_1 %pred. and FVC %pred., a Wingate anaerobic test (Bar-Or, 1987) to calculate peak power (Wpeak), an incremental cycle test (completed 45-minutes after the Wingate test) to determine VO_{2peak} and W_{peak}, and the disease specific CFQ (Quittner, 1998), at baseline and 12-weeks end of intervention, and then at a further 12-weeks follow-up.

Children in the control group were asked to maintain their normal physical activity levels and physiotherapy regimen. The supervised anaerobic training group completed 2 x 30-45 min·week^{-1} high-intensity training sessions a week for 12-weeks. Supervised training sessions consisted of 8

basic individual training programmes, repeated every 4-weeks at maximal effort and speed, and included short distance multi-directional sprints and stop-start heavy ballgames. The researchers provided the exercise programme in an online supplement to the journal publication. There were no significant differences between control and anaerobic exercise groups at baseline in FEV_1 %pred. (82.1±19.1 vs. 75.2±20.7), FVC %pred. (93.2±15.8 vs. 85.0±14.0), Wpeak (647±179 W vs. 547±178 W), VO_{2peak} (40.7±8.3 vs. 40.2±4.2); VO_{2peak} %pred. (84.2±10.4 vs. 83.1±9.1), and W_{peak} (156±26 vs. 140±20).

After 12-weeks of training, Klijn et al. (2004) reported that there were no significant between-group differences in FEV_1 %pred. and FVC %pred., however these results were not documented, which is poor practice. The results of the Wingate test showed that there was a non-significant decrease in Wpeak in the control group (-3.4±53.7 W) but a significant increase in the anaerobic exercise group (66.9±23.8 W; p>0.001). The 12-week repeat cycle ergometer test showed that VO_{2peak} and VO_{2peak} %pred. had decreased in the control group (-0.6±1.9 ml·kg·min^{-1} and -2.1±2.8%; p<0.05) but had significantly increased in the anaerobic group (1.5±2.6 ml·kg·min^{-1} and 4.7±5.6%; p<0.05).

Quality of life domains of the Cystic Fibrosis Questionnaire (CFQ-R) were not well documented, which made independent interpretation difficult. However, Klijn et al. (2004) reported that there were no significant between-group differences in quality of life over the 12-weeks intervention period, except in the domain of physical functioning. Within-group analysis showed that the anaerobic exercise group perceived their physical functioning to have significantly increased between baseline and 12-weeks (70.3±13.8 vs. 88.4±9.0; p<0.001). The control group had recorded a higher physical functioning score at baseline, and although this score had increased at 12-week assessment (83.2±18.5 vs. 87.1±17.9; p=0.20), this within-group difference was not significant.

At 12-week follow-up, lung function parameters were again not documented but reported as being not significantly different. Absolute Wpeak was significantly higher in the anaerobic exercise group (54.6±47.7 W; p<0.001) and higher in the control group (24.9±73.5 W; p=0.34), when compared to baseline results. The anaerobic groups VO_{2peak} was reported as not significantly different between

baseline and 12-week follow-up, however the control groups VO_{2peak} was significantly lower (1.5±1.7 ml·kg·min^{-1}). CFQ physical functioning domain scores for the exercising group remained significantly higher than baseline (8.3±8.4; p<0.01).

Klijn et al. (2004) showed for the first time that high-intensity anaerobic training in children with CF, could significantly improve strength and aerobic parameters, but were not maintained and returned to baseline levels. The exercise prescription, particularly with reference to the level of intensity of exercise expected of the children, was poorly reported. It may be that too much reliance on the children's ability to self-determine maximal speed during the exercise programme, had an impact on the results of the study.

2.5.5. The effects of combined aerobic and strength training

Santana-Sosa et al. (2012) evaluated the effects of chest physiotherapy versus a combination of aerobic and strength training in an 8-week study followed by 4-weeks detraining. Children were randomised to control (n=11; aged 10±2 years) and exercise groups (n=11; aged 11±3), with the control group asked to complete 2 x daily airway clearance sessions and maintain their normal physical activity level, and the exercise group were asked to maintain the same airway clearance regimen, but also completed 3 x 60 min·week^{-1} supervised exercise training sessions in the hospital gym.

The supervised and individually tailored sessions included a 10-minute warm-up, followed by 20-40 minutes on a cycle ergometer followed by 3 circuits (1 set x 12-15 reps per circuit) on 11 upper and lower body strength exercise stations. Aerobic exercise was performed at HR calculated at ventilatory threshold, which was the increase in both V_E/VO_2 and end tidal pressure of oxygen with no rise in ratio minute ventilation to rate of carbon dioxide uptake (V_E/VCO_2) during an incremental treadmill test. Strength training was progressed from 40% of a 5-repetition maximum (5RM) to 60% of 5RM by the end of the study. During the detraining period, all children were asked to maintain their airway clearance regimen and return to their usual physical activities as at baseline.

Measurements of FEV_1 %pred., VO_{2peak}, 5RM of upper and lower body strength were completed at baseline, 8-weeks, and 4-weeks after end of intervention. The Spanish version of the CFQ-R was undertaken at baseline and 8-weeks. At baseline there were no significant between-group differences in FEV_1 (1.8±0.2 vs. 1.9 vs. 0.2 L) and FVC (2.3±0.2 vs. 2.4±0.2 L), and this was similar to the results of FEV_1 (1.9±0.2 vs 1.9±0.2 L) and FVC (2.4±0.2 vs. 2.5±0.3 L) after 8-weeks training, and again for FEV_1 (1.8±0.2 vs. 1.9±0.3 L) and FVC (2.4±0.2 v. 2.6±0.3 L) after 4-weeks detraining. These results suggested that the exercise programme had no effect on lung function, and that lung function could remain stable without training.

Santana-Sosa et al. (2012) reported that there was a significant between-group differences in VO_{2peak} at baseline, in favour of the control group (p=0.02), however this data was not documented. After 8-weeks there was a non-significant decline in VO_{2peak} for the control group (-2.2 ml·kg·min^{-1}; 95%CI -5.3, 0.1; p=0.16) and again during the 4-week detraining period (-0.7 ml·kg·min^{-1}; 95%CI -4.4, 5.9; p=0.8); however, in the exercise group there was a significant increase in VO_{2peak} after 8-weeks training (3.9 ml·kg·min^{-1}; 95%CI 1.8, 6.1; p=0.002) but the effects of training were lost within 4-weeks of completing the study (-3.4 ml·kg·min^{-1}; 95%CI -5.7, -1.7; p=0.001).

Bench press and leg press strength in the control group was reported as unchanged throughout the intervention and detraining period, however again these results were not documented. The exercise group significantly increased strength in both bench press (10.5 kg; 95%CI 7.0, 14.0; p<0.001) and leg press (24.9 kg; 95%CI 14.3, 34.4; p=0.001) after training, but after detraining the strength gains in bench press (-1.2 kg; 9%% -3.6, 3.0; p=0.6) and leg press (1.0 kg; 95%CI -4.1, 3.3; p=0.8) had started to decline. There were no significant differences in baseline and after-training total CFQ-R scores for either control (649 vs. 638) or exercise groups (696 vs. 719). Neither group showed improvements in quality of life domains of the CFQ.

This study showed that 8-weeks of a combination of aerobic and strength training could significantly improve aerobic capacity and upper and lower body strength, however these gains in VO_{2peak} strength gains were not sustained after 4-weeks of detraining. These were important findings

as this would suggest that a regular exercise programme would need to be maintained to at least preserve the short-term gains of exercise.

In a follow-up study, Santana-Sosa et al. (2014) considered the effects of inspiratory muscle training combined with aerobic and strength training with standard airway clearance regimens in a hospital-based gym setting. Following the same format as the previous Santana-Sosa et al. (2012) study, children randomised to the control group (n=10; aged 10±1 year) and exercise groups (n=10; aged 11±1 year) were assessed at baseline and 8-weeks, and then after 4-weeks detraining. The control group completed 2 x daily airway clearance sessions, inspiratory muscle training at 10% of their maximal inspiratory pressure (PI_{max}) and maintained their normal physical activity level. The exercise group performed the same daily airway clearance regimen plus 2 x 5 minute (30 inspirations) inspiratory muscle training sessions and completed 3 x 60 min·week^{-1} supervised exercise training sessions in the hospital gym, as previously described. Inspiratory muscle training was progressively loaded from 40% of PI_{max} (Week 1-2), to 50% PI_{max} (Week 3-4), and then adjusted to 40% of the PI_{max} assessed at week 4 (Week 5-8).

Measurements of FEV_1 %pred., VO_{2peak}, 5RM of upper and lower body strength were completed at baseline and 8-weeks, and after 4-weeks. The Spanish version of the CFQ-R were completed at baseline and 8-weeks. There were no significant differences in FEV_1 %pred. between baseline, 8-weeks training and after 4-weeks training for control (1.6±0.3 vs. 1.6±0.3 vs 1.6±0.3 L) and exercise groups (1.7±0.2 vs. 1.7±0.2 vs. 1.7±0.2 L), and this was similar for FVC %pred. in control (1.9±3 vs. 1.9±0.3 vs. 1.9±0.3) and exercise groups (2.2±0.3 vs. 2.3±0.3 vs. 2.3±0.3). PI_{max} remained unchanged for the control group (69.5±9.7 vs. 71.8±10.0 vs. 66.7±9.4) but was significantly improved by 36.5% in the exercise group with inspiratory muscle training effects maintained after detraining (68.3±6.3 vs. 107.6±8.4 vs. 103.2±8.1; p<0.001). There was a trend towards improved total CFQ-R scores for the exercise group (629 vs. 688; p=0.07) but not for the control group (636 vs. 638).

Baseline VO_{2peak} was significantly higher in the control group at baseline (36.2±2.1 vs. 31.1±0.9 ml·kg·min^{-1}), but there were no significant changes in VO_{2peak} in the control group at the 3

assessment points (36.2±2.1 vs. 35.6±1.5 vs. 32.1±1.4 ml·kg·min^{-1}). However, after training, VO_{2peak} had significantly increased in the exercise group (6.9 ml·kg·min^{-1}; 95%CI 3.4, 10.5; p=0.002), but then significantly decreased by -1.5 ml·kg·min^{-1} (95%CI-2.7, -0.4; p=0.014) during the 4-week detraining period. Strength measurements were static for the control group, but the exercise group significantly increased leg-press strength (62.5±6.5 vs. 89.5±9.3 vs. 88.6±9.2 kg; p=0.05) and showed non-significant increases in bench-press (26.4±2.7 vs. 38.4±3.2 vs. 35.9±2.9 kg; p=0.4), and these gains were maintained despite a 4-week detraining period.

As with the first Santana-Sosa et al. (2012), there was a significant clinical and health benefits to participation in exercise, and the exercise group also seemed to benefit from inspiratory muscle training. The increased VO_{2peak} remained above baseline level after detraining, and strength gains were also mostly maintained. A 3rd group may have been appropriate in this study to evaluate for any difference between regular airway clearance regimens and the addition of 10% of PI_{max} to the regimen. Of all the 8 randomised controlled trial, these two trials had well-described methodologies and were of good quality as the reporting of results were mostly clear and consistent.

2.6. Conclusion

This review of 8 randomised controlled trials focused on exercise training in children with CF has shown that supervised programmes for children with CF produced the most significant improvements in exercise parameters, with lesser effects shown in partially supervised and unsupervised programmes. Children admitted to hospital for exacerbations also benefited from increased exercise capacity, but it was likely that IV-antibiotics had a significant therapeutic effect on increased lung function. These mostly short-term studies demonstrated that exercise could increase FEV_1, VO_{2peak} and/or W_{peak}, and these improvements could be maintained after 4-weeks of no training. However, there was evidence that the aerobic benefits were not maintained and returned to baseline levels. Importantly, the exercise programmes produced similarly beneficial results in both males and females. No single modality of exercise produced optimal outcomes, but each exercise type had benefits. *Inspire-CF* would therefore incorporate both aerobic and strength training modes. It should be noted that a comprehensive Cochrane review has since been published (Radtke et al.,

2022) on the effects of exercise on FEV_1, VO_{2peak}, and CFQ-R physical and respiratory domains, and is discussed in **Chapter 10, Subheading 10.2.3, pg. 230**

2.7. Novel approach to supervised exercise to optimise physiotherapy regimens

Although observational studies are not considered high quality evidence, 3 such studies (Black et al., 2009, Urquhart et al., 2012, Ledger et al., 2013) have shown that 12-months of supervised exercise had a positive effect on the clinical and health status of the sickest group of children with CF, and also demonstrated a cost-benefit to host institutions. The results of these studies were relevant to the research presented in this thesis, particularly as the *Frequent Flyer Programme* (Ledger et al., 2013) was a pilot study undertaken between January 2011 and April 2012 and hosted by the GOSH CF Unit, and its positive results underpinned the application for funding of *Inspire-CF*.

In 2009, a Brisbane based research group proposed a novel approach to physiotherapy management of the 10-15% of children with CF who required frequent hospital admissions for intensive IV-antibiotic treatment as part of a pre-planned admission protocol, or as a response to acute exacerbations (Black et al., 2009). The observational study was based on provision of weekly, individually supervised exercise training sessions, in addition to current specialist CF care. Black et al. (2009) enrolled 10 children (n=3 males; n=7 females; n=7 homozygous for the *p.Phe508del* mutation) aged 3-18 years (mean 13.2) in their study, who had been admitted to hospital for >40 days of IV-antibiotic treatment in the previous year. A comparison of lung function, functional exercise capacity, and admission data from the intervention year was made with the previous year's data. The study demonstrated a significant 48% reduction in IV-antibiotic requirement (67.7 days vs. 34.9 days; $p<0.001$), and significantly more levels of the 20m incremental shuttle walk test were completed (5.9 vs. 7.6; $p=0.05$). There was also a non-significant increase of 4% in FEV_1 %pred. (62% vs. 66%; $p=0.09$).

In September 2010, the *Frequent Flyer Programme* (Ledger et al., 2013) was established with the aim of replicating and confirm the findings of the Black et al. (2009) study. The *Frequent Flyer Programme*, so named because the children enrolled in the programme spent so much time in

hospital, was undertaken as a quality improvement initiative and included physiotherapy and dietetic monitoring. Physiotherapy included a physiotherapist supervised, once-weekly exercise session at a local gym facility, and 1 x per month home-based review of airway clearance and mucolytic therapy regimens. Dietetic management included 1-2 monthly monitoring of growth, absorption, appetite and intake, and nutritional education sessions.

An age appropriate individualised exercise prescription was determined from spirometry, nutritional status, cycle ergometer CPET (Godfrey and Mearns, 1971) and a 10 metre modified shuttle walk test (10m-MSWT) (Selvadurai et al., 2003). Exercise training comprised of cardiovascular training (e.g., treadmill, bike, and cross-trainer) interspersed with periods of recovery. This allowed time for recovery from breathlessness and huffing and coughing was performed to improve airway patency. Strength, core-conditioning and stretching components were also included in the exercise programme.

Based on published general exercise and training recommendations (Williams et al., 2010), children with a baseline FEV_1 ≥70% predicted, exercised for 45-60 minutes, of which 20-30 minutes was at 65-85% HR_{peak}; whilst children with a baseline FEV_1 = 39-69% predicted exercised for 30-45 minutes for 15-25 minutes at 60-80% HR_{peak}. In addition, children were also encouraged to exercise independently, and actively participate in school physical education lessons and sport for an additional 2-hours per week. Free membership to a local fitness facility was negotiated for each of the children, and this was where the physiotherapist provided the weekly training sessions.

Sixteen children (n=4 male; n=12 females; n=9 homozygous for the *p.Phe508del* mutation; n=15 pancreatic insufficient) aged 4-15 years (mean±SD; 10.9±2.93) who had been admitted to hospital for >40 days of IV-antibiotic treatment in the previous year, were enrolled in the study. The primary outcome for the intervention was total number of IV-antibiotic days required in the 12-month study period, compared to the 12-months pre-enrolment. Secondary outcome measures included exercise capacity, lung function, growth and body composition, quality of life, and cost of health care.

There were statistically significant and potentially clinically important increases in VO_{2peak} of 5 ml·kg·min^{-1} (95%CI 1.01, 8.71; p=0.02) as measured by a Godfrey cycle ergometer test. The 10m-MSWT distances and incremental levels attained improved by 229 meters (95%CI 108.76, 349.70; p<0.001) and 2 levels (95%CI 0.83, 2.56; p<0.002) respectively. There was a 9% (95%CI −3.3 to 23.0; p=0.13) decline in FEV_1 %pred. in the 12-months preceding enrolment into the *Frequent Flyer Programme*, however FEV_1 %pred. was maintained between baseline and 12-month assessments (0.6%; 95% −7.4 to 8.6; p=0.88). Although this result was not significant, it did appear to show that rate of deterioration in FEV_1 may have slowed.

The *Frequent Flyer Programme* demonstrated a 21% reduction (478 vs. 619 days in previous year) in inpatient IV-antibiotic requirement, a 24% decrease in shared-care inpatient IV requirement (189 vs. 249 days in previous year), and a 20% reduction (243 vs. 304 days in previous year) in home IV-antibiotic requirements during the intervention year. Healthcare cost analyses showed savings of £220,338 with the cost of setting up and running the programme being £100,000.

Feedback from both children and parents who participated in the *Frequent Flyer Programme* was very encouraging; with families reporting that their children had been able to spend more time at home and school and experienced less of a dip in their general quality of health. Importantly, children reported they were able to exercise at the same level or even higher than their peers.

Urquhart et al. (2012) also undertook a similar observational study, based on the Black et al. (2009) study, and enrolled 12 children (n=6 male; n=6 females; n=7 homozygous for the *p.Phe508del* mutation) aged 10.6-16.8 years (mean age 13.2 years). Children participated in a weekly supervised exercise session, led by local gym instructors, and were reviewed every 2-weeks by an outreach physiotherapist. The study demonstrated a 30% reduction in hospital based IV-antibiotic requirement (224 vs. 318 days in previous year) and a 7% reduction in home based IV-antibiotic requirement (378 vs. 406 days in previous year) with an associated healthcare cost saving of £66,384.

Participants significantly improved their 10m-MSWT distances by 208 meters (735 meters vs. 943 meters in previous year; p=0.04) and incremental shuttle level attained by 2 (9.4 vs. 11.1 in previous year; p=0.04). All children maintained their FEV_1 between baseline and 12-month assessment points.

These 3 studies represented a novel approach to physiotherapy, and focussed on incorporating structured, supervised exercise training into children's CF management. However, they were observational studies, and their results should not be over-interpreted, as there were no comparisons to a control group. It is plausible that the studies offered clinicians an opportunity to monitor children more closely for subtle changes in their clinical status, and that a Hawthorne effect was observed (Franke and Kaul, 1978), such that it was the closer monitoring rather than the exercise intervention that led to improved outcomes. Nevertheless, children had significantly improved their aerobic fitness as measured by gold-standard CPET and the 10m-MSWT, and so the Hawthorn effect may not be the primary reason positive changes were recorded.

2.8. Summary

Chapter 2 has provided a comprehensive account of the current knowledge related to randomised controlled trials that have evaluated children's physiological response to different exercise training modes. However, the review of 8 randomised controlled studies did not provide sufficient evidence to clearly define the benefits of exercise in children CF, and it was evident that there is lack of good quality longitudinal studies. The 3 observational studies that focussed on individually supervised exercise training in the sickest children with more advanced lung disease, demonstrated marked improvements in clinical outcomes and reductions in associated healthcare costs. These studies also showed that providing supervised exercise could be cost-neutral, or even cost-saving. It is evident that a randomised controlled trial is warranted to address the gap in the understanding of longitudinal response to exercise in children with a wide range of CF lung disease severity. Therefore, *Inspire-CF* was designed to address this gap in knowledge.

3.

CHAPTER 3. GENERAL METHODOLOGY

Chapter 3 describes the participants, equipment and general methods used for data collection and processing in **Chapters 5–9**.

3.1. Administrative information

3.1.1. Grant award

The *Inspire-CF* research programme was funded through a competitive, peer-reviewed process, by Great Ormond Street Hospital Children's Charity (#V1252) (**Appendix A**). Sean Ledger and Professor Eleanor Main were co-lead investigators.

3.1.2. Ethical approval and trial registration

Ethical approval was granted by the South-East Kent Research Ethics Committee (#REC 107522/338653/1/748) (**Appendix B**) and the Joint Research and Development Office at UCL Great Ormond Street Institute of Child Health (#11AR13). The study was registered as a clinical trial at the U.S. National Institutes of Health, ClinicalTrials.gov (#NCT01889927) (**Appendix C**).

3.1.3. Study design, setting and pathway

Inspire-CF was a single centre, non-blinded, randomised controlled trial with parallel groups (control vs. exercise intervention) and intention to treat analysis. The 4-years of research was hosted by the Great Ormond Street Hospital NHS Foundation Trust (GOSH) CF Unit between May 2012 and July 2016, with each participant enrolled in the study for 24-months. The exercise intervention was undertaken in private and public sector fitness facilities and school gyms. The study pathway is illustrated in **Figure 3–1**.

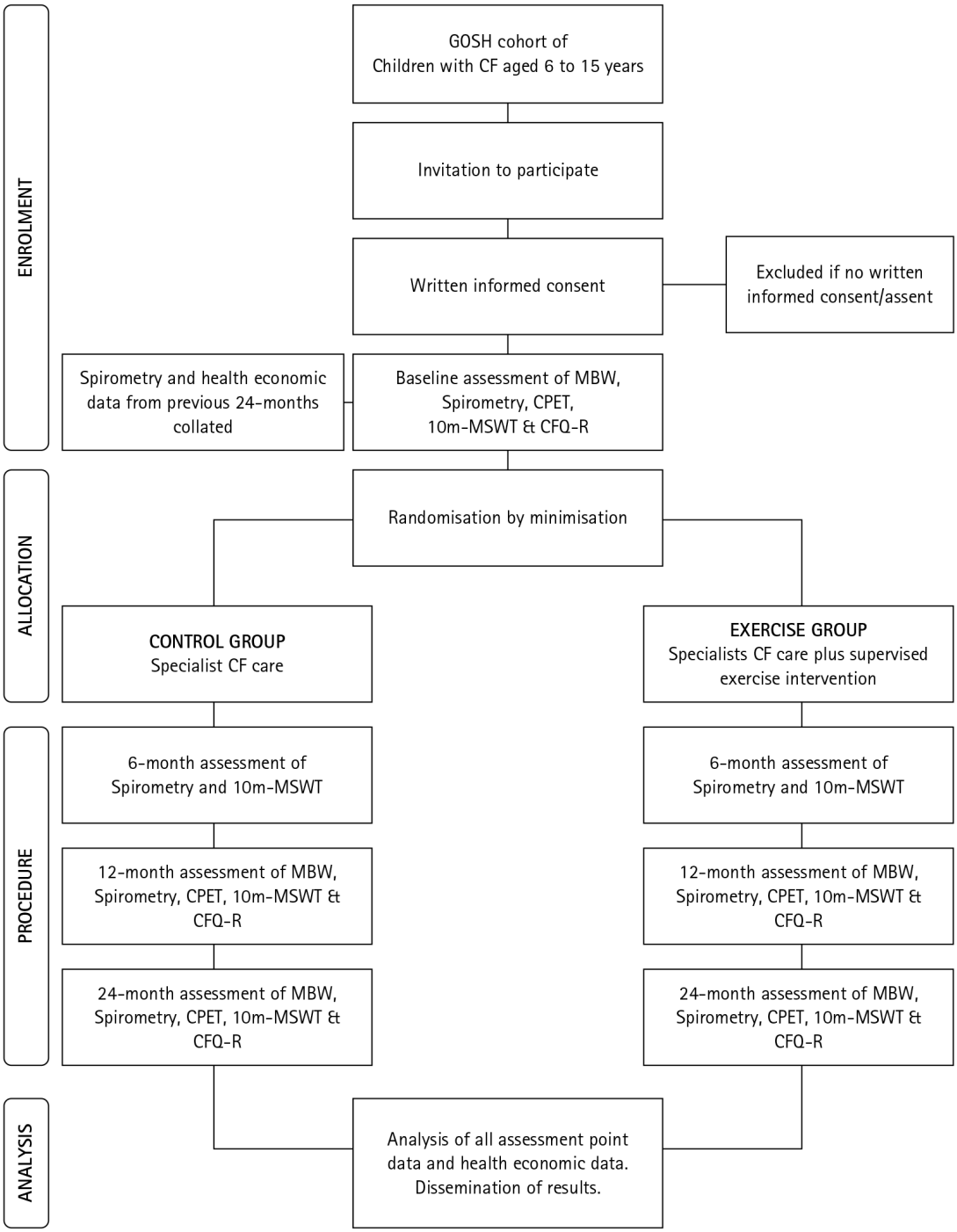

Figure 3-1: Consort diagram of the Inspire-CF study pathway

3.2. Participants

3.2.1. Eligibility to participate

To determine and justify the age range for eligibility for participation in *Inspire-CF* the research team needed to consider two key limitations identified during the pilot *Frequent Flyer Programme*.

Limitation 1: The youngest participant in the *Frequent Flyer Programme* was aged 4.7 years at baseline. However, this precluded the child from performing a CPET and 10m-MSWT at baseline, as GOSH CF exercise protocols and the Cystic Fibrosis Trust (2013) clinical guidelines suggested a minimum age of 6 years for safe and effective clinical exercise testing, and CPET (Godfrey and Mearns, 1971) and the 10m-MSWT (Selvadurai et al., 2003) had only been validated in children with CF of 6 years of age and older. Additionally, the ability of the child to actively engage in structured exercise training was only realised in the latter stages of the programme when the child was aged 5.2 years.

Limitation 2: The oldest participant to complete the *Frequent Flyer Programme* was aged 17 years, however, this was typically the age when transition to adult care occurs in the UK.

Therefore, in view of published exercise guidelines, experience with young participants, and typical transition to adult services upper age limit, the clinical research team determined that only children aged 6-15 years at baseline were eligible for participation in *Inspire-CF* . A provision was made with the GOSH CF Unit, such that those individuals who were already aged 15 years at baseline and not within 6-months of their 16th birthday, would not fully transition to adult care until they had completed the 24-month enrolment period.

3.2.2. Inclusion criteria

1. Children with a documented diagnosis of CF;
2. Male or female, aged 6 years or older at baseline, and projected to be aged less than 17 years and 6 months at the end of the study;
3. Under the primary care of the GOSH CF Unit;
4. Able to perform spirometry with a baseline FEV_1 %pred. greater than or equal to 40%, as measured on at least 3 occasions in the previous 12-months, during times of clinical stability (i.e., not during an exacerbation, and not during or within 2 weeks of IV-antibiotics);
5. The child's parent or legal guardian gave informed consent; and assent was sought from children where appropriate.

3.2.3. Exclusion criteria

1. Children who had undergone lung transplantation;
2. Children who were listed for lung transplantation; however, children would not be withdrawn if they were listed during the study;
3. Clinically significant medical condition (e.g., unstable cardiac arrhythmias or undergone cardiac surgery) other than CF or CF-related conditions, that in the opinion of the CF multidisciplinary team, would compromise the safety of the patient during exercise;
4. Orthopaedic impairment that compromised exercise performance;
5. Mental impairment leading to inability to cooperate;
6. Unable to understand both verbal and/or written instructions in English. Children needed to be able to understand exactly what the fitness instructors were asking them to do, to ensure safe and effective exercise training sessions. Information sheets and questionnaires were only available in English.
7. Children, parents, or legal guardians who were unwilling to sign consent to participate.

3.2.4. Eligibility to undertake a cardiopulmonary exercise test

The following criteria did not preclude a child from participation in the study, however, based on the GOSH cardiorespiratory exercise laboratory infection control protocol, a participant would be excluded from performing a cycle ergometer based CPET if the test could not be performed in the final test session of the day, following which a deep clean of the laboratory would be performed:

- Patients with *Methicillin-resistant Staphylococcus aureus*;
- Patients with *Burkholderia cepacia*;
- Patients with *Nontuberculous mycobacterium.*

3.2.5. Invitation to participate

All children received a formal written invitation to participate, and were invited to participate in the study at:

- Routine attendance at CF outpatient clinics (approximately 12 children per weekly clinic);
- Routine attendance at CF annual review clinics (approximately 2 children per twice-weekly clinics);
- During routine hospital admissions for IV-antibiotics (approximately 3-4 patients on Badger Ward, which is the CF ward, at any time or;
- Pre-scheduled outreach physiotherapist and/or clinical nurse specialist home visits (10-15 children per week).

3.2.6. Recruitment to the study

During an initial consultation the structure of the two-arm study was carefully explained to the child and parents or legal guardian, by a member of the research team, so that they fully understood that the process of randomisation meant that they would not be able to choose the group they were in. No children or parents changed their decision after this was explained to them.

The research team stressed that the child was under no obligation to take part in the research. Children were advised that if they wished to take part, they were also free to withdraw at any time without affecting their current medical care. At the end of the initial consultation, the child and parent or legal guardian were given the relevant age-appropriate participant (**Appendix D**) and parent/legal guardian (**Appendix E**) information sheets.

Children were given at least 48-hours to consider their participation in the research and were encouraged to discuss the information with their family and friends. They were also given the opportunity to ask any questions related to their participation with their CF medical team, and again with the research team.

3.2.7. Informed consent and assent

Written informed consent to participate in the study was obtained from all parents or legal guardians, and written assent of the child was also obtained, prior to baseline assessment.

Every child had the right to dissent (refuse participation) if he/she wished to, and the clinical research team recommended that parents not overrule their child's decision if this option was taken. Those who signed consent/assent forms completed baseline testing.

3.3. Interventions

All children enrolled in *Inspire-CF* were randomised to one of two arms of the controlled trial, after baseline assessments were completed.

3.3.1. Control group: Specialist cystic fibrosis care

Participants randomised to the control group received 24-months of specialist CF care at GOSH, as described in **Chapter 1, Subheading 1.7, pg. 34.**

3.3.2. Exercise group: Specialist cystic fibrosis care plus supervised and individualised exercise

Participants randomised to the exercise group also received 24-months of the specialist CF medical care at GOSH (as described in **Chapter 1, Subheading 1.7, pg. 34.)**, plus a weekly, structured, individually prescribed and individually supervised exercise intervention, at a local fitness facility or a school gym, as described in **Chapter 4, Subheading 4.6, pg. 106**.

3.4. Assessment points

Over the course of the study, participants in *Inspire-CF* were assessed at 4 main assessment points:

- Baseline;
- 6-months;
- 12-months;
- 24-months.

Baseline, 12- and 24-month assessments required the participant to attend the hospital, therefore these were scheduled, where possible, on days when the child had a pre-planned appointment at an outpatient clinic, to minimise inconvenience to both children and parents/legal guardians.

The 6-month reassessment could be completed at the hospital in similarly pre-planned appointments, or the research team could complete the assessments at the child's school or local gym.

3.4.1. Assessments point pathways

At baseline each participant was scheduled into the first available appointment. Depending on availability of lung function and CPET slots, participants followed one of two pathways for testing:

- **Pathway 1:** Participant first completed an MBW; followed by spirometry; then a cycle ergometer based CPET, followed by a minimum 2-hour lunch break, then a 10m-MSWT and then finally, completed an age appropriate CFQ-R; *or*
- **Pathway 2:** Participant first completed an MBW; followed by spirometry; then a 10m-MSWT followed by a minimum 2-hour lunch break, then a cycle ergometer based CPET, and then finally, completed an age appropriate CFQ-R.

For the duration of the 24-month study, the participant followed the same pathway that they were assigned at baseline. Total assessment time at baseline, 12- and 24-month assessment points were approximately 4-hours per session.

3.4.2. 6-month assessment point

At 6-months, spirometry and a 10m-MSWT, were performed to determine any early changes in lung function or functional exercise capacity. This assessment was approximately 1-hour in duration.

3.4.3. Pre-assessment day instructions

After consent and/or assent were signed and a baseline assessment date had been booked, all participants received the following general instructions prior to attendance:

Thank you for agreeing to participate in *Inspire-CF*. Please ensure you follow these instructions prior to attending your first assessment.

- Please arrive 10-minutes prior to your first scheduled appointment;
- Your assessments will take approximately 4-hours to complete;
- You will perform two lung function tests, two exercise tests and complete a questionnaire;
- Lung function tests will be performed before the exercise tests;
- Regular breaks have been scheduled between tests;
- Refrain from eating a large meal at least two hours before lung function tests;
- On the morning of your assessments, complete your normal airway clearance routine and take your all medications but avoid taking any short-acting bronchodilators (e.g., Salbutamol) and long-acting bronchodilators (e.g., Seretide®);
- After you have completed your lung function tests, please take your prescribed doses;
- If are currently taking a short-acting bronchodilator, ensure you take your prescribed dose at least 10 minutes prior to exercise tests;
- Wear comfortable clothing and running shoes suitable for exercise;
- Avoid strenuous exercise for at least 24-hours before the tests;
- Bring snacks and bottles of water/juice;
- Refrain from consuming any caffeine-based products throughout the day;
- Do not smoke cigarettes <1-hour prior to your test.

3.5. Power calculation and participant sample size

The European Medicines Agency Committee for Medicinal Products for Human Use (2009) principally recommends FEV_1 measured by spirometry, as the primary end-point for determining the effectiveness of interventions on lung function in CF clinical trials. FEV_1 is typically expressed in litres (FEV_1 L); however, to compare FEV_1 across age, gender and ethnicity, the Global Lung Initiative (GLI) all-age multi-ethnic reference equations (Quanjer et al., 2012b) were used to convert the raw FEV_1 in litres (L) data to z-scores and %pred. values. The z-score shows how many standard deviations the group is away from the mean, and accounts for the %pred. value, as well as between participant variability of measurements (Stanojevic et al., 2009). A standard deviation of ±2 z-scores is within a normal range.

FEV_1 z-score was the primary outcome measure for *Inspire-CF* and a power calculation to determine the minimum sample size of participants required was performed by a medical statistician based on published methods for determining sample size (Kirkwood and Sterne, 2012) i.e., difference between two means (0.7 z-score or 0.8 z-score) with a given power (80% or 90%), and significance level (p=0.05). Therefore, a sample size of 33 participants per group would provide 80% power at 5% significance, to detect a mean within group improvement of 0.7 in FEV_1 z-score over 24-months, and 90% power for a difference of 0.8 in FEV_1 z-score. To allow for 20% losses due to non-recruitment or subsequent dropout, this required a participant pool of 83 children with CF, and a recruitment success rate of 80%. The study was powered on between-group differences anticipated at 24-months.

The hypothesis was that there if there were no between-group differences in FEV_1 z-score at baseline, the 24-month individually supervised exercise programme would elicit an increase in FEV_1 z-score by 0.7 (80% power; p=0.05).

3.5.1. Justification of power

A FEV_1 z-score is the mathematical combination of the percentage predicted and between-participant variability, producing a single number that accounts for age and height related lung function variability that could be expected in a healthy population; with the lower limit of normal (LLN) lung function determined as -1.64 z-score (Stanojevic et al., 2010).

To explain the approximate relationship between FEV_1 z-score and FEV_1 %pred.: 1 z-score equates to approximately 15% in FEV_1 %pred.; 0.7 z-score equates to approximately 10.5% in FEV_1 %pred.; 0.5 z-score equates to approximately 7.5% in FEV_1 %pred.; and 0.2 z-score equates to approximately 3% in FEV_1 %pred. (Quanjer et al., 2012).

Annual rates of decline of between 1% and 4% in FEV_1 have previously been anticipated in children (Merkus et al., 2002, Schneiderman-Walker et al., 2005, Konstan et al., 2007, Vandenbranden et al., 2012, Waters et al., 2012). However, diminished rates of annual decline of between 0.85% and 1.55% in FEV_1 have been reported in children (Schneiderman et al., 2014, Cogen et al., 2015) and in young adults (Que et al., 2006) as a result of earlier diagnosis, and better drug and therapeutic interventions.

Two CF interventional studies that have used FEV_1 to detect a treatment response to either hypertonic saline or recombinant deoxyribonuclease, also known as DNase, in paediatric patients have reported improvements of between 7±14% and 15%±16% in FEV_1 (Eng et al., 1996, Ballmann and von der Hardt, 2002).

Using these interventional studies as reference points and given the wide range of disease severity in the GOSH CF cohort, the research team aimed for the exercise intervention to improve FEV_1 by 10% in the exercise group over the course of the 24-month trial, which equates to approximately 0.7 z-score.

3.5.2. Allocation to groups and randomisation strategy

It was not possible for the clinical research team or participants to guess which group they were allocated to by randomisation. Group allocation was not openly shared with clinicians in the CF Unit; however, this may have become apparent over the course of the research as children attended routine clinic appointments. Lung function and exercise tests were conducted according to standardised, quality-controlled protocols. Therefore, it is unlikely that the respiratory physiologists (lung function team) and cardiac physiologists and technicians (exercise laboratory team) would be influenced by group allocation.

The clinical research team knew all eligible participants; therefore, to minimise selection bias, allocation concealment was carried out by an independent statistician. Randomisation by minimisation was performed using the customised software package, *SiMin* (Wade et al., 2006). This randomisation strategy was designed to avoid a large imbalance in the numbers of participants who consented to participate in *Inspire-CF*, and to ensure an even distribution of potential confounders, which were accounted for in analysis.

3.5.3. Minimisation factors

- Age (6–8; 9–11; and 12-15 years);
- Gender (male or female);
- Disease severity based on FEV_1 %pred.
    - Mild to moderate CF lung disease: FEV_1 %pred. ≥70%;
    - Moderate to severe: FEV_1 %pred. 40% to <70%;
- Area lived in (either London; Herefordshire/Bedfordshire; Essex); and
- If the child had signed-up for a Nuffield Health gym membership or not (described in **Chapter 4, Subheading 4.3, pg. 104**).

3.6. Outcome measures, equipment, and test procedures

This section describes the outcome measures, equipment and test procedures used to measure lung function, exercise, and quality of life outcomes. Each of the result chapters will provide further detail on primary and secondary outcome measures and the variables recorded and analysed.

3.6.1. Age

Age was calculated to the nearest decimal point (0.1) of a year.

Equation 3-1: Decimal age = (date of assessment - date of birth)/365

3.6.2. Height

Height was calculated to the nearest 0.1 cm without shoes on, using a calibrated stadiometer (Harpenden Stadiometer, Holtain Ltd, Dyfed, UK), and in a method recommended by the Child Growth Foundation (Martin et al., 2007). Children removed any caps or hair ornaments, and stood with their feet flat on the floor, with their head, shoulders, buttocks, and calves pressed against the back board of the stadiometer. The child breathed in and then relaxed, maintaining an upright position, with height then recorded to the nearest 0.1 cm.

3.6.3. Weight

Weight was measured wearing light clothing and no footwear on, to the nearest 0.1 kg, on calibrated weighing scales (Marsden MBF-6010 Body Composition Scale, Rotherham, UK).

3.6.4. Body mass index

BMI was calculated using the following equation.

Equation 3-2: BMI = weight (kg) / height (m^2)

3.6.5. Spirometry

Spirometry is a non-invasive, diagnostic outcome measure that requires a person to perform maximal inspiratory and expiratory manoeuvres, from which airway function and limitations are calculated. The test is used to determine the volume of air inhaled and exhaled as a function of time, with FEV_1 and FVC the two most important outcomes measured (Miller et al., 2005).

Spirometry was performed according to GOSH laboratory protocols, which are based on the American Thoracic Society and European Respiratory Society standards (Miller et al., 2005). The tests were carried out by highly specialised paediatric respiratory physiologists and were performed by children at assessment points; clinic and annual reviews; during admissions; and when ordered by the CF medical team. Quality of all spirometry tests were checked and verified by a highly specialised senior paediatric respiratory physiologist.

Forced expiratory manoeuvres were measured using a Jaeger Master spirometer (Erich Jaeger AG, Wurzburg, Germany) in a seated, upright position with feet flat on the floor. The participant wore a nose-clip and breathed through a circuit comprised of pneumotachograph; filter; elbow; and rigid mouthpiece. Participants were asked to ensure a tight seal round the mouthpiece throughout the test procedure.

Initially, the participant breathed normally through the mouthpiece to become accustomed to the apparatus, and to attain a stable breathing pattern. At end-expiration, the participant was requested to take a maximal inspiratory breath to total lung capacity, then make a maximal expiratory effort, blowing as hard and as fully as possible, until no further breath could be exhaled. Once fully expired, the participant returned to a normal breathing pattern, removed the mouthpiece, and then rested.

A minimum of three reproducible, maximal forced expiratory manoeuvres were performed, allowing adequate time to recover before each attempt. After each attempt, the pneumotachograph was re-

zeroed. The respiratory physiologist monitored the participant to ensure that the mouthpiece was not blocked by tongue or teeth, and that there were no leaks from round the outside of the mouthpiece.

The shape of volume/time and flow/volume curves were assessed for technical acceptability, that included: (1) a rapid rise at start of the manoeuvre until peak inspiratory flow was reached; (2) time to peak expiratory flow was <300 ms.; back extrapolation volume was >5% of FVC; or 0.150 L, or, whichever was greater; (3) the curves showed a relatively smooth, continuous change in flow or volume until residual volume was reached; (4) the shape were reproducible on superimposed curves; and (5) there were no indicators of early inspiration and plateau on the volume-time curve. The results were taken as the greatest values from three technically acceptable tests.

All raw spirometry measurements of FEV_1, FVC and FEF_{25-75} were converted to z-scores and percentage of predicted, using the Global Lung Initiative reference equations (Quanjer et al., 2012b), to allow for comparison across age, gender, and ethnicity.

3.6.6. Multiple breath inert gas washout test

MBW measures the functional residual capacity (FRC) and efficiency with which an inhaled inert gas mixes with the lungs. The test determines non-uniformity of ventilation distribution across the lung, which is referred to as ventilation inhomogeneity (Gustafsson et al., 2003) and is expressed as the Lung Clearance Index (LCI). MBW was performed by highly specialist paediatric respiratory physiologists and using GOSH lung function unit laboratory protocols, which are based on published standards (Gustafsson et al., 2003, Aurora et al., 2004, Aurora et al., 2005b, Robinson et al., 2009b) to determine LCI scores; the test is typically performed once-yearly, at GOSH CF annual review clinics. The GOSH CF Unit agreed that MBW measurements completed by *Inspire-CF* participants would inform the annual review.

Normal ranges for LCI are age and height dependent (Lum et al., 2013) and also variable based on equipment and inert gas used (Subbarao et al., 2015), but broadly considered to be 5.49 to 7.81. Upper limits of normal for individuals aged >5-years are between ranges of 7.63 to 7.81. A higher

value is suggestive of more severe peripheral airway disease (Lum et al., 2013). It is important that clinicians are aware of their local centre guidelines for adopted normal ranges for LCI.

Prior to each test session, the equipment was calibrated. Participants were assessed in an upright, seated position, and watched a television programme of their choice to distract them from the test, and children were encouraged to maintain their normal breathing pattern. The respiratory physiologist monitored their breathing pattern throughout the test, such that if tidal volume dropped below 8 ml·kg^{-1} or increased above 15 ml·kg^{-1} of body weight, the participant was asked to either increase or decrease their V_T accordingly.

All participants wore a nose-clip and breathed through a Fleish No. 1 pneumotachometer attached to a mouthpiece. The pneumotachometer was connected to a differential pressure transducer (Validyne, Model MP 45-14-871, Validyne Corp, California, USA), and the flow signal demodulated and amplified (Validyne MC1-10, Validyne Corp, California, USA). A short connector linked the mouthpiece and pneumotachometer, into which a sampling tube from a respiratory mass spectrometer (AMIS 2000, Innovision A/S, Odense, Denmark) was attached. The external dead space for the mouthpiece was measured as 15 ml.

The MBW consisted of two phases: wash-in and wash-out.

1. During the wash-in phase, the participant inhaled a dry gas mixture containing 4% sulphur hexafluoride (SF_6); 4% helium (He); 21% O_2; and balanced nitrogen (N_2). A bias flow of the gas was applied at the external opening of the pneumotachometer using a T-piece, and at a level greater than the maximum inspiratory flow produced by the participant. The wash-in phase continued until inspiratory and expiratory SF_6 concentrations were stable and equal. The bias flow was stopped at this point by the respiratory physiologist, by disconnecting the T-piece, and the wash-out phase began.

2. The wash-out phase continued until the end tidal SF_6 concentration was <0.1% (1/40th) of the starting concentration. Evidence for gas leakage was continuously monitored; which

was identified by any sudden drop in tracer gas concentration, or failure of the tracer gas to equilibrate during the wash-in phase. All signals were digitally recorded at 100 Hertz (Hz) by a computer connected through a 16-channel AD conversion board (DAS-1602, Keithley Metrobyte, Taunton, MA, USA).

LCI and FRC were calculated from an average of three technically acceptable washouts as determined by the highly specialist paediatric respiratory physiologists.

FRC was determined from the cumulative volume of exhaled SF6 marker gas, divided by the difference in end tidal SF6 concentration at the start (Cet_{start}) of the wash-out phase, and at the completion of wash-out (Cet_{end}).

Equation 3-3: FRC = net volume of inert gas exhaled / (Cet_{start} – Cet_{end})

To calculate the number of lung volume turnovers at each breath during the wash-out phase, the cumulative expired volume at that breath was divided by the FRC. The cumulative expired volume was corrected for the external dead space (15 ml) in each breath.

The LCI was calculated as the total number of lung volume turnovers (cumulative expired volume divided by FRC) required to lower the end tidal SF_6 concentration to <0.1% (1/40th) of the starting concentration.

Equation 3-4: LCI = Cumulative Exhaled Volume (L) / FRC (L)

3.6.7. 10 metre incremental shuttle walk test

The 10 metre incremental walk test was first validated in adult patients with chronic obstructive pulmonary disease (Singh et al., 1992). The simple, non-invasive, painless, incremental field-based exercise test has since been modified to include additional intensity level increments, and is commonly known as the 10m-MSWT, and has been validated to measure functional aerobic capacity in children with CF (Selvadurai et al., 2003).

The test is carried out over a 10 metre circuit and participants follow the cues of an audio recording. The recently validated 25-level version of the test was performed (Elkins et al., 2009), with results recorded on an assessment (**Appendix F**). The test was completed on a flat, non-slippery, pre-marked course. Participants were fitted with a portable SpO2 monitor and soft sensor finger probe (Nonin PalmSAT Model 2500 Digital Pulse Oximeter).

Prior to the test session, participants sat for a 3-minute rest period, during which they listened to the explanation of the test procedure on the pre-recorded audio track.

The standardised procedure was: “Walk at a steady pace aiming to turn around at each end when you hear the signal. You should continue to walk or run until you feel that you are unable to maintain the required speed without becoming unduly breathless”.

After the rest period, children walked to either end of the 10 meters course to position themselves to start. There is a triple bleep to start the test. Thereafter the audio-track emits a single bleep at regularly spaced intervals. The participant aimed to be at the opposite end of the 10 metre course by the time the next bleep sounded.

After every minute, the speed of walking was increased by a small increment, such that the participant walked progressively faster; the change in incremental speed was indicated by a triple bleep.

The first speed of walking was referred to as Level 1, the second as Level 2, and so on. Each level lasted for 1-minute and the audio-recording continued for up to a maximum of 25-levels. Each level contained a pre-set number of shuttles (each of 10 meters in length), the number of which is dictated by the speed of that level. The clinical researcher initially walked alongside the participant from the start of Level 1, until the participant had established the correct adjustments to incremental changes in speed (typically by end of Level 2).

The endpoint of the test was determined by the *participant* when:

- The participant became too breathless to maintain the required speed.

The endpoint of the test was determined by the *clinical researcher* when:

- SpO_2 dropped ≥5% below resting measurements;
- Undue signs of distress including severe wheezing or chest pain;
- Failure of the participant to complete the shuttle in the time allowed i.e., if the individual was more than 0.5 meters away from the cone. If the patient was less than 0.5 meters away from the cones when the bleep sounded, another 10 meters length was permitted to give the patient the opportunity to recover the 'lost' distance. If he/she was unable to do this, the test was discontinued, and the last completed shuttle was recorded.

3.6.8. Cardiopulmonary exercise test

The validated Godfrey cycle ergometer protocol (Godfrey and Mearns, 1971) was performed, which was a continuous incremental step cycle test to volitional exhaustion; and was monitored using published standards for exercise testing in children with lung disease (Roca et al., 1997, American Thoracic Society and American College of Chest Physicians., 2003). The protocol was recommended by the European Cystic Fibrosis Exercise Working Group (Hebestreit et al., 2015) to assess aerobic capacity in CF, and is a non-invasive, painless and objective method to monitor for cardiac, pulmonary and metabolic limitations to exercise. As this was the first time that CPET would be performed by children enrolled in *Inspire-CF*, the research team carefully explained all the test procedures in advance, including the requirement for electrocardiogram (ECG) monitoring and the wearing of a facemask. Results informed an individualised exercise prescription that has been described in **Chapter 4, Subheading 4.6.1, pg. 106.**

Prior to each test, participants attended a 30-minute familiarisation session. This included an introduction and explanation of all equipment and test procedures, with a focus on face-mask size and fit; ergometer cycle size; cadence; and ECG monitoring. To overcome some of the participants concerns at having to wear a facemask, during the pre-test familiarisation sessions, children were able to fit the mask and take-off and re-apply as often as they felt necessary, and they were able to self-apply the ECG electrodes. Children were able to take the facemasks home to continue to desensitise and prepare themselves for testing. The team also showed a video-clip of one of the *Frequent Flyer Programme* participants undertaking CPET, particularly for the benefit of younger participants, so that any questions or concerns could be addressed. At the assessment point, familiarisation with cycle-equipment, setup and testing of each participant was limited to 60-minutes.

Height recorded prior to lung function tests determined the appropriate step protocol, adjusted to the height of the participant:

- Height <120 cm = 10 W;
- Height 120-150 cm = 15 W;
- Height >150 cm = 20 W.

Adjustments were made to the cycle ergometer seat height, handlebar height and pedal cranks. Participants with a height <132 cm were tested on a Corival Paediatric (Lode B.V., Groningen, Netherlands) cycle ergometer, and participants taller than 132 cm were tested on an Excalibur Sport (Lode B.V., Groningen, The Netherlands) cycle ergometer.

All equipment was calibrated and maintained according to manufacturer guidelines, and GOSH infection control protocols. Participants wore an adjustable neoprene face mask into which a silicone mouth-coupler was fitted. A preVent™ pneumotachometer (Medical Graphics UK Ltd, Gloucester, England) was then inserted into the mouth-coupler. Twelve lead ECG were fitted to the chest, and then a SpO_2 probe (Nonin Medical B.V. Europe, Amsterdam, The Netherlands) were fitted to the forehead. The participant was then positioned on the seat and feet strapped to the pedals.

Participants sat rested for 3-minutes, then started to cycle at a cadence of between 60-70 revolutions per min ($rev \cdot min^{-1}$) which was maintained throughout the test. After 3-minutes of unloaded cycling, work rate was incrementally increased every minute (10 W, 15 W or 20 W), in line with the adjusted height-based protocol. Respiratory gas exchange analysis (Medgraphics, St. Paul, Minnesota); ECG; SpO_2; blood pressure; and OMNI scale of perceived exertion (Robertson et al., 2002) were continuously monitored.

Participants were verbally encouraged throughout the tests to make a maximal effort as based on the Hebestreit et al. (2015) protocol. A test was considered maximal when the participant achieved a plateau of VO_2 despite an increase in work rate, defined as an increase in VO_2 during the final completed stage of an incremental exercise test of <2 ml·kg·min^{-1} for a 5-10% increase in exercise intensity (Sheehan et al., 1987). However, as a levelling-off of VO_2 is not typically demonstrated in children (Rowland, 1993), the test was also considered maximal if at least one of the following secondary criteria were met:

- VO_{2peak} %pred. and/or W_{peak} %pred. were achieved (American Thoracic Society and American College of Chest Physicians., 2003), and based on pre-test calculations of these outcomes using published normal reference equations (Bongers et al., 2014a);
- a HR of 180 beats·min^{-1} (Gulmans et al., 1997, Klijn et al., 2003) or 95% age-predicted HR_{max} (Stevens et al., 2009, Stevens et al., 2011);
- RER ≥1.03 (Rowland, 1996) were achieved;
- or minute ventilation (V_E) approached or exceeded maximum voluntary ventilation (American Thoracic Society and American College of Chest Physicians., 2003).

The test was stopped if there was:

- A severe drop in SpO_2 <80% when accompanied by signs and symptoms of severe hypoxemia or any other signs of respiratory distress;
- Systolic blood pressure >250 mmHg;
- Decrease in systolic blood pressure >20 mmHg or increase in diastolic blood pressure >120 mmHg;
- Loss of coordination;
- Complex cardiac ectopy; or, second- or third-degree heart block;
- Volitional exhaustion defined as a drop in cadence of ≥10 rev·min^{-1} for 5 consecutive seconds;
- Participant choice.

On completion of the test, the participant cycled for 3-minutes of unloaded recovery at a cadence of 30-40 rev·min^{-1}, followed by 3-minutes of rest whilst sitting in a chair, or until HR had returned to near resting HR. Blood pressure (BP) measurements were recorded every 3-minutes throughout the test, and during active recovery.

3.6.9. Rationale for choice of exercise tests

The decision to include a field-based and a laboratory-based exercise test was based on children's feedback from the *Frequent Flyer Programme*, where the group suggested that the incremental shuttle walk/run concept was more familiar and meaningful to them, as the 20m version of the Progressive Aerobic Cardiovascular Endurance Run test (Leger et al., 1988), was conducted annually during school physical education lessons. In addition, some of the participants in the *Frequent Flyer Programme* had refused participation in a CPET primarily due to the mask being claustrophobic, despite desensitisation strategies. Children with CF did not routinely perform CPET at GOSH, therefore the decision was made to include a functional exercise test and a maximal exercise test.

Cycle ergometer CPET was performed in the cardiac unit exercise laboratory with assistance from highly specialised cardiac physiologists, and advisory support from a consultant cardiologist. The choice for use of the Godfrey cycle protocol (Godfrey and Mearns, 1971) was in keeping with published guidance on the gold-standard maximal exercise test in CF (Hebestreit et al., 2015), and as the GOSH exercise laboratory already used a modified version of the protocol, this meant implementation of the original version of the test for the study could be accommodated.

However, the laboratory was a very busy clinical unit within GOSH, and its use required extensive planning and coordination to ensure the study protocol could be facilitated and run-on time, without affecting the demands for cardiac patient testing. The research team typically booked sessions in the early morning, lunchbreak, and late afternoons as these were the least busy laboratory times, but also suited parents and carer schedules for bring children to GOSH for testing.

Children randomised to the exercise group would be undertaking an individualised exercise training programme, therefore the research team determined that the 10m-MSWT (Selvadurai et al., 2003) provided sufficient opportunity to monitor HR, SpO_2 and rating of perceived exhaustion (RPE), to enable safe prescription of exercise in the event that CPET was refused. Both cycle ergometer CPET and the 10m-MSWT are considered maximal exercise tests, therefore comparison of HR outcomes between tests would be possible, and a safe target heart rate training range could be determined.

The recently validated 25 level version (Elkins et al., 2009) of the 10m-MSWT was selected, as the shorter 15-level version had been completed by 2 of the boys previously enrolled in the *Frequent Flyer Programme*. The 25-level version was considered more appropriate as it was possible that children enrolled in *Inspire-CF* would achieve higher levels of intensity of exercise over the 24-month intervention period.

3.6.10. Children's OMNI scale of perceived exertion

The children's OMNI scale of perceived exertion (Robertson et al., 2002, Utter et al., 2002, Robertson et al., 2005) was validated in CF (Higgins et al., 2013); and also for mixed gender and ethnicity (Robertson et al., 2000).The tool and was used to determine RPE during both exercise tests, and during the exercise training sessions.

A cycle format (**Figure 3-2**) was used during CPET, and a walk/run format (**Figure 3-3**) during the 10m-MSWT; either format was used during exercise training sessions.

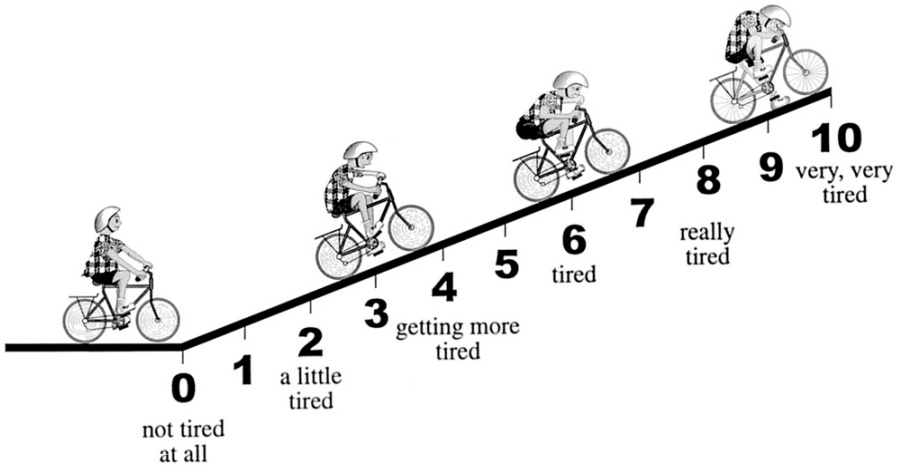

Figure 3-2: OMNI scale of perceived exertion (cycle format)

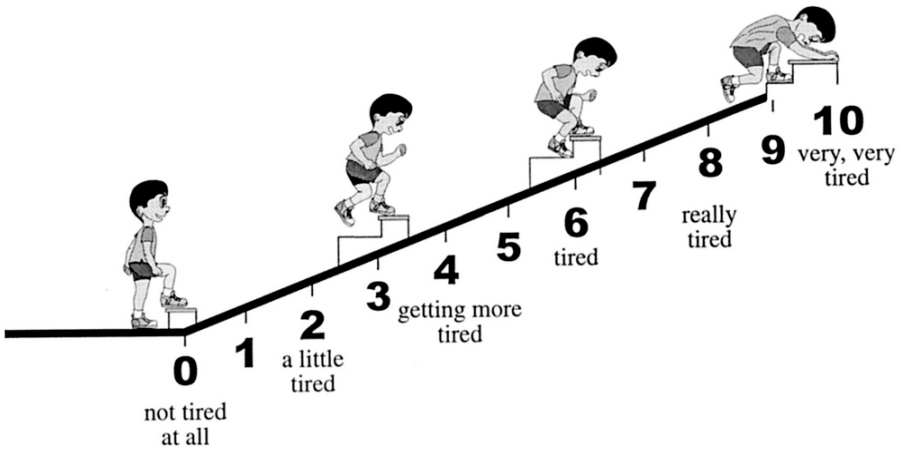

Figure 3-3: OMNI scale of perceived exertion (walk/run format)

Reprinted from: Robertson, R.J. et al. (2000) Children's OMNI scale of perceived exertion: mixed gender and race validation. Med Sci Sports Exerc., 32: 452– 458. Copyright © 2000 Lippincott, Williams, and Wilkins.

The following standardised instructions were given to the participant depending on version:

Please use the numbers on this scale to tell me how your body feels when you are cycling/walking/running:

- Please look at the person at the bottom of the hill who has just started to cycle/walk/run. If you feel like this person when you are cycling/walking/running, you will not be feeling tired at all, and your rating will be zero (0);
- Now look at the person who is barely able to cycle/walk/run at the top. If you feel like this person when you are cycling/walking/running you will feel very, very tired and your rating should be the number 10;
- If you feel somewhere between not tired at all and very, very tired give a number between 0 and 10;
- I will ask you to point to the number that tells me how your whole body feels during the test;
- There are no right or wrong answers.
- Use both the pictures and the words to help you select a number.
- Use any of the numbers to tell how you feel when you are cycling/walking/running;
- How do you feel now? Please point to a number on the scale.

3.6.11. Cystic Fibrosis Questionnaire, UK version

Quality of life was measured by the disease specific CFQ-R (Bryon et al., 2009). The CFQ-R comprises of 3 developmentally appropriate questionnaires, each designed to encompass a range of domains related to quality of life i.e., physical symptoms; role functioning (such as ability to attend school or go to work); energy/fatigue; psychological; and emotional functioning and social functioning; and domains that are CF specific i.e., body image; eating disturbances; social marginalisation; and treatment burden. Nine of the domains are common to all versions as shown in Table 1.

The 3 age-appropriate versions of the CFQ-R are:

1. CFQ-R Child version for those aged 6-13 years of age (**Appendix G**), which was provided in two age-dependent formats:
    a. An interviewer administered version for children aged 6-11 years; or
    b. A self-administered, self-reported version for children aged 12 or 13 years.
2. CFQ-R Teen/Adult version that was self-administered, and self-reported for those aged 14 years and older (**Appendix H**);
3. CFQ-R Parent/Carer version that was self-administered and self-reported and was used in conjunction with the child version (**Appendix I**).

During *Inspire-CF*, all parents filled in this questionnaire irrespective of the age of the child, to determine parent vs. child differences in perceptions of quality of life.

The CFQ-R was completed after lung function and exercise tests. For all participants, a quiet place was provided to complete the questionnaire on their own, so that answers obtained were the participants' responses, and not a parent's opinion. Similarly, parents completed the questionnaire on their own, and without input from the child. Participants and parents were asked to complete all questions and reassured that there were no right or wrong answers, and that they should respond to the questions based on their health status in previous two-week period.

Table 3-1: Domains measured by the Cystic Fibrosis Questionnaire

Domains	Child Version	Teen / Adult Version	Parent / Carer Version
Physical Functioning	✓	✓	✓
Energy, Well-being	✓	✓	✓
Emotional State	✓	✓	✓
Eating Disturbances	✓	✓	✓
Body Image	✓	✓	✓
Treatment Constraints (Burden)	✓	✓	✓
Social Limitations	✓	✓	
Role Limitations / School Performance		✓	✓
Embarrassment		✓	
Respiratory Symptoms	✓	✓	✓
Digestive Symptoms	✓	✓	✓
Weight		✓	✓
Health Perceptions		✓	✓

For children aged 6-11 years, the clinical researcher read the questions to the child, whilst those aged 12 years and older completed the questionnaire independently. The clinical researcher reviewed the completed questionnaire to ensure that all questions had been answered.

The minimum or maximum score for each domain depends on the number of items in the domain; however, the score is standardised for each domain, in a scale that ranges from 0 to 100. The interpretation of the CFQ-R scores is such that, the maximum score always corresponds to the highest quality of life, and the minimum score always corresponds to the lowest quality of life. Independent hierarchical item-analysis of the individual domains scores are appropriate and valid, and should be pre-defined in the methodology section of a study e.g. physical, respiratory, treatment burden and body image could be selectively reported in exercise studies (Quittner et al., 2005); with the minimal clinically important difference between serially repeated questionnaires considered to be a difference of 5 (Quittner et al., 2009).

It is considered appropriate to select the domain/s of interest that may be more related to a study, but results of all domains should be reported (Abbott and Hart, 2005, Quittner et al., 2005, Abbott et al., 2011). Physical functioning, respiratory symptoms and treatment burden were identified as the primary domains of interest for *Inspire-CF*, with the other domains considered secondary. Physical functioning was selected as the intervention was exercise; the respiratory symptom domain reflected change in lung function (FEV_1 z-score was primary endpoint) and associated respiratory symptoms; and treatment burden was identified as children in the intervention group would undertake weekly exercise training under supervision, and it was theorised that this may place additional burden on children's already intensive home medical regimen.

3.7. Infection control and patient safety during assessments

As is standard clinical practice for all individuals with CF, all participants were tested in isolation. All single-use equipment was disposed of immediately following testing. For the entire research period, any equipment considered re-usable (i.e., neoprene facemasks), were laundered, sterilised, labelled with the participant's unique identification code, and stored according to hospital storage protocols; and then disposed of on completion of the research. All test sessions with participants colonised with *Methicillin-resistant Staphylococcus aureus*, *Burkholderia cepacia* or *Nontuberculous mycobacterium* were followed with a deep clean of the laboratory, in accordance with GOSH infection control protocols; and all consumables were disposed of immediately. The CF and cardiac medical teams were aware of test session times and could be contacted if any adverse symptoms or arrhythmias were detected. Crash-carts and defibrillators were in situ.

3.8. Infection control and patient safety during exercise training sessions

Personal trainers may have had to manage the training times of children who were colonised with *Methicillin-resistant Staphylococcus aureus*, *Burkholderia cepacia* or *Nontuberculous mycobacteria* in accordance with GOSH infection control protocols, such that the children were trained in the last session of the day to mitigate the risk of these pathogens being passed onto other children enrolled in the study. Care was taken when accessing or using equipment or swimming pools during training sessions if a child had a Portacath, gastrostomy tube or IV lines in situ. Previous or current

musculoskeletal injuries were monitored under treatment guidance from the GOSH musculoskeletal physiotherapy team, when required.

3.9. Trial monitoring

3.9.1. Confidentiality

Participants were assigned a unique identification code after informed consent was obtained, and this was used for all computerised data entries and analysis. All information remained confidential and was stored securely.

3.9.2. Data collection, access, transfer & storage

All data were de-identified prior to data analysis, and these data were only available to the clinical research team and statistician. Members of the CF Unit were consulted where appropriate. All data were transferred, accessed, and stored in compliance with the UK Data Protection Act 1998. All non-personally identifiable data will be retained for 15-years as per standardised research governance guidelines.

3.9.3. Research governance

A Data and Safety Monitoring Committee was established for the study. This committee included 3 independent, highly experienced researchers, and ensured that baseline and post-intervention data were appropriately collected, stored, managed, monitored, and audited according to best practice. A decision to stop the trial could be undertaken by the Data and Safety Monitoring Committee. The committee met at 6- and 12-month assessments points and determined that protocols were being maintained, no adverse events had been detected, and that the trial could continue.

3.9.4. Data integrity

The entire digital versions of the spirometry database were checked and cleaned of duplicates. Spirometry measurements that were repeated on the same day were also removed, as these were related to bronchodilator reversibility tests. Data that corresponded with times when children were on oral or intravenous antibiotic for exacerbation of symptoms were identified and categorised. Oral and intravenous antibiotics have been shown to improve lung function (Que et al., 2006), therefore

only data collected during periods of stable health status were incorporated in the analysis. The data points from baseline, 6-, 12-, and 24-month were included for analysis, and crosschecked against admission dates. All data that were transferred from paper formats to digital formats were manually inputted and multi-cross checked to minimise the risk of imputation errors.

3.10. Statistical analysis

3.10.1. Databases

All raw spirometry data were digitally retrieved from the Jaeger software databases (Erich Jaeger AG, Wurzburg, Germany) and exported into Microsoft Excel® (Redmond, Washington, USA). Raw spirometry measurements of FEV_1, FVC and FEF_{25-75} were converted to z-scores and %pred. values, using GLI 2012 Desktop Software for Large Data Sets (Quanjer et al., 2013) to allow for comparison across age, gender, and ethnicity (**Table 3-2**). LCI and FRC were calculated, and data were manually entered into Microsoft Excel® spreadsheets (Redmond, Washington, USA).

Table 3-2: Global Lung Initiative ethnicity classifications

Group	Country/region
Caucasian	Europe, Israel, Australia, USA, Canada, Mexican Americans, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, Tunisia
Black	African American
South East Asian	Thailand, Taiwan and China (including Hong Kong) south of the Huaihe River and Qinling Mountains
North East Asian	Korea and China north of the Huaihe River and Qinling Mountains

Height, weight and BMI were converted to z-scores using a Microsoft Excel® Add-in, LMSGrowth-277 (Pan and Cole, 2011). The LMS method normalised height and weight data, that may be skewed in the general distribution of measurements. The CFQ-R questionnaires were digitally scored using a Microsoft Excel® calculation database (Quittner et al., 2002). All data were transferred from the Microsoft Excel® databases for analysis in IBM® SPSS® Statistics 24 (Chicago, IL, USA). Numeric data were expressed as mean, SD, or median (IQR) as appropriate, and measurements are presented with 95%CI. A p-value ≤0.05 was established for statistical significance.

3.10.2. Normality distribution tests

The Kolmogorov-Smirnov Test and the Shapiro-Wilk Test (p>0.05) were performed to assess for normal distribution of data.

3.10.3. Independent t-tests

Independent t-tests determined between-group differences at each assessment point, and were considered robust (Lumley et al., 2002, Rasch and Guiard, 2004) to detect the time-point specific between-group differences, in data collected at each of the 4 assessment points.

For independent t-tests performed at each assessment point, the mean difference was calculated as exercise group (coded 1) minus control group (coded 0).

3.10.4. Simple linear regression

Simple linear regression was used to determine the relationship between the continuous dependent variables (e.g., FEV_1, W_{peak}, VO_{2peak}) and the minimisation factors of gender, disease severity, area lived in and Nuffield membership status. The change in the continuous dependent variable since baseline was calculated as assessment point minus baseline data (e.g., 24-month minus baseline; 12-month minus baseline).

The following assumptions related to the analysis of the data were met:

- There was a linear relationship between the variables;
- There was homoscedasticity of data, such that the residual plots from the fitted model were randomly dispersed around the horizonal axis.

3.10.5. Model-coefficients (B)

The letter 'B' signifies the model-coefficient and represents the slope of the line between the predictor variable and the dependent variable. The model coefficients give the average change in the outcome for a unit of change in that predictor i.e. If the model-coefficient were positive, the interpretation was that for every 1-unit increase in the predictor variable, the outcome variable

increased by the value of the model-coefficient, however if the model-coefficient were negative, the interpretation was that for every 1-unit decrease in the predictor variable, the outcome variable decreased by the value of the model-coefficient.

3.10.6. Multilevel mixed model analysis

The main interest of the study was to consider the longitudinal effects of the weekly-supervised exercise training sessions on the primary outcome measure of FEV_1 z-score. To model the trajectories and account for the repeated measurements required a multilevel mixed effects model with child as a random effect. Interest lay in the interaction between time (i.e., number of days in the study), number of weeks trained and group membership. The anticipation was that there would be no differences in the groups at baseline, but if the exercise programme was effective, then there would be an interaction between time, exercise, and group (i.e., the differences between the exercise group and control group would increase with time and as more exercise sessions were completed). The model was *a priori* adjusted for minimisation factors.

3.10.7. Odds Ratio and Relative Risk

Odds ratios were used to determine the association between exercise and any potential change in exercise capacity (i.e., that it increased or decreased). The odds ratio represented the odds (likelihood) that a change in exercise capacity would occur, given the exercise groups exposure to exercise, compared to the odds of that change happening if they had not undertaken exercise.

The relative risk or risk ratio, was used to determine the ratio of the probability of the exercise group being admitted to hospital for an exacerbation of respiratory symptoms, compared to the probability of the control group being admitted to hospital for the same reason.

4.

CHAPTER 4. THE DESIGN OF THE INSPIRE-CF EXERCISE PROGRAMME

4.1. Aims and objectives

The aim of Chapter 4 is to describe the design and development of the *Inspire-CF* exercise prescription and exercise training programme.

The objectives were to explain the:

- Recruitment of a team of exercise professionals to implement the exercise programme;
- Development of a network of private and public sector fitness facilities, that offered free access to the centre for each child recruited to the exercise group;
- Design of the exercise prescription that would be documented at baseline, and then adapted after 6- and 12-month assessments;
- Design of the 3-phase exercise training programme;
- Design of the pre-exercise training health screening checklist that was used to assess for any change in health status that may affect the participants ability to exercise.

4.3. Personal training team

The full-time co-lead investigator, a Band 7 CF Specialist Physiotherapist, recruited 3 part-time (0.5 WTE) staff members to work on *Inspire-CF*: a Band 7 CF Specialist Physiotherapist, a Band 5 Physiotherapist and Research Assistant, and a Band 5 Sports and Exercise Scientist. For ease of reference for the children enrolled on the study, this core team of 4 were referred to as "personal trainers".

The lead personal trainer (co-lead investigator) provided a 5-day (x 5-hour/day) training programme that included: (1) CPET training in the laboratory with assistance from the cardiac technicians; (2) 10m-MSWT protocol training; (3) interpretation of exercise outcomes; (4) documentation of exercise prescriptions; (4) pre-exercise checklist documentation; (5) time spent in the gym going through each exercise and how to adapt, regress, or progress the exercise programme. All elements of the exercise programme were discussed in detail to ensure that children were treated equally, irrespective of group allocation.

An additional 6 independent and highly experienced personal trainers who worked for some of the network of fitness facilities volunteered to provide free personalised training sessions. This highly valued team would train participants who lived in geographical locations that were further than was reasonably expected for the research team to travel to on a weekly basis. These trainers underwent a 2-hour training session on CF, followed by a 1-hour pre-exercise checklist assessment and documentation session, and then 3-hours in the gym going through each exercise, to understand reasons for adaptations, regressions, or progressions of the exercise training programme.

Each of the 4-core personal trainers were assigned 8 –11 children who they trained each week, with 6 children assigned to the 6 independent personal trainers. Every 3-month the core personal trainers switched to work with another group of children for 1-week, to ensure there was consistency in application of exercise prescriptions and implementation of exercise training protocols. The independent personal trainers were linked to one of the 4 core personal trainers who would be available telephonically to discuss any concerns and/or arrange site visits.

4.4. Great Ormond Street Children's Hospital and Nuffield collaboration

All children enrolled in the *Frequent Flyer Programme* between January 2011 and April 2012 were able to access Nuffield Health, a UK national fitness provider and charity fitness facility, when they were admitted to hospital for routine IV-antibiotics or for exacerbations. The facility was within 5-minutes walking distance of GOSH. The arrangement meant that children could continue to exercise in a similar environment as during their weekly individualised exercise training sessions, and this arrangement was highly regarded by the Nuffield management team and the GOSH CF Unit.

In 2011, a mutually beneficial collaboration was formally established between GOSH and Nuffield Health national fitness centres. The collaborative arrangement was such that all children treated by the GOSH CF unit could avail of a free membership at their closest Nuffield centre. Children could take part in children's group classes, a weekly personal training session and any other exercise or physical activities offered by the centre. Families could also sign-up to a reduced cost membership. This meant that on completion of the *Frequent Flyer Programme*, all children admitted to the CF ward could continue to access and use the centre within walking distance of the hospital, under the supervision of the physiotherapy team or local personal trainers.

4.5. Network of private and public sector fitness facilities

The success of the *Frequent Flyer Programme* to provide weekly exercise training sessions at a centre local to the child, required access to a network of private and public health sector fitness facilities and schools – all of whom provides free access to the centres for the lead physiotherapist and child. In total, 12 facilities formed this network, and it was on the backbone of this network that the *Inspire-CF* network of fitness facilities was developed.

Free access and/or membership to a public or private sector health and fitness facility with a gym was negotiated for each participant in the *Inspire-CF* exercise group. In some cases, schools that had a fitness suite were also used. A network of 46 fitness facilities and schools provided access to fitness facilities within the London, Hertfordshire, Bedfordshire, and Essex counties. The arrangement was such that the participant and personal trainer could freely access all equipment

and facilities at the centre, at a pre-arranged session time each week, and for the 24-month duration of the study. Flexibility of these hours was arranged with the centre, based on each child's school mid-term breaks and holiday periods.

Most of the exercise sessions were scheduled either pre-school or after school, or at times that were convenient to the child's school if the fitness facility was used at school, and always arranged to fit into family schedules. Experience gained through the *Frequent Flyer Programme* suggested that some schools either lacked a physical education programme that provided an inclusive environment for children with CF to participate, and/or had limited extramural sporting clubs. In these cases, the personal trainers worked with the schools to schedule in an exercise training session during school hours. These arrangements were well received during the *Frequent Flyer Programme* by both parents and school staff, and often reduced the burden of care placed on both parties. For this reason, similar arrangements were made, where appropriate, for *Inspire-CF* participants. The trainers also coordinated with physical education teachers and sports club staff, where necessary, to encourage each child to take part in more intensive, daily physical activity to achieve targets outlined in the child's exercise prescription.

Some children in the exercise group may have availed of a Nuffield membership prior to enrolling in *Inspire-CF*, therefore this membership was accounted for in the randomisation by minimisation process (**Chapter 3, Subheading 3.52, pg. 79**). It should be noted that a new gym membership might have been negotiated with an alternative fitness facility, if that centre was more local to the child's home or school for the duration of *Inspire-CF*, than the Nuffield the child held a membership with.

4.6. Admission to hospital protocol for both groups

When a participant in either group was admitted to GOSH for any CF-related treatment, the child would receive the usual standard of specialised CF medical care and follow inpatient treatment pathways. Where possible, children in the exercise group, continued to receive a once per week, exercise training session that followed their individually prescribed exercise training programme. If their clinical status was considered unstable the session was delayed until medical clearance was

given to continue with exercise. When a child was admitted to a shared-care hospital for CF-related therapy, the trainer would co-ordinate with the clinicians at the shared-care hospital. If training sessions could be coordinated during the admission, then this was arranged, if not, then the exercise sessions continued after the admission.

4.7. Inspire-CF Exercise Programme

Appendix J includes all the resources created for exercise prescription and exercise training, and monitoring of health status prior to each session. Children randomised to the exercise group completed spirometry, CPET and 10m-MSWT and then a baseline exercise prescription was documented. The exercise prescription was reviewed and adapted at 6- and 12 months. At each training session the personal trainer completed a 6-point health screening questionnaire and recorded the components of exercise training completed, as well as the intensity of exercise achieved.

4.7.1. Inspire-CF Exercise Prescription

Children are not miniature adults therefore exercise training in children should account for anatomical and physiological differences (Plowman, 2001a, Plowman, 2001b, Faigenbaum et al., 2009, Faigenbaum and Myer, 2010a, Faigenbaum and Myer, 2010b). This statement would also be true in CF, therefore, the exercise prescription for *Inspire-CF* needed to reflect this. Exercise in CF should be fun, to keep children motivated to exercise and establish a routine of regular exercise (Rand and Prasad, 2012), and this may help with increasing adherence to exercise too (Sawicki et al., 2015).

The *Inspire-CF* exercise prescription included previously published CF parameters (Williams et al., 2010), but was constructed using the acronym: **FITT-CF-KIDZ**, which reflected the following principles: **F** – Frequency; **I** – Intensity; **T**- Time; **T** – Type; **CF** – Cystic Fibrosis; **K** – Kids (Children); **I** – Individualised; **D** – Dynamic; **Z** – Training zones that children needed to understand.

Frequency

- Each participant would receive 1 x weekly individualised training session at a fixed time each week at a local fitness facility;
- Each participant would be actively encouraged to undertake a minimum of 2-3 hours additional exercise or physical activity each week;
- Participants would be encouraged to actively participate in school physical education lessons and individual or group sports.

Intensity

- **Participants with a FEV_1 ≥55%:** Target heart rate training range of 70-85% of HR_{peak} during the aerobic/anaerobic component; **Participants with a baseline FEV_1 ≤55%:** Target heart rate training range of 60-80% of HR_{peak} during the aerobic/anaerobic component;
- High intensity interval training (**Chapter 4, Subheading 4.6.5.1, pg. 112**) would be performed for half of each of the exercise training sessions, therefore an upper limit of 5% higher than the target heart rate training range was documented.

Time

- **Participants with a FEV_1 ≥ 55%:** 45-60 minutes in duration. Comprised of 20-30 minutes aerobic/anaerobic training; 15-25 minutes of muscle strength and core-conditioning; 5-10 minutes stretching; **Participants with a baseline FEV_1 ≤ 55%:** 30-45 minutes in duration. Comprised of 15-25 minutes aerobic/anaerobic training; 10-20 minutes of muscle strength and core-conditioning; 5-10 minutes stretching.

Type

Children would undertake a wide range of exercise that would include:

- High intensity exercise training e.g., treadmill, stationary bike, X-trainer etc, trampolines, obstacle courses, games; Swimming where available;
- Strength training and stretching e.g., weights, resistance bands, body weight; Swiss ball, mat-work, balance boards.

Cystic Fibrosis

- All children enrolled in *Inspire-CF*, were diagnosed with CF and therefore the associated limitations of the disease should be accounted for, when training the children;
- Periods of time to allow for airway clearance may need to be included at regular intervals during the exercise session.

Kids

- Children are not miniature adults; therefore, it was important to consider growth parameter, muscle development, epiphyseal plates, fat, and physiological response to exercise.

Individualised

- Keep the exercise programme individualised to the child and aim to meet their exact needs and capabilities, and to include training that was specific to their preferred sports or physical activities.

Dynamic

- Make it fun, avoid regimentation, and offer a variety of activities that can be performed indoors and outdoors and in swimming pools.

Zones

- Children should exercise in and out of “comfort zones”;
- Teach children to use target heart rate ranges and breathlessness zones.

4.7.2. Exercise prescription adjusted for lung function status

The personal trainers could safely guide the child through an exercise training session and adaptations to training could be made in consultation with the lead personal trainer and based on the following pre-determined criteria.

4.7.2.1. Participants with a baseline FEV_1 ≥55% predicted

- **Frequency:** 1 x individualised exercise training session per week plus 3-4 hours additional exercise or physical activity including physical education sessions;
- **Intensity:** Heart rate training range of 70-85% of HR_{peak} during the aerobic/anaerobic component, with an upper limit of 90% HR_{peak};
- **Time:** 45-60 minutes in duration;
- **Type:** Comprised 20-30 minutes aerobic/anaerobic training; 20-30 minutes of muscle strength and core conditioning.

4.7.2.2. Participants with a baseline FEV_1 <55% predicted

- **Frequency:** 1 individualised exercise training session per week;
- **Intensity:** Heart rate training range of 60-80% of HR_{peak} during the aerobic/anaerobic component, with an upper limit of 85% HR_{peak};
- **Time:** 30-45 minutes in duration;
- **Type:** Comprised 15-25 minutes aerobic/anaerobic training; 15-25 minutes of muscle strength and core conditioning.

4.7.2.3. Exercise prescription after decrease in FEV_1 <55% predicted

If a participant with a baseline of FEV_1 >55% demonstrated an FEV_1 <55% during the intervention period, and the drop was ≥10% predicted, the trainer could:

- Continue to exercise the participant as prescribed if the participant was maintaining exercise tolerance; or
- If the participant struggled to maintain exercise tolerance, the trainer could adapt the aerobic/anaerobic component of the prescription, such that the participant maintained a heart rate training range of 60-70% of HR_{peak}, and/or
- The trainer could reduce the duration of the session or stop the session if the child could not continue.

4.7.2.4. Exercise prescription after an increase in FEV_1 ≥55%

If a participant with a baseline or 12-month measurement of FEV_1 ≤ 55% demonstrated an increase in FEV_1 ≥ 55% during the intervention period, the trainer could:

- Adapt the aerobic/anaerobic component of the prescription such that the participant maintained a heart rate training range of 70-85% of HRpeak; and/or
- The trainer could increase the duration of the session, to a maximum of 60 minutes.

4.7.3. Target heart rate training range

A target heart rate training range (THRR) was determined for personal training sessions with recommendations for additional exercise or physical activities. The rationale for using HR instead of VO_{2peak}, was that children would be able to understand change in HR and as the programme progressed, and children became more involved in determination of all components of their training session, they could use the THRR to monitor their own training level intensity. To determine THRR, HR_{peak} was recorded during CPET and the 10m-MSWT, and an age-predicted HR_{peak} based on published references (Bongers et al., 2014a) was documented. If a maximal effort CPET was performed (**Chapter 3, Subheading 3.6.8, pg. 87**), THRR was determined using the HR_{peak} recorded during the CPET. However, if the participant did not achieve a maximal effort, the HR_{peak} was cross matched to the HR_{peak} recorded during the 10m-MSWT, and the average of the ranges of both tests was used to determine the THRR.

4.7.4. Inspire-CF 6-point Pre-exercise Health Screening Checklist

The personal trainers were tasked with providing one supervised, individualised training session per week and to actively promote an additional 3-hours exercise or physical activity per week, but not if FEV_1 <55%. The trainers would not provide clinical assessments i.e., chest auscultation, lung function or any other assessment that may have been undertaken by the outreach physiotherapy team. However, as with the *Frequent Flyer Programme*, more regular contact with clinicians, meant that early changes in health status could be identified. This meant that oral antibiotics could potentially be prescribed earlier, or admissions to hospital brought forward if an exacerbation was identified or pushed back if health was being maintained. It was therefore important to design a pre-exercise questionnaire that all personal trainers, including the 6 independent personal trainers, could complete prior to the exercise session. The 6-point checklist questionnaire (**Appendix J**) used a cascading series of questions to assess for any changes in health status, that may be a contraindication to moderate to high intensity exercise. If a child's health status had deteriorated this triggered a referral to the CF Unit or CF outreach physiotherapist for follow-up. Any red flags (serious concerns) were reported immediately to the CF Unit and the exercise sessions did not continue, until the CF multidisciplinary team (MDT) had reviewed and escalated treatment for the child.

4.7.5. Inspire-CF 3-Phase Exercise Training Programme

Children randomised to the intervention group participated in a comprehensive, 3-phase exercise programme. As the child progressed through the study, and completed each of the assessment points, the exercise training programme was adapted.

- Phase 1: 6-month duration (Year 1);
- Phase 2: 6-month duration (Year 1);
- Phase 3: 12-month duration (Year 2).

Each phase included 2 primary components:

- High Intensity Interval Training;
- Muscle strength training.

4.7.5.1. High Intensity Interval Training

High intensity interval training (HIIT) consists of repeated short-burst bouts of high-intensity exercise interspersed with recovery periods (Buchheit and Laursen, 2013). HIIT was adopted as the aerobic component of the exercise training programme for *Inspire-CF*, as short-burst intervals of movement is similar to normal activity patterns in children, and also in individuals with chronic obstructive pulmonary disease (Butcher and Jones, 2006).

The HIIT method was used during the *Frequent Flyer Programme* (Ledger et al., 2013) and was well tolerated by children with advanced lung disease, with no adverse effects reported. The benefits of HIIT have not been widely studied in children with CF, but positive benefits to cardiovascular health, metabolic capacity, and aerobic performance have been shown in healthy children (Baquet et al., 2004, Gamelin et al., 2009). A single case-report of a 16-year-old female with CF who participated in HIIT whilst on IV-antibiotics demonstrated improved lung function and exercise capacity (Hulzebos et al., 2011).

Breathlessness is a common physiological limitation to exercise in CF (O' Neill et al., 1987), however in children with mild CF lung disease, breathlessness is uncommon as lung function is typically within normal ranges , and they do no demonstrate ventilatory limitations during sub-maximal (Parazzi et al., 2015) and maximal exercise (Bongers et al., 2014b). Nevertheless, the short-burst bouts in HIIT allow for breathing rate to recover to tolerable levels during the recovery periods, which may be of benefit to those with ventilation limitations (Keochkerian et al., 2005), and mimics physical activity patters in children. There are a wide range of HIIT methods with different durations of interval work-to-recovery periods, however research in health populations has shown that the optimal work-to-recovery ratio is 2:1 i.e., for every length of duration of intense work, there should be at least half that time to recover (Helgerud et al., 2007, Dunham and Harms, 2012, Laurent et al., 2014).

For *Inspire-CF* the aim was to design a HIIT session that ensured progressive intensity but that was adaptable for each child and could be completed on a treadmill, spinning-bike, stationary-bike, or cross-trainer. The maximum duration of workout was 30-minutes. The session incorporated a warm-up period (in addition to pre-exercise warm-up), intervals of work-to-recovery, and a cool-down period. HIIT was always performed prior to muscle strength training. In each single bout of HIIT that children performed, work-to-recovery ratios of 2:1 and 1:1 were adopted, where the final 1:1 component aimed to elicit maximal effort (i.e., 90% HR_{peak} in individuals with and FEV_1 ≥55% predicted or 85% HR_{peak} in in individuals with and FEV_1 <55% predicted) by the end of the training session.

In each single bout of HIIT, the personal trainer adapted the intensity of the session based on the participants HR achieved during exercise. Intensity was increased if HR was below the prescribed THRR or decreased if HR was above the THRR. Perceived exhaustion was monitored using the OMNI Scale, and adaptations were made if the:

- HR > 90% THRR (FEV_1 ≥ 55% predicted) or HR > 85% THRR (FEV_1 <55% predicted);
- Child became too breathless to maintain the required speed;
- Child stated an OMNI score of >9.
- SpO_2 dropped ≥5% below resting measurements;
- Undue signs of distress such as wheezing or chest pain.

4.7.5.2. Muscle-strength training exercise

Guidelines for strength training in CF are not available, but inclusion of strength exercises have been shown to be safe (Orenstein et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014). Guidelines from healthy children were used to define the parameters of strength training (Benson et al., 2008, Dahab and McCambridge, 2009, Faigenbaum et al., 2009, Faigenbaum and Myer, 2010b, Faigenbaum et al., 2012, Faigenbaum et al., 2013).

Muscle strength training maintenance, progression and regression was determined by the child's personal trainer, and was based on the following parameters:

- **Sets:** 3-4
- **Repetitions:** 8-20
- **Tempo: 2:1 or 3:1** (e.g., 2-3 seconds concentric contraction of muscle; 1-second eccentric contraction)
    - Extended eccentric contraction could be introduced after 6-months, and only once children understood the need for controlled movement; this was mainly achieved in children aged 10-years and over.
- **Weight:**
    - **Upper body** (e.g., biceps, triceps, and deltoids)
        - Starting point of up to a maximum of 10% of the child's body weight;
            - e.g., Child's weight = 30 kg (starting range of weights = 0.5-3 kg).
    - **Lower body and back** (e.g., quadriceps, hamstrings, latissimus dorsi)
        - Starting point of up to a maximum of 50% of the child's body weight;
            - e.g., Child's weight = 30 kg (starting range of weights = 1-15 kg).

4.8. Discussion

CF specialist physiotherapists based in the UK would typically look to the Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis (Cystic Fibrosis Trust, 2013) and the European Cystic Fibrosis Exercise Working Group Statement on Exercise Testing (Hebestreit et al., 2015) as the primary guidelines for implementing the three core components of exercise: (1) exercise testing, (2) exercise prescription and (3) exercise training, into clinical practice. The Cystic Fibrosis Trust (2013) physiotherapy guidelines on exercise testing state that all children aged 10 years and over should perform an exercise test at annual review, but children over the age of 5 years could start to be tested to familiarise them with exercise testing protocols. Regular participation in structured exercise, sport and physical activities should also be actively encouraged, irrespective of the severity of lung disease.

The protocols for exercise tests in children with CF have been documented, and the European Cystic Fibrosis Exercise Working Group's Statement on Exercise (Hebestreit et al., 2015) provided a list of the most important outcomes to be reported from CPET, and the most important outcomes to be reported from 10m-MSWT are also well defined (Singh et al., 1992, Selvadurai et al., 2003), therefore these guidelines were adopted for the *Inspire-CF* research programme (described in **Chapter 7**). Prior to the *Frequent Flyer Programme*, the GOSH CF specialist physiotherapy team advocated exercise, however there was no single preferred field-based exercise test undertaken at annual review, outpatient clinics or during admissions to hospital, and CPET had only been performed as part of research. CPET and a 10m-MSWT were both completed by children enrolled in the pilot *Frequent Flyer Programme* and each test had provided important information on physiological responses to exercise, and the clinical and health benefits the children achieved. The *Inspire-CF* research team agreed that both CPET and a 10m-MSWT should be performed by the children. Both tests had been validated in children aged 6 years and over and would help to determine limitations to exercise and provide measurements of maximal and functional exercise capacity, that would inform individual exercise prescriptions.

Based on the results of exercise tests, the 4 standardised exercise prescription principles of (1) frequency, (2) intensity, (3) time, and (4) type, commonly known as FITT principles, are recommended to be included to guide an age appropriate, individualised exercise training programme in CF (Williams et al., 2010). **Table 4-1** shows the only defined guidelines for exercise prescription and training in children and adolescents with CF, with recommendations of activities to participate in and to avoid.

Table 4-1: General exercise and training recommendations in cystic fibrosis

	Patients with mild to moderate CF lung disease	Patients with severe CF lung disease
Recommended activities	Cycling, walking, hiking, aerobics, running, rowing, tennis, swimming, strength training, climbing, roller-skating, trampolining	Ergometric cycling, walking, strengthening exercises, gymnastics, and day-to-day activities
Method	Intervals and steady state	Intervals
Frequency	3–5 times per week	5 times per week
Intensity	70%–85% HR_{peak}; 60%–80% VO_2peak; Lactate threshold Gas exchange threshold	60%–80% HR_{peak}; 50%–70% VO_2peak; Lactate threshold Gas exchange threshold
Time	45-60 minutes	30-45 minutes
Oxygen supplementation	Indicated, if SpO_2 dropped below 90% during exercise	Indicated, if SpO_2 dropped below 90% during exercise
Activities to avoid	Bungee-jumping, high diving, and scuba diving	Bungee-jumping, high diving, scuba diving, and hiking in high altitude
Potential risks associated with exercise, and training	Dehydration; hypoxemia; bronchoconstriction; pneumothorax; hypoglycaemia*; haemoptysis; oesophageal bleedings; cardiac arrhythmias; rupture of liver and spleen; spontaneous fractures** *Depending on the existence of an impaired glucose tolerance. **Depending on the existence of untreated CF-related bone disease.	

Adapted from: Williams, C. A., Benden, C., Stevens, D., and Radtke, T. (2010) Exercise training in children and adolescents with cystic fibrosis: theory into practice. *Int J Pediatr.* 2010, 1-7.

The translation of exercise programmes from CF research into clinical practice have not been effective as clinicians have had limited access to the resources used and/or developed. If the exercise prescription and training programmes were published as comprehensively as exercise test methodologies, this may enhance the translation of research outcomes to clinical practice. As such, it is recommended that exercise prescription and training programmes should be published in full as supplementary information if authors are unable to fully describe in published papers. Therefore, the *Inspire-CF* research team planned to extend the exercise prescription recommendations of Williams et al. (2010) and developed a set of exercise prescription and training exercise resources that could be disseminated to the wider CF community (**Appendix J)**. Children would need access to a fitness facility to be able to undertake an age-appropriate and disease specific exercise programme, that was progressive and adaptable, and that could be continued when children were admitted to hospital for IV-antibiotic treatment.

Exercise training by definition is planned, structured and repetitive skeletal muscle movement that results in either low, medium or high energy expenditure; and may comprise of single or multiple components of aerobic, anaerobic, muscle strength and conditioning and flexibility movements, and performed over varied duration (Caspersen et al., 1985). The 8 randomised controlled trials showed that aerobic or strength training or a combination of both, improved exercise capacity. However, scant detail was provided on the structure and content of the exercise training programmes. The *Inspire-CF* exercise programme was designed to be disease specific and provide a structure that could be adapted and individualised for each child. The exercise training programme will be published when the results of *Inspire-CF* are disseminated.

In addition to lung disease, children with CF may be affected by growth, pancreatic, and nutritional deficiencies (Penafortes et al., 2013), peripheral muscle weakness (Moser et al., 2000, Hussey et al., 2002) and CF-related hypoglycaemia, and previously prescribed steroid use (Ruf et al., 2010). It was therefore important that consideration was given to these when designing the *Inspire-CF* exercise prescription and training programme. Microbiology was also considered so that all precautions, such as regular use of bacterial wipes on equipment, could be employed to limit cross-infection. Children

with *Methicillin-resistant Staphylococcus aureus* and *Burkholderia cepacia* were not excluded from participation in *Inspire-CF*, but they would need to be exercise tested and trained at the end of a day to limit the risk of cross-infection. Gastrostomy tubes, Portacath or a peripherally inserted central catheter that were in situ, as well as incontinence issues and any musculoskeletal injuries or concerns, would also need to be accounted for.

Injuries to the epiphyseal plate or growth, particularly of the lower limb have been reported in healthy children, and these may cause damage to the growing cells, resulting in growth disturbances (Caine et al., 2006) because the epiphysis is often replaced by bony tissue that may lead to angular and rotational deformities and adversely affect joint mechanics (Shaw et al., 2018). Velocity and intensive controlled eccentric contractions during strength training exercise have been shown to increase the risk of physeal injuries in healthy children (Risser, 1991). Therefore, no velocity type resistance training or intensive controlled eccentric contractions were included in *Inspire-CF* to reduce the risk of physeal injuries. Tempo of concentric and eccentric contraction during strength training would be carefully monitored to reduce stress on the epiphyseal plate.

4.9. Summary

Chapter 4 provided a description of the exercise prescription and exercise training programme that was designed for *Inspire-CF* and linked to the resources that were developed to monitor for change in health status and exercise capacity, and to track responses to exercise training. The exercise training programme will be published when the results of *Inspire-CF* are disseminated. The research team wanted sessions to be adaptable and fun to ensure that children would want to remain actively engaged and would want to attend the sessions. It was important that the research team understood the current level of self-reported participation in exercise and/or physical activities, and it was also essential that adherence to the supervised exercise training sessions was tracked.

5.

CHAPTER 5. OVERVIEW OF THE STUDY POPULATION

5.1. Aims and objectives

The aim of **Chapter 5** was to provide an overview of the *Inspire-CF* population, recruitment rates and reasons for participant dropout, self-reported level of participation in physical activity and exercise over the duration of the study, as well as attendance levels to the once weekly supervised exercise sessions by children randomised to the exercise group. Change in anthropometric measurements following 24-months of enrolment in *Inspire-CF* are also reported.

The objectives were to determine the:

- Population characteristics of the control and exercise groups;
- Types of exercise and physical activities children participated in;
- Differences, if any, in self-reported minutes of weekly activity completed;
- Differences, if any, weekly energy expenditure defined as a metabolic equivalent task (MET);
- Exercise groups levels of attendance to individually supervised training sessions, and identified reasons for non-attendance;
- Differences, if any, in anthropometric measurements of height, weight and BMI.

5.2. Methods

The methodology related to the *Inspire-CF* population was described in **Chapter 3**. The methods of statistical analysis were described in **Chapter 3, Subheading 3.10, pg. 99**. Statistical significance was accepted at $p \leq 0.05$, and all data are presented as mean±SD, 95%CI and *p-value* unless otherwise stated.

5.3. Results

5.3.1. Recruitment pool

In the week that *Inspire-CF* recruitment started, the GOSH CF Unit were treating 176 children with CF, and of these, 84 children were aged 6 to 15 years, and provided the recruitment pool for the study (**Figure 5-1**). Children were invited to participate, and those who met the inclusion criteria and signed assent forms, and who had consent of their parents/legal guardians to participate in *Inspire-CF,* were scheduled for baseline assessments.

A total of 71 children (n=36 male vs. n=35 female) were recruited to *Inspire-CF* (a recruitment rate of 84.5%). The 13 children (n=8 male; 5=female) who were excluded from participation included: 1 child (female, aged 11 years) who had undergone previous cardiac surgery; 4 children who lived outside the counties of London, Essex, and Hertfordshire and Bedfordshire, and their parents declined their child's participation; parents of 3 children diagnosed with autism declined their participation; and the other 5 children were not interested in participation.

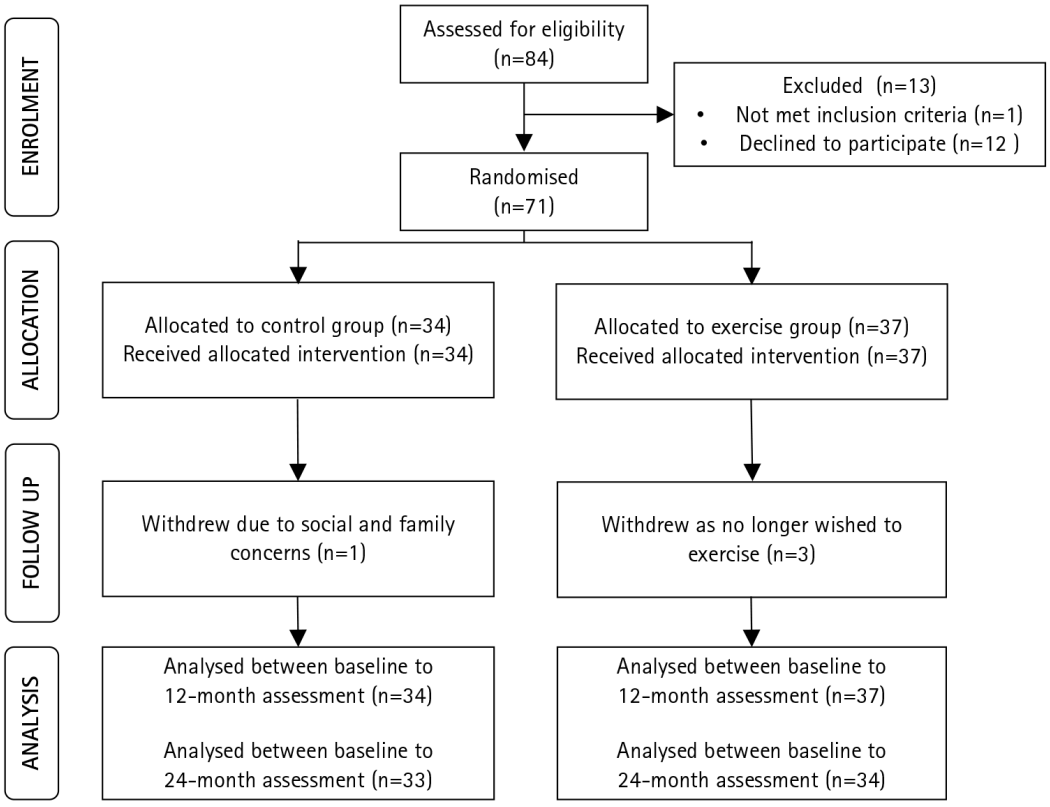

Figure 5-1: Flow diagram of the recruitment of the control and exercise groups to Inspire-CF

5.3.2. Study population

The 71 children were randomised into a control group (n=34) and an exercise group (n=37). **Table 5-1** summarises baseline group characteristics after randomisation by minimisation. The groups demographics were similar at baseline.

Table 5-1: Baseline group demographics for control and exercise groups after minimisation

Variable	Category	Control	Exercise
Group	Participants	34	37
Age	Mean age±SD [range]	10.3±3.2 [6 to 16.6]	9.8±2.9 [6.1 to 15.0]
Age group*	6-8 years	13	17
	9-11 years	10	10
	12-15 years	11	10
Gender*	Male/Female	18/16	18/19
Disease severity*	FEV_1 %pred. ≥70%	29	35
	FEV_1 %pred. <70%	5	2
Area lived in*	London	13	10
	Hertfordshire/Bedfordshire	12	17
	Essex	9	10
Nuffield membership*	Active vs. No membership	14 vs. 20	13 vs. 24
Ethnicity	Caucasian	32	35
	Black	1	1
	South East Asian	1	1

*Minimisation criteria

CFTR genotypes, endocrine status and microbiology profiles for each group are shown in **Table 5-2**. The most prevalent CFTR genotype was *p.Phe508del*, with 91.5% of participants carrying at least one copy of the mutation. Three children (4%) had one copy of the *p.Gly551Asp* mutation and had not been prescribed *Ivacaftor*® (*Kalydeco*®, Vertex Pharmaceuticals, Massachusetts, USA). Sixty-eight children (96%) were pancreatic insufficient, and 3 children (4%; control=1; exercise=2) were pancreatic sufficient.

Table 5-2: CFTR genotype, endocrine status, and microbiology profiles

Variable	Category		Control	Exercise
CFTR mutations	p.Phe508del	p.Phe508del	23	19
(Allele 1 and 2)	p.Phe508del	p.Gly551Asp	1	2
	p.Phe508del	other	7	13
	other mutation	other mutation	3	3
Endocrine	Pancreatic insufficiency		33 (97%)	35 (95%)
	CF-related diabetes		6	4
	CF-related diabetes on oral glucose tolerance test;		1	3
	Impaired glucose tolerance		4	2
	Indeterminate glycaemia		2	3
Microbiology	Chronic Pseudomonas aeruginosa		23 (68%)	21 (57%)
	Chronic Staphylococcus aureus		12 (35%)	7 (19%)
	History of Nontuberculous mycobacterium		2 (<1%)	1 (<1%)
	History of Methicillin-resistant Staphylococcus aureus		3 (<1%)	2 (<1%)
	History of Allergic Bronchopulmonary Aspergillosis		7 (21%)	8 (22%)

5.3.3. Drop-outs from Inspire-CF

There were 4 drops outs (5.6%) from the study; 1 male (aged 12 years) dropped out of the control group after 3-months in the study, due to social circumstances. His mother had passed away in the 12-months prior to enrolment, and he had developed behavioural concerns at home and had refused attendance at school and CF outpatient appointments. He and his father decided that withdrawal from *Inspire-CF* was in his best interests. The 3 other participants dropped out of the exercise group after 12-month assessment (1 male, aged 9 years moved hospitals and out of the catchment area for GOSH; and 1 male and 1 female (both aged 15 years) no longer wanted to participate in exercise.

5.3.4. Participation in exercise and physical activities

Analysis of the self-reported records of participation in exercise and physical activity at baseline showed that children in each group partook in a diverse range of sports and general physical activities, and these are shown in **Table 5-3**. All children reported that they participated in at least one school physical education class of between 30 – 90 minutes duration and football was the most popular sport. Gym based exercise was also reported, which suggested that some children were actively using their Nuffield memberships. Over the duration of the study, the same diverse range of activities were reported.

Table 5-3: Types of general physical activities children participated in at baseline

School or club sport	Gym-based	Dance or Martial arts
Athletics	Aerobics	Ballet
Badminton	Body weight	Cheerleading
Basketball	Cardio-stepper	Irish dancing
Boxing	Cross-trainer	Karate
Cricket	Kickboxing	Modern dance
Cross country/running	Resistance machines	School sports and activities
Football	Rowing machine	Dodgeball
Golf	Treadmill	Indoor/outdoor football
Gymnastics	Weight training	Handball
Hockey	Yoga	Multisport
Horse riding	Zumba	PE class
Netball	Cycling or Skating	Rounder's
Rugby	BMX/Cycling	Tag or touch rugby
Skiing	Ice-skating	Home-based activities
Squash	Roller skating	Dog walking
Swimming	Skateboarding	Trampolining
Tennis/Table tennis	Scootering	Walking to and from school

5.3.5. Analysis of weekly activity and energy expenditures

Table 5-4 shows the mean and ranges of weekly activities and energy expenditures at each assessment point. At baseline the exercise group were less physically active than the control group (-106.1±62.3 min·week^{-1}; 95%CI -230.4, 18.2; p=0.09) However, there was a wide range of self-reported activity levels in both groups at baseline; e.g., 5 children (2 control; 3 exercise) reported zero participation in any type of physical activity and 1 child spent up to 1779 min·week^{-1} (30 hr·week^{-1}) participating in cycling/BMX and skateboarding activities.

In **Table 5-5** the change in activity and energy expenditure levels show that the control group initially decreased, and then increased duration of exercise per week, between baseline and 24-month assessments, but maintained the same mean energy expenditure. The exercise group increased their level of activity level between baseline and 12-month assessment, to match the level of activity of the control group. The exercise group continued to increase their level of activity between 12- and 24-month assessment. Analysis of the MET conversion scales showed the level of intensity of activity was different between groups at 12- month assessment, with the exercise group maintaining a higher energy expenditure than the control group. **Figure 5-2** illustrates the mean change in weekly activity and energy expenditure during *Inspire-CF*.

Table 5-4: Analysis of weekly activity and energy expenditure

Variable	Assessment	Control	Range	Exercise	Range
Activity level in min·week^{-1}	baseline	362±327	0 to 1780	256±184	0 to 711
	12-month	331±258	0 to 930	335±172	45 to 771
	24-month	383±339	0 to 1481	385±192	45 to 785
MET exp·week^{-1}	baseline	38±37	0 to 203	26±18	0 to 66
	12-month	36±29	0 to 100	33±16	6 to 74
	24-month	39±32	0 to 141	40±20	6 to 83

Table 5-5: Differences in activity level and energy expenditure

Variable	Duration	Control	Range	Exercise	Range
ΔActivity level in min·week^{-1}	baseline to 12-month	-36±211	920 to 250	79±131	-315 to 480
	baseline to 24-month	16±397	-1300 to 1321	119±150	-315 to 405
ΔMET exp·week^{-1}	baseline to 12-month	-2±24	-111 to 35	8±11	-26 to 36
	baseline to 24-month	0±38	-150 to 96	13±16	-28 to 48

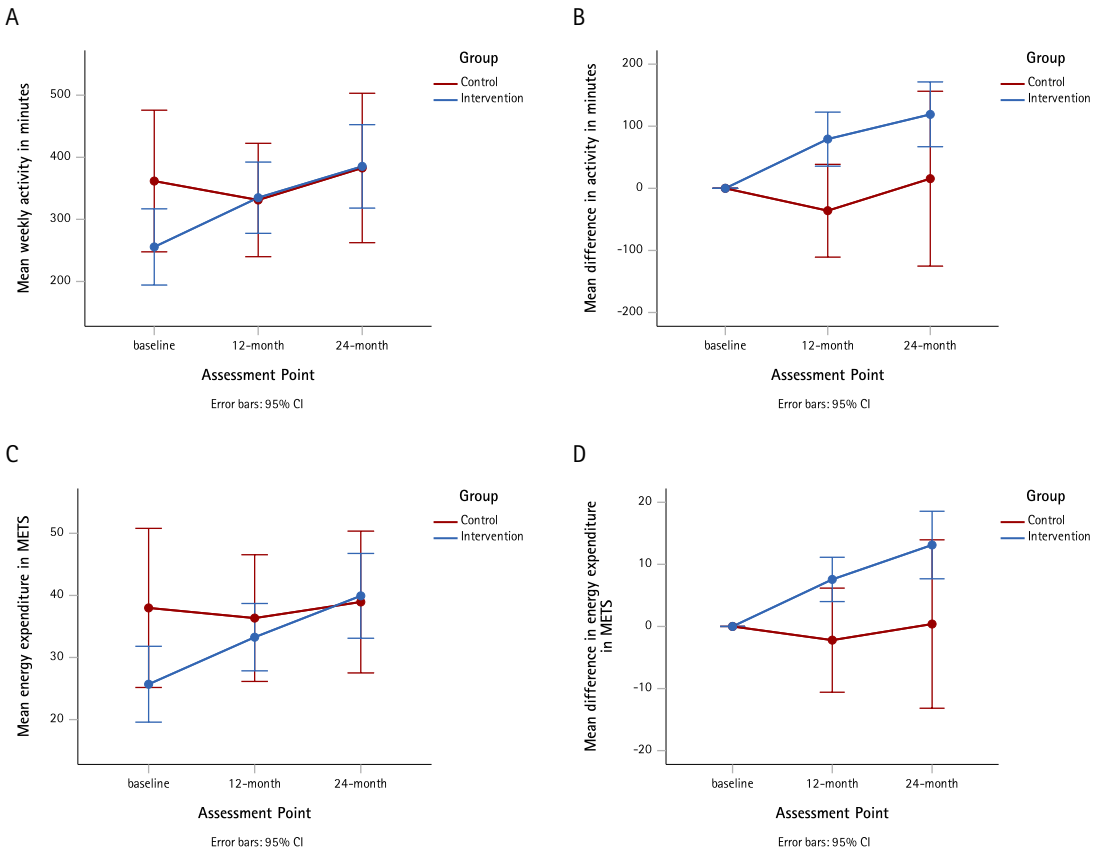

Figure 5-2: A: Mean weekly activity performed in minutes; B: Mean difference in weekly activity performed in minutes; C: Mean energy expenditure in METS; D: Mean difference in energy expenditure in METS.

5.3.6. Attendance to individually supervised training sessions

Attendance and reasons for non-attendance to supervised exercise training sessions were systematically recorded throughout *Inspire-CF* (**Table 5–6**). There was a total of 3848 potential weekly training sessions available (i.e., 37 participants in the exercise group x 104 training sessions), however an adjustment was made to this total to account for the 3 dropouts from the exercise group at 12-months. Therefore, there was a total of 3692 (3848 minus 156 weeks) potential weekly training sessions available, of which children attended 2274 sessions (61.6%).

There were 1418 sessions (38.4%) missed between baseline and 24-month assessment points. The major and minor reasons for non-attendance to exercise sessions are shown in **Table 5–7**. Despite best efforts to secure gym membership or similar facilities, this was the primary reason for non-attendance between baseline and 12-month assessment. Nine children (5=male; 4=female) were affected by between 10–19 weeks, because an agreement could not be reached with their local fitness facility, and no other facility was available within a 30-minute drive from home. Eight children started training in the week following baseline testing, and the remainder of the children (n=20) started within 2-9 weeks of completing baseline testing. The primary reason for these children not starting exercise training in the week following baseline testing was that family schedules required adaptations to accommodate training. Family holidays, trainer holidays, and unexplained non-attendance accounted for other major reasons.

The 2 most common minor reasons were child illness not related to admissions, and trainers undertaking *Inspire-CF* related assessments. Children missed 41.4% of sessions in the first 12-months, and 35.2% of sessions in the second 12-months, and a total of 38.4% of all potential exercise training sessions.

Table 5-6: Attendance to exercise training between baseline and 24-month assessment points

Percentage of attended exercise training sessions	No.	Mean±SD	Individual ranges	Total
Between baseline and 12-month assessment	37	59%±17%	9% to 92%	796
Between 12-month and 24-month assessment	34	65%±15%	11% to 91%	622
Between baseline & 24-month assessment for those participants that completed the study	34	66%±14%	16% to 92%	1418
Total number of weeks of exercise completed	No.	Mean±SD	Individual ranges	Total
Between baseline and 12-month assessment	37	30±9	5 to 49	1120
Between 12-month and 24-month assessment	34	34±9	6 to 50	1154
Between baseline and 24-month assessment by participants that completed the study	34	65±15	17 to 99	2274
Gender differences in attended exercise training sessions	No.	Female	Male	
Between baseline and 12-month assessment	37	54% (n=18)	61% (n=19)	
Between 12-month and 24-month assessment	34	60% (n=17)	67% (n=17)	
Attendance between baseline & 24-month assessment for those participants that completed the study	34	58% (n=17)	66% (n=17)	

Table 5-7: Reasons for non-attendance to exercise training sessions

	Baseline to 12-month assessment point			12-month to 24-month assessment point			Baseline to 24-month assessment point		
Major reasons for non-attendance	**Mean weeks±SD**	**Range**	**Total**	**Mean weeks±SD**	**Range**	**Total**	**Mean weeks±SD**	**Range**	**Total**
No membership agreement in place with fitness centre	6±5	0 to 19	224	-	-	-	6±5	0 to 19	224
Family holidays	3±3	0 to 12	116	4±3	0 to 12	118	6±5	0 to 20	234
Personal trainer holidays	2±2	0 to 7	53	5±3	0 to 10	157	6±4	0 to 14	240
Unexplained non-attendance (i.e., did not arrive for session)	2±7	0 to 38	85	2±6	0 to 34	56	4±10	0 to 45	141
Minor reasons for non-attendance									
Child illness	1±4	0 to 16	52	2±3	0 to 14	55	3±6	0 to 30	107
GOSH admissions	1±3	0 to 16	24	0.4±1	0 to 3	13	1±3	0 to 16	37
Shared care Hospital admissions	1±2	0 to 9	19	1±1	0 to 4	16	1±3	0 to 13	35
Clinic appointments	1±1	0 to 3	20	0.4±1	0 to 3	15	1±1	0 to 4	35
Public holidays	1±1	0 to 5	25	2±2	0 to 6	57	2±3	0 to 11	82
Family event (family outing; no reason; parent sickness)	1±2	0 to 8	50	1±2	0 to 6	38	2±3	0 to 10	88
School events (parent/teach evenings; sports day)	1±2	0 to 10	37	1±1	0 to 6	35	2±3	0 to 11	72
Personal trainer event (conference; assessments; training)	2±2	0 to 5	59	2±2	0 to 5	61	4±3	0 to 10	120
Arrived but risk to training based on 6-point pre-training checklist	0.1±0.1	0 to 2	2	0.1±0.1	0 to 1	1	0.1±0.1	0 to 3	3
Total weeks missed			**796**			**622**			**1418**
Percentage of weeks missed			**41.4%**			**35.2%**			**38.4%**

5.3.7. Anthropometric measurements

At baseline, there were no significant between group differences in anthropometric measurements of height, weight, and BMI, and there were no significant between-group differences for all other anthropometric measurements throughout the duration of the study. **Table 5-8** shows the analysis of between group differences in anthropometric measurement and shows the adjusted differences. **Figure 5-3** illustrates the mean between-group differences in anthropometric measurements.

Table 5-8: Analysis of between-group differences in anthropometric measurements

Variable	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
Height in cm	baseline	136.4±17.2	136.7±15.3	0.2 (-7.5, 7.9)	0.95
	6-month	139.8±17.1	139.1±14.4	-0.7 (-8.5, 7.2)	0.87
	12-month	141.8±17.0	142.0±14.3	0.2 (-7.3, 7.8)	0.95
	24-month	147.0±17.3	145.7±13.1	-1.3 (-8.8, 6.1)	0.72
Height z-score	baseline	-0.2±0.8	-0.4±1.1	-0.2 (-0.7, 0.3)	0.39
	6-month	-0.3±0.9	-0.3±1.0	0.0 (-0.5, 0.4)	0.86
	12-month	-0.5±1.1	-0.1±0.9	0.4 (-0.1, 0.8)	0.13
	24-month	-0.3±0.8	-0.2±1.0	0.1 (-0.3, 0.6)	0.62
Weight in kg	baseline	32.9±11.2	33.9±12.5	1.0 (-4.6, 6.7)	0.72
	6-month	35.4±12.3	34.9±12.1	-0.5 (-6.6, 5.5)	0.86
	12-month	36.8±13.4	37.6±12.9	0.8 (-5.5, 7.1)	0.81
	24-month	40.1±14.5	39.4±13.3	-0.7 (-7.5, 6.1)	0.83
Weight z-score	baseline	0.0±0.9	-0.3±1.1	-0.2 (-0.7, 0.2)	0.31
	6-month	-0.2±1.2	-0.2±1.0	0.0 (-0.5, 0.6)	0.92
	12-month	-0.3±1.1	0.0±0.9	0.3 (-0.1, 0.9)	0.14
	24-month	-0.1±0.9	-0.3, 1.1	-0.2 (-0.6, 0.3)	0.52
BMI in $kg.m^2$	baseline	17.1±2.0	17.5±2.8	0.4 (-0.8, 1.6)	0.50
	6-month	17.5±2.3	17.5±3.0	0.0 (-1.3, 1.3)	0.98
	12-month	17.6±2.6	18.1±3.0	0.5 (-0.9, 1.8)	0.50
	24-month	17.9±2.7	18.1±93.2	0.2 (-1.3, 1.6)	0.81
BMI z-score	baseline	0.1±1.0	-0.1±0.9	-0.1 (-0.6, 0.3)	0.60
	6-month	-0.1±1.3	0.0±1.0	0.1 (-0.5, 0.6)	0.77
	12-month	-0.1±0.9	0.1±0.9	0.2 (-0.2, 0.7)	0.36
	24-month	0.1±1.0	-0.2±1.3	-0.3 (-0.9, 0.2)	0.23

Mean differences were calculated as exercise minus control group; *statistically significant $p \leq 0.05$

Table 5-9: Adjusted differences in anthropometric measurements

Variable	Duration	B	95%CI	*p*-value
ΔHeight in cm	baseline to 6-month	-0.05	-0.74, 0.64	0.89
	baseline to 12-month	-0.49	-1.50, 0.52	0.34
	baseline to 24-month	-0.83	-2.63, 0.97	0.36
ΔHeight z-score	baseline to 6-month	0.1	-0.6, 0.8	0.85
	baseline to 12-month	0.5	-0.2, 1.2	0.34
	baseline to 24-month	0.4	-0.2, 1.1	0.17
ΔWeight in kg	baseline to 6-month	-0.29	-1.50, 0.92	0.63
	baseline to 12-month	-0.27	-1.63, 1.08	0.69
	baseline to 24-month	-0.53	-3.04, 1.98	0.67
ΔWeight z-score	baseline to 6-month	0.1	-0.6, 0.9	0.70
	baseline to 12-month	0.5	-0.1, 1.3	0.24
	baseline to 24-month	0.2	-0.5, 0.9	0.51
ΔBMI	baseline to 6-month	-0.09	-0.60, 0.42	0.74
	baseline to 12-month	0.10	-0.40, 0.59	0.69
	baseline to 24-month	0.03	-0.71, 0.78	0.93
ΔBMI z-score	baseline to 6-month	0.1	-0.7, 0.9	0.75
	baseline to 12-month	0.2	-0.6, 0.9	0.67
	baseline to 24-month	-0.1	-0.9, 0.6	0.77

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status.

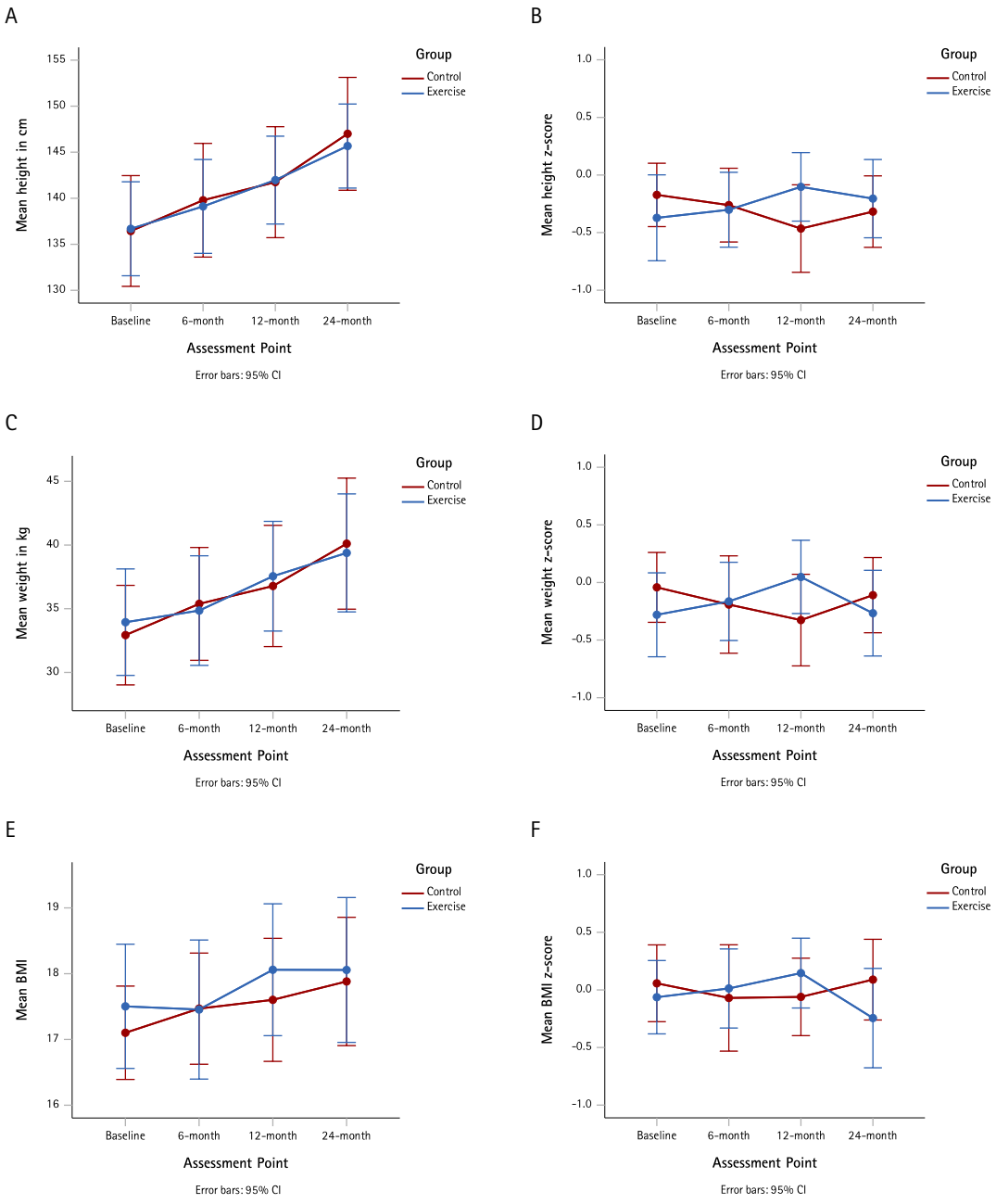

Figure 5-3: A and B show the mean height in meters and z-score; C and D show the mean weight in kg and z-score; E and F show the mean BMI in kg.m² and z-score

5.4. Discussion

At the start of *Inspire-CF*, the UK Cystic Fibrosis Registry Annual Data Report (Cystic Fibrosis Trust, 2012) indicated that there were 31 paediatric clinical centres in the UK, and that GOSH treated children with a similarly wide range of lung disease severity as other specialist CF hospitals (Cystic Fibrosis Trust, 2014). *Inspire-CF* recorded an 85% recruitment rate, and after randomisation the control and exercise groups were similar at baseline and representative of the age, gender, lung disease severity, and regional distribution of the GOSH CF cohort. There was a 6% dropout rate over the 24-month intervention period and this was recognised as an important achievement, as dropout rates of 20% or more from randomised controlled trials that included children with CF have been reported (Karlson and Rapoff, 2009). Effective between-group comparisons could be made and type II errors could be avoided (Jones et al., 2003), as the defined sample size of 33 participants per group and 80% statistical power at 5% significance was maintained (**Chapter 3, Subheading 3.5, pg. 77**) Meaningful comparisons could be made between the *Inspire-CF* cohort and the wider UK CF cohort of children aged 6 years and over, when summarising and synthesising the results of *Inspire-CF* in **Chapter 10.**

The GOSH specialist CF physiotherapy team actively encouraged all children to participate in regular physical activity, and this included school or club level sport, physical education classes at school, gym-based exercise, and recreational activities. Some children and their parents had availed of Nuffield Health memberships and the *Inspire-CF* research team were provided with a list of those children with an active membership status. However, of those with active memberships, there was no simple method of obtaining reliable attendance levels from the fitness facilities once registered. Membership cards were provided to families; however, children and parents or carers had reported that they were mostly given immediate access through the main entrances to the facilities by the receptionists, without swiping their access cards. Therefore, it was important that the *Inspire-CF* research team recorded current levels of activity and recorded if the child had a Nuffield membership.

To assess for types and levels of participation in regular physical activity at baseline, all the children enrolled in *Inspire-CF* recorded their current weekly physical activities, with assistance from parents or carers. Data was recorded as frequency of participation in the activity over a week and duration of the activity in minutes. These data were then cumulatively recorded as total minutes of physical activity per week and coded according to published metabolic equivalent (MET) values (Ainsworth et al., 2011). This process was repeated at 12- and 24-month assessment points. Children allocated to the exercise group were asked to include the once per week supervised training session on their forms at 12- and 24-month assessment.

All children randomised to the exercise group were offered 24-months of weekly personalised exercise training session (i.e., a total of 52 sessions in each 12-month period). However, some 24-month assessments were delayed for participants, mostly due to admissions to hospital or inability for the participant to attend the precise assessment date. There was no more than a 4-week delay in any assessment point. In the case of the exercise group, training was maintained until the participant completed the associated assessment, which was not within two-weeks preceding or following an admission to hospital for IV-antibiotic treatment.

Analysis of self-reported exercise and physical activity showed that children were already participating in a wide range of physical activities, though of varying intensities, at the start of *Inspire-CF*. There were significant differences in the number of minutes of activity that each group performed each week, with the exercise group performing less at baseline. *Inspire-CF* introduced children in the exercise group to structured exercise in a fitness facility, and therefore there was an expectation that children in this group would report an increase in activity level over the duration of the study. The control group reported similar levels of activity throughout the study, whilst the exercise group reported consecutive increases in activity each year. However, it is important that the self-reported minutes of activity are treated with caution, as self-reported outcomes have been shown to be overestimated in CF (Daniels et al., 2011).

Tomezsko et al. (1994) found that children with CF have higher resting energy expenditure than healthy children, and this would contribute to higher energy expenditure during physical activity. Conversion of MET values related to energy expenditure in healthy individuals (Ainsworth et al., 2011) may therefore not be appropriate and may result in lower classification of energy expenditure for children in CF. Additionally, conversion of estimated physical activity to energy expenditure is known to be problematic, without the inclusion of an objective tool such as accelerometery (Hills et al., 2014). *Inspire-CF* did not include a quantifiable outcome measurement of daily activity and participation in physical activities such as accelerometery and relied solely on self-report by children with the assistance of their parents or carers. It is therefore important that the results of MET conversions are also not overinterpreted. Nevertheless, the analysis undertaken in **Chapter 5** was an attempt at an objective between-groups comparison of self-reported activities levels that may contribute to the interpretation of exercise test results that are reported in **Chapter 7**.

The analysis of attendance levels to once weekly individualised exercise training illustrated the significant challenges of implementing a supervised exercise programme in children with CF. Home, school, and medical care impacted on adherence to participation in the exercise training sessions, despite advanced planning with families. It was recognised during the planning stages of *Inspire-CF* that it was unlikely that 100% attendance could be achieved in a long-term supervised exercise intervention, and that attendance levels should be tracked. Average attendance over the duration of the study was 66%, with males attending more sessions (66%) than females (58%). There was one male (aged 6 years at baseline) who attended 95% (99/104 sessions) of his scheduled sessions, however by contrast, there was also a female (aged 15 years at baseline) who attended only 17% (18/104) of her scheduled sessions. In **Chapter 6, Subheading 6.3.5, pg. 145** this wide variation in levels of attendance will be considered in analysis that was aimed at identifying the dose-related effect of exercise, if any, on lung function.

In **Chapter 2, Table 2–3** levels of adherence during 8 randomised controlled trials (Braggion et al., 1989, Cerny, 1989, Schneiderman-Walker et al., 2000, Selvadurai et al., 2002a, Klijn et al., 2004, Orenstein et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014) showed that studies of

shorter-duration had high-adherence rates. The 2 studies of 14-day duration, which were completed whilst children were admitted to hospital, reported 90% adherence to the interventions (Cerny, 1989, Selvadurai et al., 2002a). The 3 studies of 12-weeks duration reported adherence rates above 95% (Klijn et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014), of which the latter 2 were outpatient based supervised exercise programmes, whilst Braggion et al. (1989) reported a 75% adherence rate in a 16-week community-based programme. Orenstein et al. (2004) did not report levels of adherence to a 12-month exercise intervention, however, Schneiderman-Walker et al. (2000) reported 60% adherence to a 36-month partially supervised intervention.

Inspire-CF adherence rate was 66%, which was less than all previous studies of 12-month duration or less (Braggion et al., 1989, Cerny, 1989, Selvadurai et al., 2002a, Klijn et al., 2004, Orenstein et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014), but was slightly more than the study of 36-month duration (Schneiderman-Walker et al., 2000). It was not possible to compare the major and minor reasons for non-attendance identified in *Inspire-CF* to the other studies as similarly comprehensive data was not published. However, child illness, school examinations and dehydration were reported as a reason for missing sessions in 2 studies (Santana-Sosa et al., 2012, Santana-Sosa et al., 2014).

Overall, males attended more of the *Inspire-CF* exercise training sessions than females, however, comparisons of gender differences in attendance levels were not possible with the 8 previous randomised controlled trials, as this data was not reported. In a randomised controlled trial that included 159 children aged 9-17 years with CF, and assessed gender differences in habitual physical activity, Selvadurai et al. (2004) reported that there were no significant differences in activity levels in prepubescent males and females. However, pubescent females participated in significantly less physical activity than males, and this difference was more evident as disease severity worsened. Another study in 344 children, adolescents and adults by Gruber et al. (2011b), also reported that males participated in more organised sport and that daily activity levels were higher than females, however precise differences were not reported. In a study of 109 children aged 7-17 years, Schneiderman-Walker et al. (2005), also found that females had lower physical activity levels than

males, and suggested that lower activity levels may partly contribute to higher mortality rates in females with CF. The gender differences identified during *Inspire-CF* were comparable to these studies and again raises the importance of encouraging increased activity levels in females with CF.

During the first 12-month period of the study, securing membership of a gym proved more difficult for 9 of the participants. Despite assurances to centres that children would always be supervised, 5 of the 51 fitness facilities that were approached, rejected requests for access to the centres. The most common reason for rejecting the request for access was due to centre managers concerns for the safety of children in areas where free-weights and resistance machines were located. The second most cited reason was that additional insurance cover would be required to provide access for children. Consequently, one child who lived the furthest distance from GOSH, was delayed a start of 19 weeks. There were no other viable alternative centres within reasonable driving distance for the child to train in, and the school gym was undergoing refurbishment. A local personal trainer responded to a request for help in training the child and provided once weekly training for the remainder of the study at a university fitness centre. Other major reasons for missing training sessions were family and personal trainer holidays, and this included typical holiday periods of Easter and Christmas. Where possible, personal trainers did increase their allocated number of children trained in a week, when other personal trainers were on holiday.

Unexplained non-attendance or refusal to train in the first 12 months were primarily related to 3 female participants who refused more than 11 consecutive sessions each due to unwillingness to exercise. One of these participants (aged 15 years) attended 5 training sessions but refused 38 sessions, and then withdrew after the 12-month re-assessment. Both the child and family had expressed enthusiasm for her allocation to the exercise group after randomisation. One reason for the change in focus may have been that this participant was a carrier of the *p.Gly551Asp* mutation and was prescribed and started *Ivacaftor*® in the first 3-months of the study. It may have been the positive publicity surrounding the drug that reassured the child and her parents that she was likely to benefit from increased lung function, and therefore the exercise programme was considered less important. However, the opposite was true of one girl (aged 6 years) who was also prescribed

Ivacaftor® 3-months after starting exercise training, and she and her parents were determined that she continue to participate in the *Inspire-CF* exercise programme.

During the *Frequent Flyer Programme*, nutritional status of the children was monitored every 2-3 months by a dietician (Ledger et al., 2013), as exocrine pancreatic insufficiency, which causes the malabsorption of fat, vitamins, and minerals, may have limited the ability of the children to meet the increased energy demands of the weekly exercise (Boucher et al., 1997). Children's weight was more variable after starting exercise, and 13 of the 16 children required high calorie oral supplementation to maintain their weight. As tolerance for exercise at any given intensity may be limited by the nutritional status of the child (Marcotte et al., 1986, Marin et al., 2004), growth outcomes were tracked for all children enrolled in *Inspire-CF*.

More than 95% of the children enrolled in *Inspire-CF* were pancreatic insufficient and may therefore have had decreased fat storage. It was therefore important that growth parameters were monitored for the duration of the study. Importantly, there were no significant changes in weight and BMI z-scores for either group throughout the duration of the study, with both groups tracking near identical trajectories. During the *Frequent Flyer Programme*, weight was variable after starting exercise, and 82% of children required high calorie oral supplementation to maintain their weight. The analysis of between-group differences in *Inspire-CF* did not show that the exercise intervention affected weight or BMI. There was variation over the 24-months in both groups, but the GOSH CF dieticians did not report any overall concerns to the *Inspire-CF* research team.

One 16-year-old female (Δ*p.Phe508del*/*Δp.Phe508del*; pancreatic insufficient) in the exercise group, and in the final 12-months of the study, was identified at annual review with weight loss. She reported that her and her mother were intentionally limiting calorie intake, and independently training 2-4 x per week, in addition to the weekly *Inspire-CF* session. Despite increased support from the clinical team, including during a 14-day admission for IV-antibiotic treatment for respiratory exacerbation, she continued to lose weight. Her perceptions of physical, weight, body image and health improved in the CFQ-R, despite the weight loss. Body image due to the increased

exercise and active calorie limitation may have contributed to her developing an eating disorder. Members of the clinical team suggested that exercise be discouraged, whilst others advocated on-going exercise with closer monitoring and support, and referral to an Eating Disorder Service. She agreed to be referred to an Eating Disorder Service and her weight and body image concerns were addressed; she was able to safely continue with *Inspire-CF* exercise training sessions until the end of the study.

5.5. Summary

Inspire-CF recruited a representative sample of children aged 6-15 years with a wide range of lung disease severity, and the control and exercise groups were similar at baseline. Children partook in a wide range of organised sport and physical activities, including physical education classes at school. The control group self-reported higher activity levels at baseline and maintained these levels throughout the 24-month intervention period, whilst the exercise group consecutively increased their activity levels. Self-reported outcomes are problematic as children with CF and their parents and carers are known to over report adherence. Children with CF have higher resting expenditure levels, therefore using MET conversion tables for comparison to healthy populations to identify intensity of energy expenditure in CF, may result in misclassification. Growth parameters in both groups were maintained, which was important, as exercise had impacted on weight during the pilot *Frequent Flyer Programme*. There was wide variation in levels of attendance to *Inspire-CF* exercise training sessions, and these results may help explain any dose-related effect of exercise on lung function, which will be explored in **Chapter 6**.

6.

CHAPTER 6. THE EFFECTS OF SUPERVISED EXERCISE ON LUNG FUNCTION

6.1. Hypothesis, aims and objects

The primary hypothesis of **Chapter 6** was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of an increase in FEV_1 z-score of 0.7 z-score.

The aim was to consider the effects of 24-months of once weekly, supervised and individually prescribed exercise training on lung function parameters of FEV_1, FVC, FEF_{25-75} and LCI. Additionally, associations between changes in lung function and levels of attendance to training sessions were explored to identify any dose-related effects of exercise.

The objectives were to determine:

- Between-group differences, if any, in FEV_1, FVC and FEF_{25-75};
- Between-group differences, if any, in LCI;
- Determine the dose-related effect of exercise, if any, on lung function.

6.2. Methods

The methodology related to the *Inspire-CF* population was described in **Chapter 3**. Spirometry data collected during periods of health stability were incorporated in the analysis i.e., not during an exacerbation, and not during or within 2 weeks of completing IV-antibiotics. FEV_1, FVC and FEF_{25-75} raw data were converted to z-scores and %pred. The methods of statistical analysis were described in **Chapter 3, Subheading 3.10, pg. 99**. Statistical significance was accepted at $p \leq 0.05$, and all data are presented as mean±SD, 95%CI and *p*-value unless otherwise stated.

6.3. Results

6.3.1. Participants

All 71 participants completed spirometry assessment at baseline, and 69 participants successfully performed a MBW test. One child from the control group was unable to perform a MBW due to equipment failure and an alternative test date could not be rescheduled due to the distance of travel between home and the hospital; and one child from the exercise group could not maintain an acceptable technique.

6.3.2. Variability of FEV_1

Figure 6-1 illustrates that there was a wide range of CF lung disease severity in the control and exercise groups, and there was variation in FEV_1 even during periods of stability.

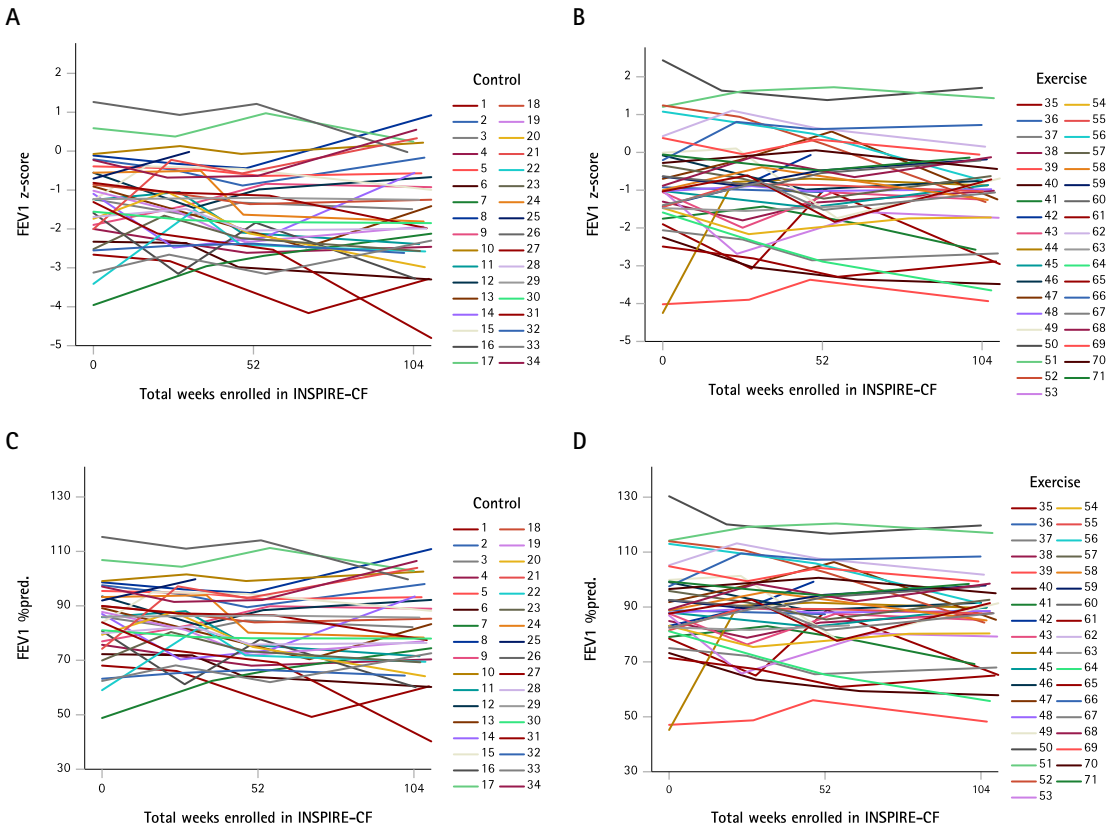

Figure 6-1: A & C: Variation in FEV_1 z-score and FEV_1 %pred. for the control group; B & D: Variation in FEV_1 and FEV_1 %pred. for the exercise group over the 24-month duration of *Inspire-CF*.

6.3.3. Spirometry

Table 6–1 shows the results of the between-group analysis of spirometry measurements. At baseline, the primary outcome measure of FEV_1 z-score was slightly lower in the control group (-1.3±1.1) than in the exercise group (-0.9±1.3), however this difference was not significant (0.4; 95%CI -0.1, 1.0; p=0.14), and both group means were within normal ranges. At 12-month assessment, the exercise group had maintained their FEV_1 z-score, however the control group recorded a decrease in their FEV_1 z-score, and this difference was statistically significant (0.6; 95%CI 0.1, 1.2; p=0.03). At 24-month assessment, the control group (-1.5±1.3) and the exercise group (-1.1±1.3) had recorded lower FEV_1 z-scores than baseline, but the between-group difference was not significant (0.5; 95%CI -0.2, 1.1; p=0.17). A significant between-group difference in FEV_1 %pred., FVC z-score and FVC %pred. was recorded at 12-months, but these differences were not maintained at 24-months.

Table 6–2 shows the adjusted between-group difference in spirometry measurements between baseline and 12-month assessment, and baseline and 24-month assessment. After adjusting for baseline differences and accounting for the minimisation factors there were no significant differences in FEV_1 z-score at 12-month (0.2; 95%CI -0.2, 0.6; p=0.26) and 24-month (0.1; 95%CI -0.4, 0.6; p=0.64) assessments. There were also no significant adjusted differences in any of the other spirometry measurements between baseline and 12-month, and baseline and 24-month assessments.

Overall, between baseline and 24-month assessment, each group had shown a deterioration of 0.2 z-score or 3% in FEV_1 %pred., which was an annual deterioration of 0.1 z-score or 1.5 in FEV_1%pred. per year. **Figure 6–2: A–H** illustrates the mean and mean changes in FEV_1, FVC and FEF_{25-75} outcomes and illustrates the trajectory of FEV_1 z-score between baseline and 24-month assessment for the control and exercise group.

Table 6-1: Analysis of between-group differences in spirometry measurements

		Control	Exercise	Mean diff. (95%CI)	*p*-value
FEV_1 z-score	baseline	-1.3±1.1	-0.9±1.3	0.4 (-0.1, 1.0)	0.14
	12-month	**-1.6±1.2**	**-0.9±1.3**	**0.6 (0.1, 1.2)**	**0.03***
	24-month	-1.5±1.3	-1.1±1.3	0.5 (-0.2, 1.1)	0.17
FEV_1 %pred.	baseline	83.8±13.9	89.2±16.3	5.4 (-1.9, 12.6)	0.14
	12-month	**80.9±14.0**	**88.6±15.2**	**7.7 (0.7, 14.7)**	**0.03***
	24-month	81.3±16.5	86.8±16.2	5.4 (-2.5, 13.4)	0.18
FEV_1 L	baseline	1.7±0.6	1.7±0.6	0.1 (-0.2, 0.4)	0.70
	12-month	1.8±0.7	1.9±0.7	0.1 (-0.2, 0.4)	0.53
	24-month	2.0±0.9	2.0±0.7	0.0 (-0.4, 0.4)	0.91
FVC z-score	baseline	-0.7±0.8	-0.3±1.3	0.4 (-0.2, 0.9)	0.19
	12-month	**-1.0±1.1**	**-0.3±1.3**	**0.6 (0.1, 1.2)**	**0.03***
	24-month	-0.9±1.3	-0.6±1.2	0.3 (-0.3, 1.0)	0.28
FVC %pred.	baseline	92.0±10.2	96.3±16.0	4.3 (-2.1, 10.7)	0.19
	12-month	**88.6±12.5**	**96.2±14.7**	**7.5 (1.0, 14.1)**	**0.03***
	24-month	89.5±15.1	93.4±14.5	3.9 (-3.3. 11.1)	0.28
FVC L	baseline	2.1±0.8	2.2±0.9	0.1 (-0.3, 0.5)	0.72
	12-month	2.3±0.9	2.4±0.9	0.1 (-0.3, 0.6)	0.56
	24-month	2.6±1.1	2.5±0.9	-0.1 (-0.6, 0.4)	0.79
FEF_{25-75} z-score	baseline	-1.8±1.4	-1.3±1.1	0.5 (-0.1, 1.1)	0.11
	12-month	-1.8±1.3	-1.4±1.2	0.4 (-0.1, 1.0)	0.14
	24-month	-1.8±1.3	-1.2±1.3	0.6 (-0.1, 1.2)	0.09
FEF_{25-75} L	baseline	1.6±0.8	1.7±0.7	0.1 (-0.2, 0.5)	0.47
	12-month	1.7±0.8	1.9±0.8	0.2 (-0.2, 0.5)	0.41
	24-month	1.9±1.1	2.1±0.8	0.2 (-0.3, 0.6)	0.50

Mean differences were calculated as exercise minus control group; *statistically significant $p \leq 0.05$

Table 6-2: Adjusted differences in spirometry measurements

		B	95%CI	*p*-value
ΔFEV_1 z-score	baseline to 12-month	0.2	-0.2, 0.6	0.26
	baseline to 24-month	0.1	-0.4, 0.6	0.64
ΔFEV_1 %pred.	baseline to 12-month	2.6	-2.2, 7.4	0.28
	baseline to 24-month	1.4	-4.9, 7.6	0.67
ΔFEV_1 L	baseline to 12-month	0.03	-0.1, 0.2	0.55
	baseline to 24-month	0.00	-0.2, 0.2	0.97
ΔFVC z-score	baseline to 12-month	0.3	-0.1, 0.7	0.09
	baseline to 24-month	0.2	-0.3, 0.7	0.45
ΔFVC %pred.	baseline to 12-month	3.8	-0.6, 8.2	0.09
	baseline to 24-month	2.0	-3.9, 7.9	0.49
ΔFVC L	baseline to 12-month	0.1	-0.1, 0.2	0.42
	baseline to 24-month	-0.01	-0.2, 0.2	0.93
ΔFEF_{25-75} z-score	baseline to 12-month	0.01	-0.5, 0.5	0.98
	baseline to 24-month	0.2	-0.4, 0.7	0.58
ΔFEF_{25-75} L	baseline to 12-month	0.01	-0.2, 0.2	0.89
	baseline to 24-month	0.1	-0.2, 0.4	0.51

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status.

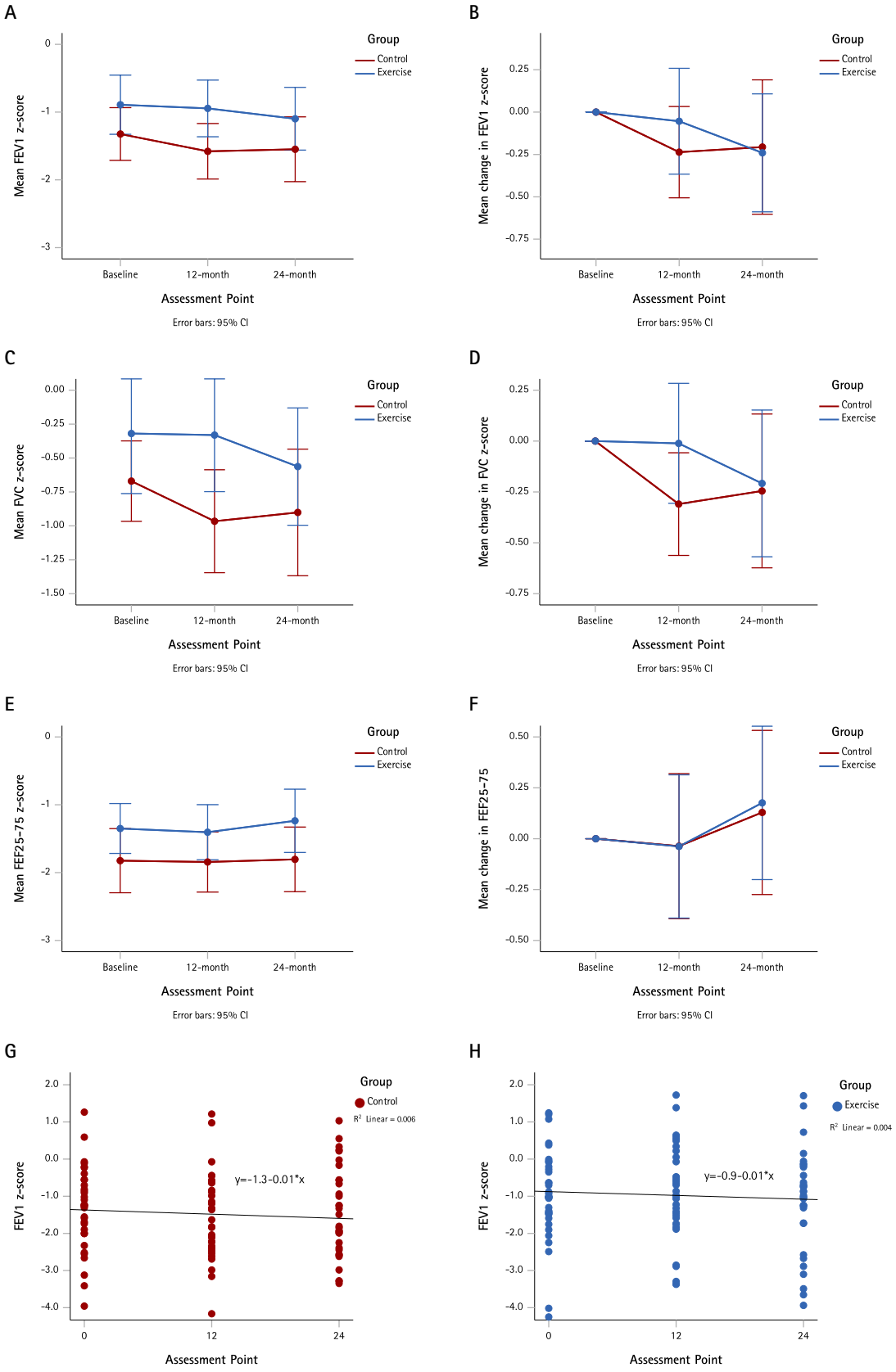

Figure 6-2: (A) Mean FEV_1 z-score, (B) Mean change in FEV_1 z-score, (C) Mean FVC z-score, (D) Mean change in FVC z-score, (E) Mean FEF_{25-75}, (F) Mean change in FEF_{25-75}, and trajectory of FEV_1 score for the (G) control group and (H) exercise group

6.3.4. Multiple breath inert gas washout test

Table 6-3 shows the analysis of between group difference in LCI and FRC and

Table 6-4 shows the adjusted changes in LCI and FRC. At baseline the between-group difference in control group (9.6 ±2.9) and exercise group (8.6 ±2.0) LCI, approached significance (-1.1; 95%CI -2.2, 0.1; p=0.08). Both groups had an LCI above the normal range of 5.49 - 7.81, however the control groups small airways disease was worse than the exercise group. At 12-months the difference remained (-0.9; 95%CI -2.0, 0.3; p=0.14) but was not significant. LCI had increased in the exercise group (8.9 ±2.0) at 24-month assessment, but more so in the control group 10.3 ±3.2, and the difference again approached statistical significance (-1.3; 95%CI -2.8, 0.1; p=0.07). After adjusting for baseline differences and accounting for the minimisation factors there were no significant differences LCI between baseline and 12-months, and baseline and 24-month assessments. There were no significant between group differences or adjusted differences in FRC.

Table 6-3: Analysis of between-group differences in multiple inert gas washout test measurements

		Control	Exercise	Mean diff. (95%CI)	p-value
LCI	Baseline	9.6 ±2.9	8.6 ±2.0	-1.1 (-2.2, 0.1)	0.08
	12-months	9.3 ±3.1	8.4 ±1.5	-0.9 (-2.0, 0.3)	0.14
	24-months	10.3 ±3.2	8.9 ±2.0	-1.3 (-2.8, 0.1)	0.07
FRC	Baseline	1.2 ±0.5	1.1 ±0.4	0.1 (-0.2, 0.2)	0.82
	12-months	1.3 ±0.5	1.3 ±0.5	-0.1 (-0.3, 0.2)	0.65
	24-months	1.4 ±0.6	1.3 ±0.5	-0.1 (-0.4, 0.2)	0.56

Mean differences were calculated as exercise minus control group.

Table 6-4: Adjusted differences in differences in multiple inert gas washout test measurements

		B	95%CI	p-value
LCI	baseline to 12-month	0.2	-0.56, 1.0	0.64
	baseline to 24-month	-0.8	-1.9, 0.3	0.15
FRC	baseline to 12-month	-0.04	-0.1, 0.1	0.45
	baseline to 24-month	0.02	-0.2, 0.2	0.84

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status.

Figure 6-3: A and B show the mean and mean changes in LCI respectively, over the duration of the 24-month intervention. **Figure 6-3: B** also illustrates that the exercise group maintained their LCI, more so than the control group.

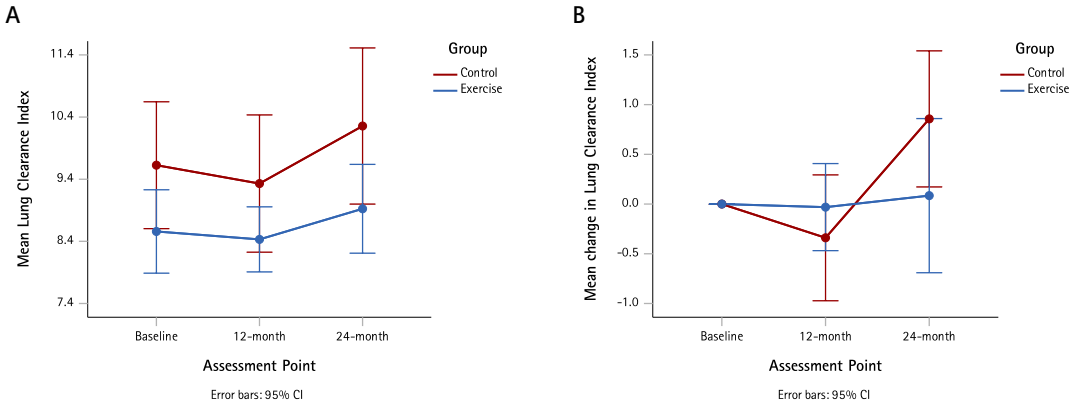

Figure 6-3: (A) Mean Lung Clearance Index, and (B) mean change in Lung Clearance Index from baseline

6.3.5. Multilevel mixed effects model analysis

In **Chapter 5, Subheading 5.3.6, pg. 126** levels of attendance and reasons for non-attendance were described. Participants in the exercise group attended a mean of 63±15% of training sessions, however there was a wide range of attendance levels from 17 to 99 weeks out of a total of 104 weeks. This created a theoretical possibility that exercise may have a dose-related effect on lung function i.e., that children who exercised more frequently might demonstrate a different effect on lung function than those who exercised less frequently.

Multilevel mixed models with random intercept were used to determine the associations between lung function and number of weeks trained by each participant. As in the analysis of all lung function measurements, only data collected at each of the 4 main assessment points were included in this analysis as the data was not confounded by exacerbation of symptoms and the associated effects of IV-antibiotics or prescribed oral antibiotics.

Table 6-5 shows the results of the multilevel mixed model analysis of FEV_1 z-score. There were no significant between-group differences in FEV_1 z-score (-0.2; 95%CI -0.6, 0.2; p=0.33), after controlling for minimisation factors of gender, age group, disease severity, area lived in, and the status of Nuffield membership. There was significant variation between the children at baseline (var =0.63, p<0.005) and there was significant variance in the slopes (p=0.007).

There was a significant interaction between group and time, which suggested that children in the exercise group did experience a deterioration of -0.002 in FEV_1 z-score (95%CI -0.005, -0.00001; p=0.05) for every week that they were in the study. However, there was also a significant positive interaction between FEV_1 z-score and the total number of weeks of exercise training completed (0.02; 95%CI 0.01, 0.04; p=0.01). It appeared that for children who exercised more regularly, there was some offset of the deterioration in FEV_1 z-score that they might otherwise have experienced.

The multilevel mixed model suggested that for each weekly training session completed, children could expect to see an increase in their FEV_1. Using the mixed model as a predictor, and extrapolating the weekly data, children who attended at least 52 weeks of training over 24-months might expect an improvement in their FEV_1 of 1.0 z-score (95%CI 0.5, 2.1; p=0.01), which equates to 15% in FEV_1 over 24-months or 7.5% annually. **Figure 6-4** illustrates that 11 children did experience an increase in FEV_1 z-score after completing at least 52-weeks or more of exercise training over the duration of *Inspire-CF*, which would suggest a dose-related effect of exercise on FEV_1.

The multilevel mixed model analysis was performed on FVC z-score (**Table 6-6** and **Figure 6-5**), FEF_{25-75} (**Table 6-7** and **Figure 6-6**) and LCI (**Table 6-8** and **Figure 6-7**). The results of these analyses demonstrated that there was also a significant dose-related effect of exercise on both FVC and FEF_{25-75}. However, a dose-related effect was not demonstrated in LCI.

Table 6-5: FEV_1 z-score mixed model for associations between group, weeks in study, number of weeks trained and minimisation factors

Variable	Estimate (95%CI)	*p*-value
Group		
Control vs. exercise	-0.2 (-0.6, 0.2)	0.33
Days in Study		
Group x weeks in study	**-0.002 (-0.005, -0.00001)**	**0.05***
Dose related effect of exercise training		
Number of weeks trained by exercise group	**0.02 (0.01, 0.04)**	**0.01***
Gender		
Males vs. Females	0.3 (-0.1, 0.7)	0.18
Disease severity		
FEV_1 ≥ 70%pred. vs. FEV_1 < 70%pred.	**2.2 (1.2, 2.6)**	**<0.001***
Age group		
Age 6-8 years	**0.5 (0.001, 1.0)**	**0.05***
Age 9-11 years	-0.02 (-0.6, 0.5)	0.93
Age 12-15 years	Baseline	
Area lived in		
London	0.1 (-0.4, 0.7)	0.61
Hertfordshire/Bedfordshire	0.2 (-0.3, 0.7)	0.50
Essex	Baseline	
Nuffield		
Member vs non-member	0.05 (-0.4, 0.5)	0.81

*Statistically significant $p \leq 0.05$.

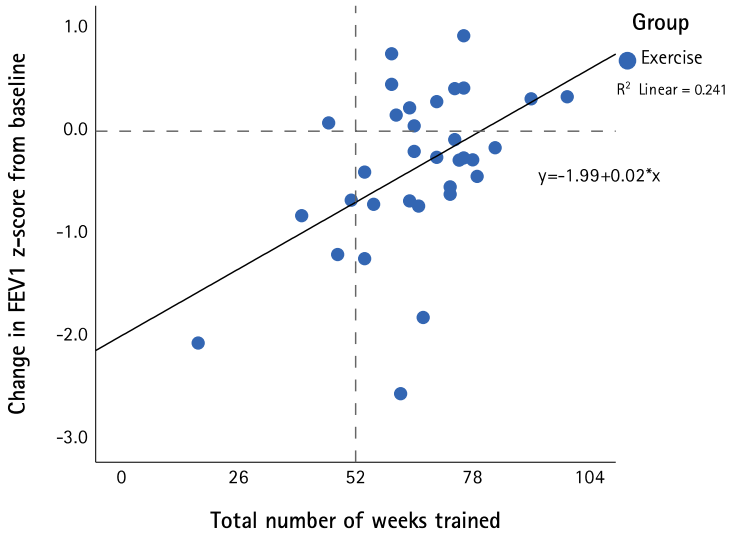

Figure 6-4: The exercise groups change in FEV_1 z-score plotted against total number of weeks trained during Inspire-CF

Table 6-6: FVC z-score mixed model for associations between group, weeks in study, number of weeks trained and minimisation factors

Variable	Estimate (95%CI)	*p*-value
Group		
Control vs. exercise	-0.2 (-0.7, 0.2)	0.24
Days in Study		
Group x weeks in study	**-0.002 (-0.003, -0.0007)**	**0.003***
Dose related effect of exercise training		
Number of weeks trained by exercise group	**0.02 (0.001, 0.04)**	**0.001***
Gender		
Males vs. Females	0.3 (-0.1, 0.7)	0.18
Disease severity		
FEV_1 ≥ 70%pred. vs. FEV_1 < 70%pred.	**1.6 (0.9, 2.4)**	**<0.001***
Age group		
Age 6-8 years	0.2 (-0.3, 0.7)	0.47
Age 9-11 years	-0.2 (-0.7, 0.4)	0.58
Age 12-15 years	Baseline	
Area lived in		
London	0.1 (-0.4, 0.7)	0.64
Hertfordshire/Bedfordshire	0.3 (-0.3, 0.8)	0.30
Essex	Baseline	
Nuffield		
Member vs non-member	0.04 (-0.4, 0.7)	0.86

*Statistically significant $p \leq 0.05$.

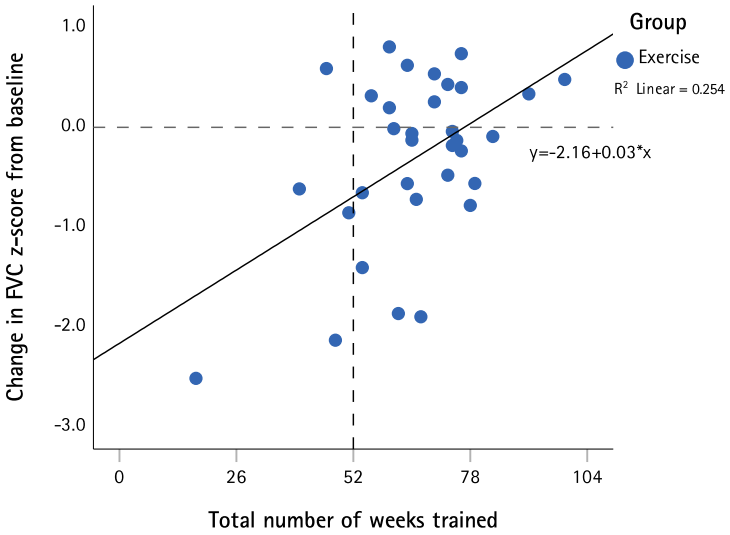

Figure 6-5: The exercise groups change in FVC z-score plotted against total number of weeks trained during Inspire-CF

Table 6-7: FEF_{25-75} z-score mixed model for associations between group, weeks in study, number of weeks trained and minimisation factors

Variable	Estimate (95%CI)	*p*-value
Group		
Control vs. exercise	-0.2 (-0.6, 0.2)	0.41
Days in Study		
Group x weeks in study	**-0.002 (-0.003, -0.0003)**	**0.02***
Dose related effect of exercise training		
Number of weeks trained by exercise group	**0.02 (0.001, 0.04)**	**0.03***
Gender		
Males vs. Females	0.4 (-0.05, 0.8)	0.08
Disease severity		
FEV_1 ≥ 70%pred. vs. FEV_1 < 70%pred.	**2.2 (1.5, 2.9)**	**<0.001***
Age group		
Age 6-8 years	0.5 (-0.04, 1.0)	0.07
Age 9-11 years	-0.06 (-0.6, 0.5)	0.82
Age 12-15 years	Baseline	
Area lived in		
London	0.01 (-0.5, 0.5)	0.94
Hertfordshire/Bedfordshire	-0.13 (-0.7, 0.4)	0.62
Essex	Baseline	
Nuffield		
Member vs non-member	0.06 (-0.4, 0.5)	0.79

*Statistically significant $p \leq 0.05$.

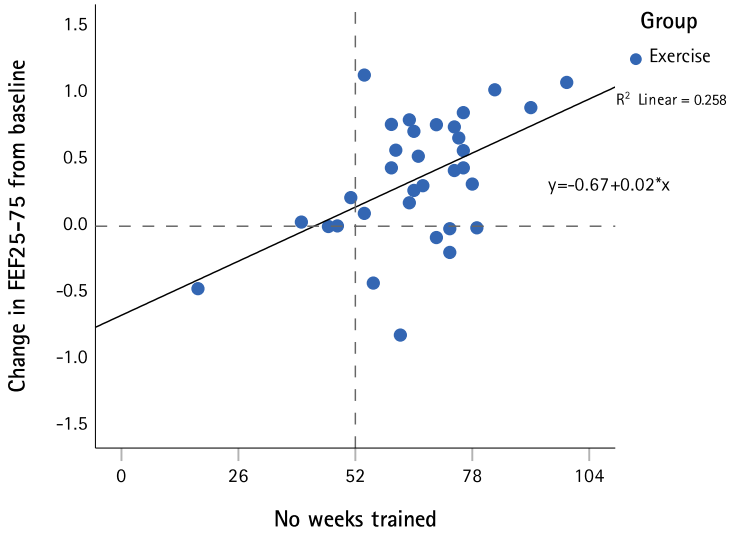

Figure 6-6: The exercise groups change in FEF_{25-75} z-score plotted against total number of weeks trained during Inspire-CF.

Table 6-8: LCI mixed model for associations between group, weeks in study, number of weeks trained and minimisation factors

Variable	Estimate (95%CI)	*p*-value
Group		
Control vs. exercise	-0.3 (-0.6, 1.3)	0.44
Days in Study		
Group x weeks in study	-0.0001 (-0.003, 0.003)	0.93
Dose related effect of exercise training		
Number of weeks trained by exercise group	-0.01 (-0.05, 0.03)	0.68
Gender		
Males vs. Females	-0.2 (-1.1, 0.7)	0.70
Disease severity		
FEV_1 ≥ 70%pred. vs. FEV_1 < 70%pred.	**-3.9 (-5.5, -2.3)**	**<0.001***
Age group		
Age 6-8 years	-1.0 (-2.1, 0.1)	0.08
Age 9-11 years	-0.7 (-1.9, 0.5)	0.25
Age 12-15 years	Baseline	
Area lived in		
London	-0.02 (-1.2, 1.2)	0.98
Hertfordshire/Bedfordshire	-0.2 (-1.4, 0.9)	0.71
Essex	Baseline	
Nuffield		
Member vs non-member	0.8 (-0.2, 1.8)	0.10

*Statistically significant $p \leq 0.05$.

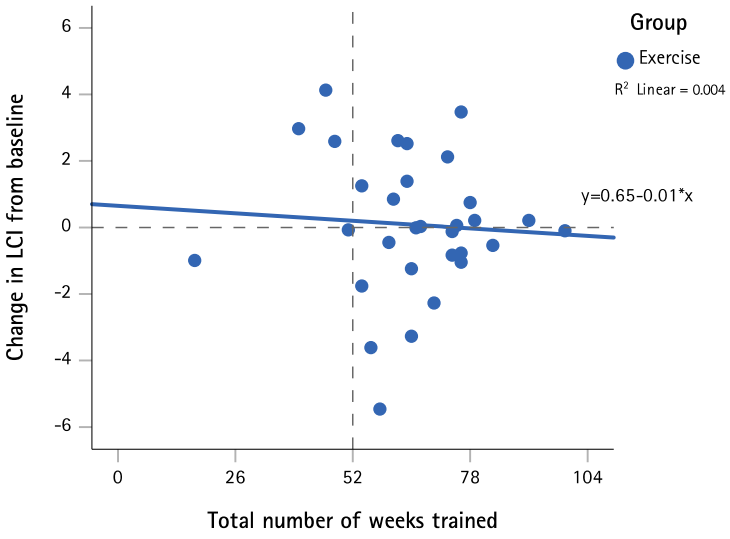

Figure 6-7: The exercise groups change in LCI z-score plotted against total number of weeks trained during Inspire-CF.

6.4. Discussion

The *Inspire-CF* exercise programme had aimed to increase exercise capacity, with the objective of improving improve FEV_1 z-score by 0.7 z-score over 24-months. This was not achieved; therefore, the primary hypothesis must be rejected. A once-weekly, supervised exercise programme did not demonstrate any significant effect of exercise on FEV_1, FVC and FEF_{25-75}, and that the exercise group recorded the same annual rate of deterioration of 1.5% in FEV_1 as the control group.

There was an average of 66% attendance to all exercise training sessions, and wide variation in levels of attendance. The realisation of a dose-related effect of exercise on lung function in some children who attended regular training sessions throughout the 24-month intervention period, might explain the reason some children recorded an increase in lung function, whilst others did not. For the first time in an exercise-based randomised controlled study in children with CF, a dose-related effect of up to 7.5% annual improvement in the primary outcome measure of FEV_1 z-score was achieved. However, this benefit was only realised in children who attended 52 sessions of more of exercise, out of the potential 104 training sessions. *Inspire-CF* demonstrated that at least one moderate-to-high intensity training session per fortnight that combined high intensity interval training and strength training exercise may offer some level of protection from deterioration in lung function that would otherwise be expected in CF. The same dose-related effect was also demonstrated in FVC and FEF_{25-75} z-scores.

Not all children who completed at least 52 sessions of exercise realised an increase in lung function, however rate of deterioration in FEV_1, FVC and FEF_{25-75} may have slowed. Analysis of LCI data may help to explain this finding. The exercise groups LCI were maintained over the duration of *Inspire-CF*, whilst the control group recorded an increase in LCI. There was a trend towards a significant between-group difference in LCI at baseline and this was maintained at 24-month, however, there was no significant dose-related effect of exercise on LCI. The minimally clinically important change in LCI has yet to be determined, however, it is plausible maintenance of LCI being maintained may be clinically important.

Prior to *Inspire-CF*, no other CF-related study in children had considered the dose-related effect of exercise on lung function. Understanding more about the minimum dose of exercise required to at least maintain lung function, would help CF clinicians when prescribing exercise to children with CF. The term "dose" refers to the product of exercise variables i.e., frequency of exercise, exercise intensity, exercise duration, and type of exercise (Blair et al., 1992, Strath et al., 2013). Frequency is the number of exercise sessions over an extended period; intensity refers to the metabolic cost of performing an activity at a percentage of measurable maximal capacity; duration is the accrued time of a single bout of exercise; and type refers to mechanism or exercise i.e., aerobic or strength (Wasfy and Baggish, 2016). "Dose response" refers to the physiological effects of these exercise variable on a physiological parameter e.g., FEV_1 (Blair et al., 1992). A minimum dose of 60 min·week^{-1} of moderate-to-vigorous vigorous intensity of physical activity is recommended for healthy children aged 6-17 years (Thompson, 2010). *Inspire-CF* has shown that children with CF age 6-17 years, should establish a routine of at 45-60 min·week^{-1} of moderate-to-high intensity exercise to preserve lung function.

Two randomised controlled studies that have used hypertonic saline or recombinant deoxyribonuclease, also known as DNase, in paediatric patients reported significant improvements in FEV_1 of between 7±14% and 15%±16% (Eng et al., 1996, Ballmann and von der Hardt, 2002). More recently, the CFTR modulator drug, *Ivacaftor®* (which was made available on the NHS during *Inspire-CF*), improved FEV_1 by between 4.9%-10.5% in adults and 10%-12.5% in children with the *p.Gly551Asp* mutation (Kotha and Clancy, 2013). The *Lumacaftor-Ivacaftor®* combination CFTR modulator drug for use in *p.Phe508del* mutations, improved FEV_1 by between 2.6%-4% (Wainwright et al., 2015). The dose-related effect of exercise demonstrated in *Inspire-CF*, was of a similar magnitude to these drug studies but only in those children who did at least 52 weeks of training over the duration of 24-months. This may be an important consideration for clinicians when prescribing the drugs. Regularly maintained moderate-to-high intensity exercise may offer some protection of lung function, particularly in children aged 6-12 years with CF, who have not been prescribed the drug.

In 2005, the mean range for FEV_1 %pred. for children aged 6-15 years in the UK was 78.3% to 88.2%, however improvements in medical management and advances in drug therapy have been reflected in the 2014 mean range, which was 79.3% to 91% (Cystic Fibrosis Trust, 2014). The annual rate of deterioration in FEV_1 in children aged 6 and over with CF was variable. Merkus et al. (2002) reported deterioration of 1.3% to 5.6% per year in Dutch children, whilst Konstan et al. (2007) reported 1.1% to 2.3% in American children. Both *Inspire-CF* groups demonstrated an annual deterioration of 1.5% per year, and these were comparable to the predictions in decline of between 0.86%-1.5% that were reported by Cogen et al. (2015). Studies in children aimed at determining the effects of exercise and physical activity on lung function in children with CF have produced variable results. A 9-year epidemiological study in children aged 7-17 years by Schneiderman et al. (2014) suggested that long term participation in physical activity may have a positive effect on FEV_1, such that deterioration was 1.9% annually in children with low physical activity levels, whilst deterioration was at a lesser rate of 1.39% annually in children with high physical activity levels. The rate of deterioration in the exercise group was concerning, as it was theorised that exercise would help to maintain lung function, as had been demonstrated in the *Frequent Flyer Programme*.

Comparison of *Inspire-CF* results to the 8 randomised controlled trials that included FEV_1 as an outcome measure is difficult. The only two studies that showed a significant benefit of exercise on FEV_1 included participants who were undergoing IV-antibiotic treatment. Cerny (1989) reported 18.4% increase in FEV_1 %pred. and Selvadurai et al. (2002a) reported a 10.1% and 6.5% increase in FEV_1 %pred. after 2-weeks either aerobic or strength training respectively. However, children in both studies were being treated with IV-antibiotics for exacerbations of respiratory symptoms, and it is likely the therapeutic effects of IV-antibiotics masked the effects, if any, of 14-days of exercise. Braggion et al. (1989) compared CF and healthy children who completed an aerobic and strength training programme, but there were no changes in FEV_1. Three studies reported no change in FEV_1 after anaerobic training (Klijn et al., 2004) or a combination of aerobic and strength training (Santana-Sosa et al., 2012, Santana-Sosa et al., 2014). The findings of *Inspire-CF* similarly did not demonstrate between group differences when dose effect was not accounted for. The two studies of longest duration, (Schneiderman-Walker et al., 2000, Orenstein et al., 2004) also reported no between

group differences in FEV_1, but each of the studies exercise groups recorded a deterioration of ~1.5% annually. This annual deterioration was equivalent to both *Inspire-CF* groups.

The 3 observational studies tracked FEV_1 over 12-months in children with moderate-to-severe lung disease. Black et al. (2009) reported a non-significant increase of 4% in FEV_1 %pred. whilst (Ledger et al., 2013) and Urquhart et al. (2012) reported that FEV_1 was maintained over the duration of the studies. These were important findings in a group of children who typically required multiple admission to hospital for prophylactic routine IV-antibiotics or exacerbation of respiratory symptoms over a course of a year. In the year preceding the *Frequent Flyer Programme*, the same group of children saw an average deterioration of 9% in FEV_1. *Inspire-CF* included children with milder, and a wider range of lung disease severity, and overall FEV_1 deteriorated. For children with milder lung disease to be able to increase their FEV_1 by as much as 7.5% annually, requires regular and consistent exercise of at least one session per fortnight. Without this frequency and intensity of exercise, lung function is unlikely to be protected and may deteriorate.

Levels of attendance were variable, and it was not possible to determine if the dose-related effect of exercise was linear. It was evident that some children who attended more sessions benefitted from increased FEV_1, however variation in the intensity of exercise at each session, despite best efforts to control, varied depending on the motivation, energy levels and current health status of the child. Children may have attended multiple consecutive exercise sessions, but then gone on an extended family holiday, and therefore not maintained their fitness levels. Previous studies (Santana-Sosa et al., 2012, Santana-Sosa et al., 2014) have shown that any improvements in physiological markers were not sustained beyond 4 weeks, therefore these breaks may have affected the outcomes. Several children were affected by the unavailability of a fitness centre within proximity of their home and had a delayed start to their training programme. It is also plausible that these events had a negative impact on the children's outcomes at the next assessment point.

Inspire-CF included high intensity interval training and strength training, and there were no adverse effects of the programme on lung function. Dose-related effects of exercise in CF have not been

previously explored, and this opens a new opportunity for future research. It was reassuring that the dose-related effect was evident in all the parameters of spirometry recorded in *Inspire-CF*. This study identified that a regular and sustained routine of exercise is important, and clinicians should educate children and their parents and carers on this important finding.

LCI has not previously been reported in other randomised controlled trials, however given the exercise groups maintenance of LCI, this outcome should be considered in future studies. Spirometry does not detect small airway changes, therefore an MBW may be a more appropriate test, especially in children with FEV_1 and FVC above 80% of predicted. *Inspire-CF* enrolled representative sample of children aged 6-15 years, and the findings of the study may be comparable to children with CF treated by other specialist centres in the UK, however, this study was limited to a single hospital. The Nuffield collaboration and extensive network of fitness facilities that was developed for *Inspire-CF*, was a challenge to manage and establish, but may be replicable in other national and international centres, without the associated costs of gym memberships.

6.5. Summary

Chapter 6 has shown that once-weekly supervised exercise may offer some protection of lung function to children who establish a routine of regular exercise and that is sustained. This provides a new direction for further research into minimum levels of exercise required to maintain or improve lung function. However, *Inspire-CF* did not replicate the maintenance of FEV_1 that was demonstrated in sicker children and lung function declined at the same rate as the control group. *Inspire-CF* has demonstrated the significant challenge in eliciting a positive change in the trajectory of lung function in children with CF. Clinicians should continue to advocate exercise, however caution should apply when educating children and parents and carers on the effects of exercise on lung function. It is important that the clinician's emphasise that sporadic and inconsistent participation in exercise will not preserve or slow the deterioration of lung function. Moderate-to-high exercise needs to be performed at regularly and consistently, in addition to the specialist CF care they already receive, to potentially benefit from an increase in lung function.

7.

CHAPTER 7. THE EFFECTS OF SUPERVISED EXERCISE ON EXERCISE CAPACITY

7.1. Hypothesis, aims and objectives

The primary hypothesis of **Chapter 7** was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of an increase in W_{peak} and VO_{2peak}.

The aim of was to consider the effects of the 24-month exercise individually supervised exercise programme on exercise capacity, using a functional 10m-MSWT and a laboratory based, cycle ergometer CPET.

The objectives were to determine:

- Between-group differences, if any, in distance run/walked in meters and level completed in the 10m-MSWT.
- Between-group differences, if any, in peak work rate (W_{peak}) and peak oxygen uptake (VO_{2peak}) during CPET.
- Likelihood of children increasing initial fitness levels.

7.2. Methods

The methodology related to the *Inspire-CF* population was described in **Chapter 3**. The methods of statistical analysis were described in **Chapter 3, Subheading 3.10, pg. 99**. Statistical significance was accepted at $p \leq 0.05$, and all data are presented as mean±SD, 95%CI and *p*-values unless otherwise stated.

7.3. Results

7.3.1. Participants

All 71 children completed the 10m-MSWT at baseline, 6-, and 12-months assessments; however, 4 children had dropped out after 12 months (**Chapter 5, Subheading 5.3.3, pg. 122**), therefore 67 children completed the 24-month assessments. Fifty-nine children (control=29; exercise=30) completed CPET and their data were included in analysis. The 4 dropouts (control=1; exercise=3) also declined to perform CPET after baseline tests. An additional, 3 children in the control group (1 male; age 6 years, and 2 females; age 7 and 14 years) declined to perform CPET due to the anxiety of wearing the facemask despite desensitisation strategies being implemented, and 1 child (1 male; age 14 years) declined re-testing without explanation. There were 3 children in the exercise group (male=2; age 6 years; and female=1; age 14 years) who had poor cycling technique and were unable to maintain cadence after each incremental increase in resistance and repeatedly stopped cycling. One boy (age 6 years) in the exercise group was diagnosed with ataxia and despite best efforts could not maintain balance, coordination, and cadence after each incremental increase in resistance. The data from these 12 children (control= 5; exercise=7) were not included in analysis of CPET data.

7.3.2. 10 metre modified shuttle walk test (25-level)

Analysis of the 10m-MSWT is shown in **Table 7-1** and **Table 7-2**, and **Figure 7-1** illustrates the mean changes in distance and levels completed for the 10m-MSWT. At baseline, the exercise group (916.2m±238.5m) covered less distance than the control group (962.6m±254.5m), however this difference was not statistically significant (-46.4m, 95%CI -163.5, 70.7, p=0.43). At 12-months, the exercise group (1057.0m±237.7m) covered more distance than the control group (1018.5m±222.7m), but these differences were not significant (38.5m, 95%CI -71.3, 148.4). At 24-month assessment,

there was a significant improvement in 10m-MSWT distance (157.0m, 95%CI 29.9, 284.3, p=0.002) in the exercise group (1181.8m±220.8m) when compared to the control group (1024.8m±291.3m). After adjusting for minimisation factors (gender, age group, disease severity, area, and Nuffield membership) the difference at 24-months further increased to 224.8m (95%CI 148.2, 301.5, p<0.001).

The minimally clinically important difference for the 10m-MSWT test in children was reported as 60m in (del Corral et al., 2020), which confirmed the clinical importance of the *Inspire-CF* results. At baseline and 12-month assessments there were small but non-significant differences in levels completed, however at 24-month assessment, the exercise group (12.7 levels) were able to complete a significant 1.0 level (0.2, 1.8, p=0.02) more than the control group (11.7 levels). There are no studies that have identified the minimally clinically important difference in level change for the 10m-MSWT.

There were no significant between group differences in HR_{peak} at any of the assessment points. However, there was a significant between-grou$p$-difference in $HR_{recovery}$ at 24-months (-6.8 beats·min^{-1}, 95%CI -12.6, -1.0), which indicated that the children in the exercise group (107.6±10.7) were cardio vascularly fitter that the control group (114.4±12.8). The adjusted difference in $HR_{recovery}$ was -5.1 beats·min^{-1} (95%CI -11.9, 1.8, p=0.14), but this difference was no longer significant. All children maintained an SpO_2 within the normal range of 94-98% across all assessment points, and there were no between-group differences detected.

There were no between-group differences in OMNI perceived exertion scales at baseline and 12-month assessment points, however at 24-month assessment the exercise group (9.2±0.7) reported a significantly higher exertion score (0.8, 95%CI 0.4, 1.3, p<0.001) than the control group (8.3±1.1), likely due to increased incremental pace and further distance covered. The adjusted difference showed a significant increase of 1.3 (95%CI 0.3, 2.3, p=0.01) in level achieved. OMNIrecovery at 3-minutes was also lower for the exercise group (2.2±1.3) when compared to the control group (3.0±1.8), and this difference approached statistical significance (-0.7, 95%CI -1.5, 0.0, p=0.06). However, the adjusted difference was not significant, and remained at -0.7 (95%CI -1.7, 0.3, p=0.18).

Table 7-1: Analysis of between-group differences in 10m-MSWT

Variable	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
Distance in meters	baseline	962.6±254.5	916.2±238.5	-46.4 (-163.5, 70.7)	0.43
	12-month	1018.5±222.7	1057.0±237.7	38.5 (-71.3, 148.4)	0.49
	24-month	**1024.8±291.3**	**1181.8±220.8**	**157.0 (29.9, 284.3)**	**0.02***
Levels completed	baseline	11.1±1.9	10.8±1.7	-0.3 (-1.1, 0.6)	0.51
	12-month	11.6±1.6	11.8±1.7	0.2 (-0.6, 0.9)	0.70
	24-month	**11.7±2.0**	**12.7±1.4**	**1.0 (0.2, 1.8)**	**0.02***
HR_{peak}	baseline	182.2±13.6	180.6±11.3	-1.6 (-7.6, 4.4	0.59
	12-month	180.5±9.5	181.4±12.5	0.8 (-4.4, 6.1)	0.75
	24-month	182.2±13.8	185.8±13.8	3.6 (-2.5, 9.7)	0.24
HR_{peak} %pred.	baseline	89.6±6.7	88.7±5.8	0.9 (-3.9, 2.1)	0.55
	12-month	89.1±4.9	89.4±4.9	0.3 (-2.4, 3.0)	0.82
	24-month	90.2±5.5	91.8±7.0	1.6 (-1.5, 4.6)	0.32
$HR_{recovery}$	baseline	113.8±11.2	114.4±10.8	0.6 (-4.7, 5.8)	0.83
	12-month	114.1±10.0	112.5±10.6	-1.6 (-6.5, 3.3)	0.52
	24-month	**114.4±12.8**	**107.6±10.7**	**-6.8 (-12.6, -1.0)**	**0.02***
$OMNI_{peak}$	baseline	8.3±1.5	8.0±2.0	-0.3 (-1.1, 0.5)	0.49
	12-month	8.5±1.3	8.9±1.1	0.4 (-0.2, 1.0)	0.21
	24-month	**8.3±1.1**	**9.2±0.7**	**0.8 (0.4, 1.3)**	**<0.001***
$OMNI_{recovery}$	baseline	3.6±2.0	3.6±2.0	0.0 (-0.9, 1.0)	0.99
	12-month	3.8±2.4	3.4±2.3	-0.4 (-1.5, 0.7)	0.46
	24-month	3.0±1.8	2.2±1.3	-0.7 (-1.5, 0.0)	0.06

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 7-2: Adjusted differences in 10m-MSWT outcomes from baseline to 12 and 24 months

Variable	Duration	B	95%CI	*p*-value
ΔDistance in meters	baseline to 12-month	118.5	25.4, 159.4	0.01*
	baseline to 24-month	**224.8**	**148.2, 301.5**	**<0.001***
ΔLevels completed	baseline to 12-month	0.4	-0.1, 1	0.12
	baseline to 24-month	**1.4**	**0.8, 1.9**	**<0.001***
ΔHR_{peak}	baseline to 12-month	2.3	-3.5, 8.1	0.43
	baseline to 24-month	5.2	-2.5, 12.8	0.18
ΔHR_{peak} %pred.	baseline to 12-month	1.1	-1.7, 4.0	0.43
	baseline to 24-month	2.5	-1.3, 6.3	0.19
$\Delta HR_{recovery}$	baseline to 12-month	-1.6	-8.4, 5.2	0.64
	baseline to 24-month	-5.1	-11.9, 1.8	0.14
$\Delta OMNI_{peak}$	baseline to 12-month	0.8	-0.2, 1.7	0.11
	baseline to 24-month	**1.3**	**0.3, 2.3**	**0.01***
$\Delta OMNI_{recovery}$	baseline to 12-month	-0.4	-1.9, 1.1	0.61
	baseline to 24-month	-0.7	-1.7, 0.3	0.18

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

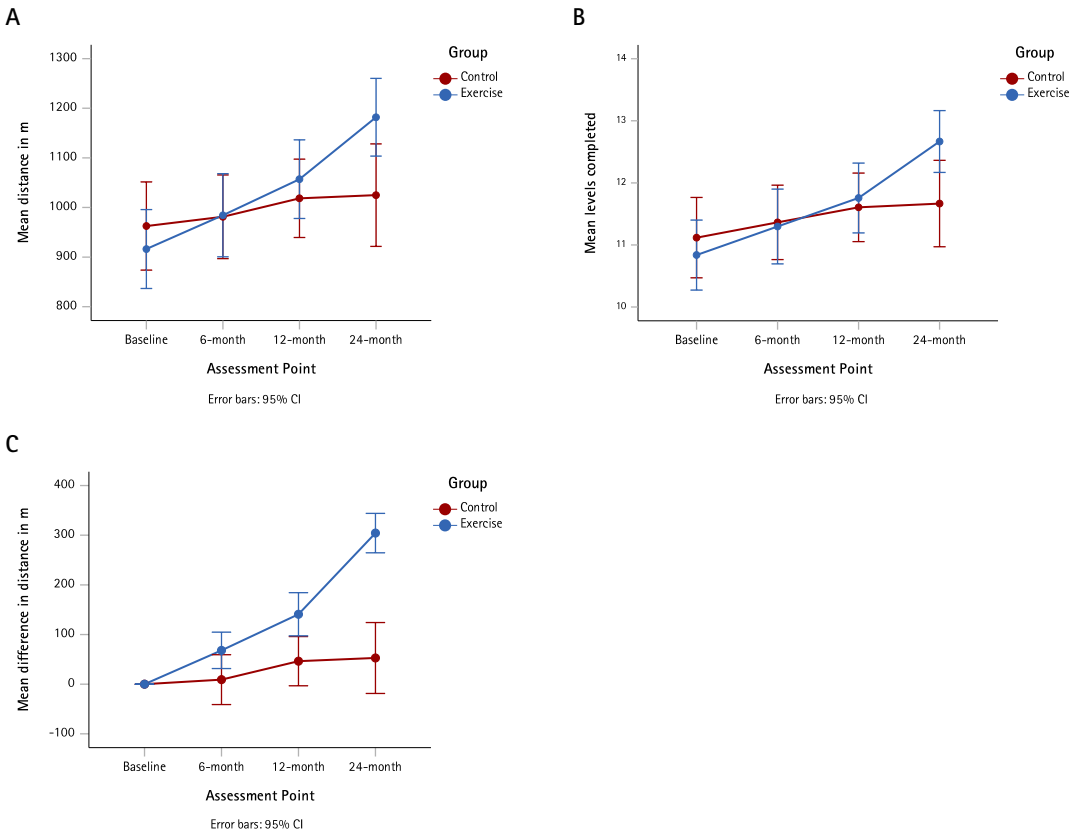

Figure 7-1: A: Mean between-group differences in distance walked/run during the 10-MSWT, B: Mean between-group differences in levels completed during the 10-MSWT, C; Mean change in distance walked/run during the 10-MSWT between baseline and 24-months

7.3.3. Cardiopulmonary exercise tests

Between-group differences in work rate and VO_2 were considered the two most important endpoints for determining change in exercise capacity, with all other outcomes considered secondary.

7.3.3.1. Peak work rate

Analysis of work rate is presented in **Table 7-3** and **Table 7-4** and **Figure 7-2: A-H**. There were no significant between-group differences in peak work rate (W_{peak}) at baseline (control=89.7±47.6 vs. exercise=87.0±42.6) and 24-month assessment (control=112.5±46.3 vs. exercise 117.2±45.4). Both groups had increased W_{peak} >20 and at a near identical rate. There were also no between-differences in work rate adjusted for body mass in kg ($W \cdot kg^{-1}$) at baseline and this was maintained at 12- and 24-month assessment. **Figure 7-2: G** illustrates a positive relationship between W_{peak} and age, and in **Figure 7-2: H**. there is a small but positive relationship between $W \cdot kg^{-1}$ and age. This may explain the increase in W_{peak} in both groups.

However, there was a significant between-group difference in W_{peak} %pred. at baseline (11.8, 95%CI 0.4, 23.2, p=0.04), in favour of the exercise group (86.6±20.2) vs. control group (75.0+23.2). This difference was maintained at 12-month assessment (8.5, 95%CI -2.9, 20.0, p=0.14), but was no longer significant. At 24-months, there was a statically significant difference of 8.3 (95%CI 0.5, 16.0, p=0.04) in favour of the exercise group in W_{peak} %pred. Neither the control group (76.6±15.5) or the exercise group (84.9±13.3) had improved on their baseline W_{peak} %pred. This suggested that the exercise groups lower limb, peripheral muscle strength was greater than the control group at baseline and they maintained this strength through the 24-months. Analysis of work rate at the gas exchange threshold (W_{GET}) showed both groups progressively increased their ability to work harder between baseline and 24-month assessment, but again there were no significant between-group differences. Adjusted differences for all work rate outcomes were not significant and did not further explain the results. Normal ranges for $W \cdot kg^{-1}$ in healthy children have been reported as between 3.4±0.7–4.0±0.6 $W \cdot kg^{-1}$ for males, and 3.1±0.5–3.7±0.7 $W \cdot kg^{-1}$ in females, aged 8-18 years respectively (Bongers et al., 2014a). This would suggest that at baseline, *Inspire-CF* groups presented with lower-than-normal $W \cdot kg^{-1}$ but these had increased to near normal ranges after 24 months.

Table 7-3: Analysis of between-group differences in peak work rate measurements

Variable	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
W_{peak}	baseline	89.7±47.6	87.0±42.6	-2.7 (-26.0, 20.7)	0.82
	12-month	105.9±54.5	102.0±45.8	-3.8 (-30.1, 22.5)	0.77
	24-month	112.5±46.3	117.2±45.4	4.7 (-19.9, 29.3)	0.70
W_{peak} %pred.	**baseline**	**75.0±23.2**	**86.8±20.2**	**11.8 (0.4, 23.2)**	**0.04***
	12-month	77.1±25.8	85.6±17.2	8.5 (-2.9, 20.0)	0.14
	24-month	**76.6±15.5**	**84.9±13.3**	**8.3 (0.5, 16.0)**	**0.04***
$W{\cdot}kg^{-1}$	baseline	2.5±0.7	2.6±0.6	0.1 (-0.3, 0.4)	0.85
	12-month	2.8±0.8	2.7±0.6	-0.1 (-0.4, 0.4)	0.98
	24-month	2.9±0.5	3.0±0.5	0.1 (-0.2, 0.3)	0.73
$W{\cdot}kg^{-1}$ %pred.	baseline	77.7±17.2	82.0±18.2	4.3 (-4.9, 13.6)	0.35
	12-month	81.6±22.7	83.8±16.5	2.2 (-8.1, 12.5)	0.67
	24-month	85.0±13.5	87.4±14.4	3.7 (-5.1, 9.8)	0.52
W_{GET}	baseline	53.7±27.0	48.3±26.7	-5.4 (-19.3, 8.5)	0.44
	12-month	73.8±28.0	65.1±35.8	-8.6 (-25.4, 8.2)	0.70
	24-month	74.2±26.3	76.6±27.0	2.4 (-11.9, 16.7)	0.74

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 7-4: Adjusted differences in peak work rate measurements

Variable	Duration	B	95%CI	*p*-value
ΔW_{peak}	baseline to 12-month	-0.4	-8.1, 7.2	0.91
	baseline to 24-month	1.9	-6.0, 9.8	0.64
ΔW_{peak} %pred.	baseline to 12-month	-0.7	-8.0, 6.6	0.85
	baseline to 24-month	-1.8	-10.2, 6.5	0.66
$\Delta W{\cdot}kg^{-1}$	baseline to 12-month	-0.1	-0.3, 0.2	0.62
	baseline to 24-month	0.0	-0.2, 0.2	0.83
$\Delta W{\cdot}kg^{-1}$ %pred.	baseline to 12-month	-0.5	-7.4, 6.5	0.89
	baseline to 24-month	-1.0	-8.2, 6.1	0.77
ΔW_{GET}	baseline to 12-month	-0.2	-0.6, 0.3	0.51
	baseline to 24-month	0.1	-0.2, 0.5	0.40

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

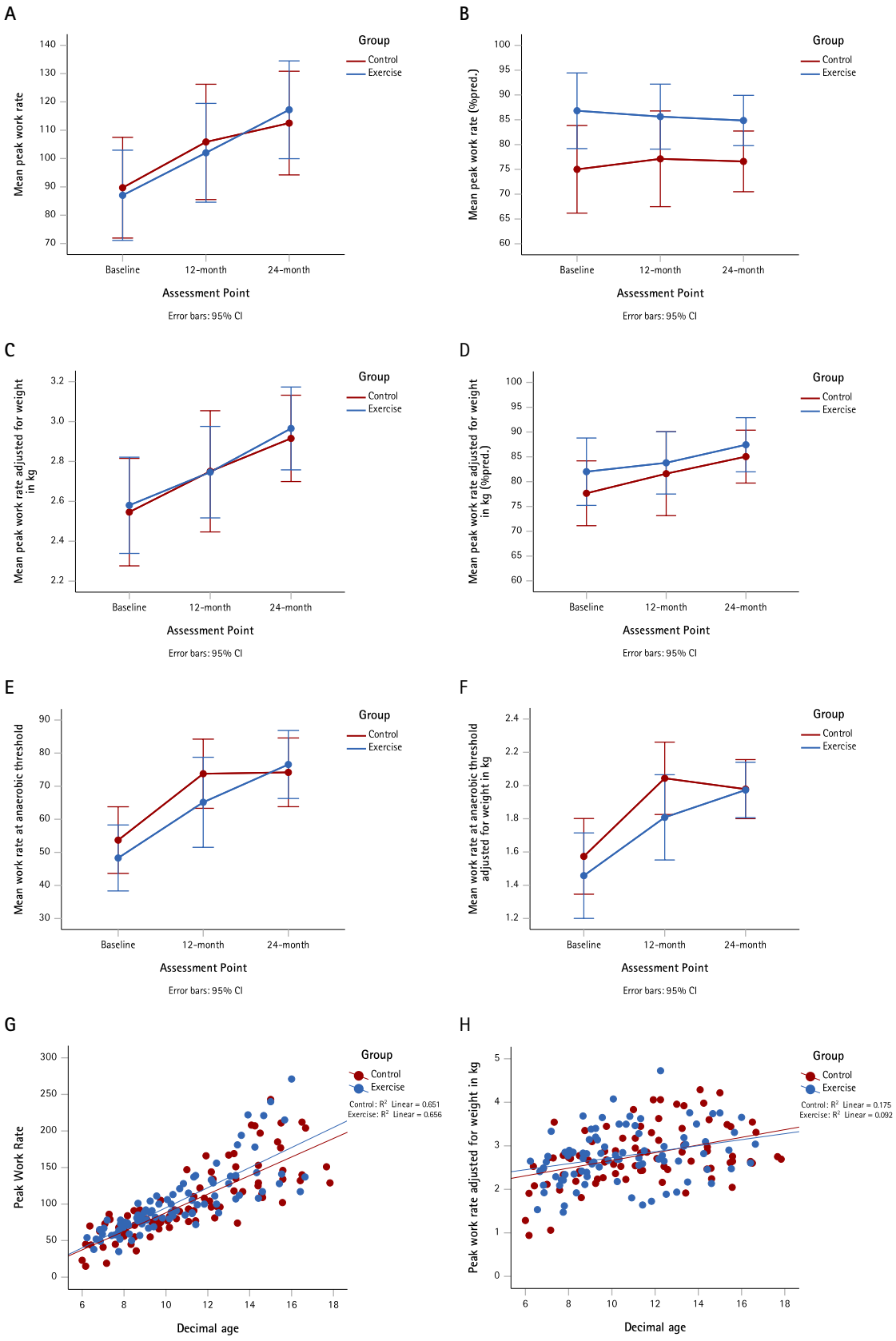

Figure 7-2: A-F: mean differences in peak work rate and work rate at the gas exchange threshold, and G: shows the change in peak work rate with age, and H: shows peak work rate adjusted for weight with age

7.3.3.2. Peak oxygen uptake

Analysis of VO_2 parameters are presented in **Table 7-5** and **Table 7-6** and in **Figure 7-3: A-H.** There were no significant between-groups differences in VO_{2peak} in ml·kg·min^{-1}, VO_{2peak} in ml·min^{-1}, and VO_2 at GET at baseline, 12- and 24-month assessments, which suggested that there was no effect of the exercise intervention on VO_2 parameters. However, each group had increased their VO_{2peak} >5 ml·kg·min^{-1}, between baseline (control= 36.9±7.3 vs. exercise=36.1±8.6) and 24-month assessment (control=42.5±7.5 vs. exercise=43.5±8.7). This equated to an increase in VO_{2peak} %pred. >10% between baseline (control= 84.4±14.0 vs. exercise=83.2±17.3) and 24-month assessment (control=96.0±15.9 vs. exercise=98.4±8.7).

Figure 7-3: G illustrates a negative relationship between VO_{2peak} in ml·min^{-1} and age, however, **Figure 7-3: H** illustrates no relationship between VO_{2peak} in ml·kg·min^{-1} and age in the exercise group, but a marginal positive relationship between VO_{2peak} in ml·kg·min^{-1} and age in the control group. This would suggest that improvements in VO_{2peak} were less likely to be a consequence of growth. Again, adjusted differences for all VO_2 outcomes were not significant and did not further explain the outcomes. Normal ranges for VO_{2peak} in ml·kg·min^{-1} in healthy populations are reported as between 46.4±6.0–48.1±64 ml·kg·min^{-1} for males, and 40.7±4.9–42.2±7.6 ml·kg·min^{-1} in females, aged 8-18 years respectively (Bongers et al., 2014a). Comparatively, this would suggest that at baseline both *Inspire-CF* groups presented with lower-than-normal VO_{2peak} in ml·kg·min^{-1} but had increased to near normal ranges after 24 months

Table 7-5: Analysis of between-group differences in VO_2 measurements

Variable	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
VO_{2peak} ml·kg·min^{-1}	baseline	36.9±7.3	36.1±8.6	-0.8 (-4.6, 3.0)	0.68
	12-month	39.5±7.4	37.6±9.6	-1.9 (-6.2, 2.4)	0.37
	24-month	42.5±7.5	43.5±8.7	1.0 (-3.1, 5.2)	0.63
VO_{2peak} %pred.	baseline	84.4±14.0	83.2±17.3	-1.2 (-8.8, 6.4)	0.75
	12-month	89.7±15.3	85.4±19.7	-4.2 (-12.9, 4.5)	0.34
	24-month	96.0±15.9	98.4±17.4	2.4 (-6.2, 11.0)	0.58
VO_{2peak} ml·min^{-1}	baseline	119.5±39.3	120.1±52.4	0.6 (-21.5, 22.7)	0.96
	12-month	117.7±45.7	112.4±49.7	-5.3 (-29.0, 18.3)	0.65
	24-month	122.2±41.5	125.7±56.7	3.5 (-21.9, 28.9)	0.78
VO_2 at GET ml·kg·min^{-1}	baseline	23.1±6.6	20.8±7.3	-2.3 (-5.6, 1.1)	0.19
	12-month	**27.4±7.5**	**23.5±8.4**	**-3.9 (-7.9, 0.0)**	**0.05***
	24-month	28.6±5.9	26.2±6.6	-2.3 (-5.5, 0.9)	0.16
VO_2 at GET ml·min^{-1}	baseline	771.5±311.7	695.1±391.1	-76.4 (-228.3, 75.5)	0.32
	12-month	1005.7±373.5	849.5±390.7	-156.2 (-345.7, 33.2)	0.10
	24-month	1024.3±408.7	1008.5±357.7	-15.7 (-217.0, 185)	0.88

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 7-6: Adjusted differences in VO_2 measurements

Variable	Duration	B	95%CI	*p*-value
ΔVO_{2peak} ml·kg·min^{-1}	baseline to 12-month	-1.8	-4.9, 1.2	0.24
	baseline to 24-month	1.5	-1.8, 4.9	0.37
ΔVO_{2peak} %pred.	baseline to 12-month	-3.1	-10.3, 4.0	0.38
	baseline to 24-month	3.7	-4.2, 11.7	0.35
ΔVO_{2peak} ml·min^{-1}	baseline to 12-month	-7.0	-19.4, 5.5	0.27
	baseline to 24-month	3.5	-9.2, 16.2	0.35
ΔVO_2 at GET ml·kg·min^{-1}	baseline to 12-month	-2.1	-6.5, 2.2	0.32
	baseline to 24-month	-0.5	-4.2, 3.2	0.79

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

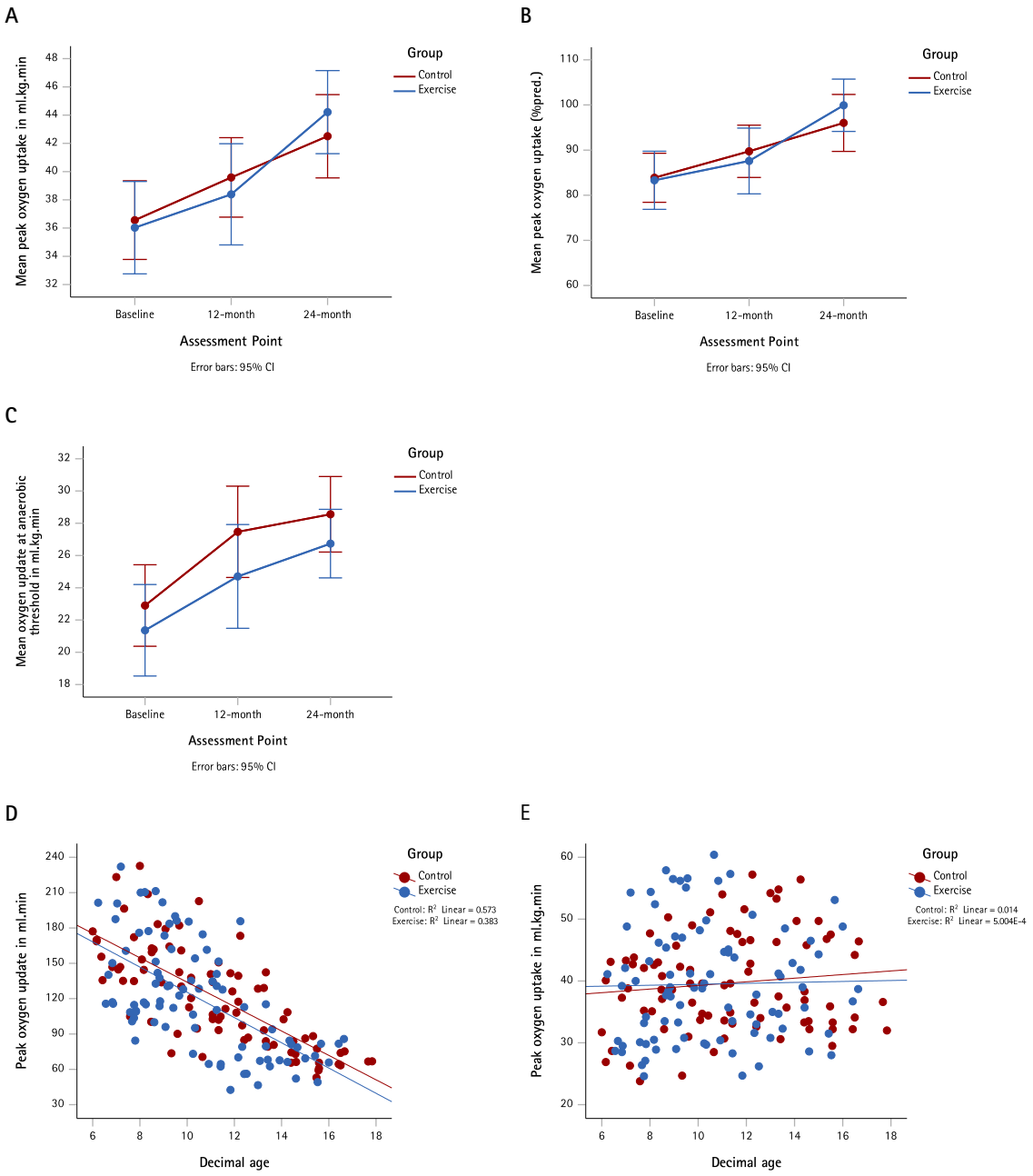

Figure 7-3: A-C: mean differences in peak oxygen uptake and oxygen uptake at the gas exchange threshold; D: shows the change in oxygen uptake with age, and E: shows peak oxygen uptake adjusted for weight with age

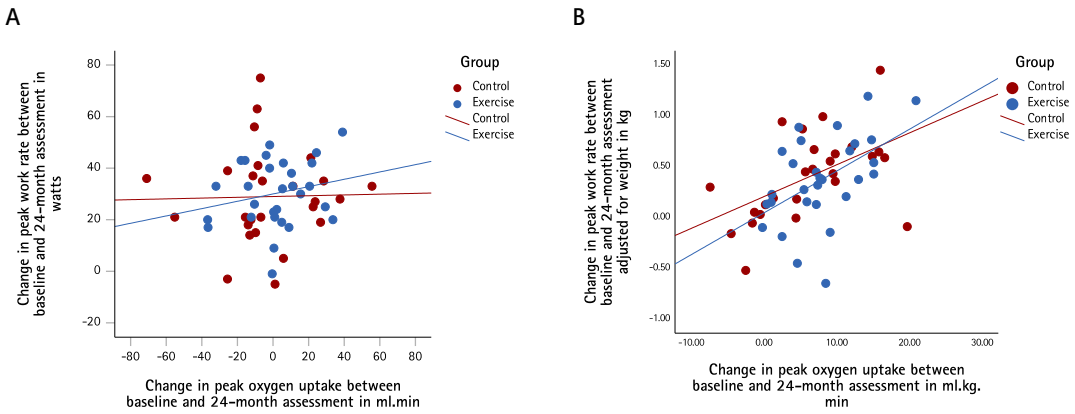

Figure 7-4: A & B show change in peak work rate versus peak oxygen uptake between baseline and 24-months

7.3.3.3. Heart rate

Mean HR_{peak} of >85% pred. was achieved by both groups at baseline, 12- and 24-month assessment points. At baseline, the exercise group achieved a slightly higher HR_{peak} %pred. (93.6±7.9) than the control group (89.9±8.6), this difference approached significance (3.7, 95%CI -0.6, 8.0, p=0.09). HR_{peak} %pred. was not significantly different at 12-months (2.6, 95%CI -1.1, 6.3; p=0.16), but again there was a significant between-group difference (control=93.6±6.9 vs. exercise=97.5±5.1) at 24-month assessment (3.9, 95%CI 0.6, 7.2, p=0.02). These results suggest that children in both groups were exerting themselves at a level that would be considered maximal. HR_{peak} was not significantly different at baseline and 12-month assessment points, but the exercise group (183.3±9.7 beats·min^{-1}) recorded a significantly higher HR_{peak} at 24-month assessment (7.1, 95%CI 0.8, 13.5, p=0.03) when compared to the control group (176.2±13.4 beats·min^{-1}). The adjusted differences in HR parameters were not significant.

Table 7-7: Analysis of between-group differences in HR, RER and V_E/VCO_2

Variable	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
HR_{peak}	baseline	168.8±17.2	174.4±15.7	4. (-2.9, 14.2)	0.19
	12-month	174.0±15.7	178.2±11.5	4.3 (-2.9,11.5)	0.24
	24-month	**176.2±13.4**	**183.3±9.7**	**7.1 (0.8, 13.5)**	**0.03***
HR_{peak} %pred.	baseline	89.9±8.6	93.6±7.9	3.7 (-0.6, 8.0)	0.09
	12-month	92.6±8.1	95.2±5.9	2.6 (-1.1, 6.3)	0.16
	24-month	**93.6±6.9**	**97.5±5.1**	**3.9 (0.6, 7.2)**	**0.02***
RER	baseline	1.1±0.1	1.1±0.1	0.0 (-1.0, 0.1)	0.78
	12-month	1.1±0.1	1.2±0.2	0.1 (-0.01, 0.1)	0.11
	24-month	1.2±0.1	1.1±0.1	0.1 (-0.1, 0.01	0.69
V_E/VCO_2	baseline	33.5±3.9	31.9±3.5	-1.6 (-3.5, 0.3)	0.10
	12-month	33.1±4.6	32.6±3.9	0.4 (-2.7, 1.8)	0.69
	24-month	32.5±3.7	32.6±4.5	0.1 (-2.2, 2.2)	0.98

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 7-8: Adjusted differences in HR, RER and V_E/VCO_2

Variable	Duration	B	95%CI	*p*-value
ΔHR_{peak}	baseline to 12-month	-1.7	-8.9, 5.6	0.65
	baseline to 24-month	-0.6	-8.6, 7.3	0.87
ΔHR_{peak} %pred.	baseline to 12-month	-0.5	-4.4, 3.4	0.79
	baseline to 24-month	-0.9	-5.2, 3.4	0.67
ΔRER	baseline to 12-month	0.05	-0.03, 0.13	0.25
	baseline to 24-month	-0.03	-0.09, 0.03	0.33
$\Delta V_E/VCO_2$	baseline to 12-month	1.2	-1.1, 3.6	0.29
	baseline to 24-month	1.9	-0.3, 4.2	0.09

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

7.3.4. Oxygen saturation and OMNI exertion scales

All children maintained an SpO_2 within normal range of 94-98% across all assessment points, and there were no between-group differences detected. Similarly, there were no significant between-group differences in OMNI exertion scales, with each group reporting similar levels of exertion.

7.3.5. Odds ratio for change in initial fitness level

After baseline measurements of CPET were completed, participants were categorised according to initial fitness level (Nixon et al., 1992, Gruber et al., 2011a). One child (exercise=1) had a low VO_{2peak} %pred. (≤58%); 28 children (control=13; exercise=15) had a medium VO_{2peak} %pred. (59 to 81%); and 31 children (control=17; exercise=14) had a high VO_{2peak} %pred. (≥ 82%). At 24-month assessment 2 children in the control group has dropped from a high to medium fitness level, and 6 children in the control group had increased from medium to high fitness levels. In the exercise group, 14 children had increased from medium to high fitness levels. Adjusted odds for participants moving from a lower to higher fitness category between baseline and 24-month assessment were 3.5 times higher (95%CI 2.35, 4.65; p=0.02) in the exercise group and this difference was statistically significant.

7.3.6. Cardiac monitoring

Except for an 11-year-old girl (genotype *p.Phe508del*/unknown; FEV_1 1.43L; and FEV_1 %pred.; pancreatic insufficient), there were no abnormal ECG traces reported in any children who completed CPET. This girl performed baseline spirometry testing and 10m-MSWT followed by CPET, and at rest, her ECG detected a delta wave, but she was asymptomatic (SpO_2 95%; HR 110 beats·min^{-1}, BP 118/60) and as per protocol, CPET was performed. She remained asymptomatic throughout the test, however the delta wave remained unresolved, so she was referred for cardiac monitoring and review, and a diagnosis of Wolff Parkinson White syndrome was confirmed (Douglas et al., 2015).

7.4. Discussion

The primary hypothesis was that a 24-month individually supervised exercise programme would elicit a significant between-group increase CPET outcomes of W_{peak} and VO_{2peak}, in favour of the exercise group. This was not achieved therefore this hypothesis should be rejected. However, *Inspire-CF* has shown that 24-months of individually supervised exercise had a significant effect on functional exercise capacity, and this may be clinically important too. Children were able to cover more distance and completed more levels of the 10m-MSWT, which suggested improved endurance fitness. Children who exercised achieved up to 90% of their age predicted HR during the 10m-MSWT and demonstrated significantly quicker recovery of HR, and perception of exertion to near resting levels, than the control group. However, the study did not demonstrate any significant impact of the exercise intervention on gold standard CPET parameters of W_{peak}, W_{GET}, VO_{2peak} and VO_2 at GET. This outcome was contradictory and therefore difficult to explain.

W_{peak} %pred. and $W{\cdot}kg^{-1}$ %pred., were significantly higher in the exercise group at baseline and 24-month assessments, however there was no relative change in these measurements in either group, including at the gas exchange threshold. This outcome was counter-intuitive given the significant increase in distance covered in the 10m-MSWT. At baseline, children demonstrated slightly lower than normal ranges of VO_{2peak} in $ml{\cdot}kg{\cdot}min^{-1}$ (~36.5 $ml{\cdot}kg{\cdot}min^{-1}$), but both groups demonstrated increases of 5.ml·kg·min in VO_{2peak} (~43.5 $ml{\cdot}kg{\cdot}min^{-1}$), which is an important outcome as a VO_{2peak} of 45 $ml{\cdot}kg{\cdot}min^{-1}$ and above is a significant predictor of lower mortality (Pianosi et al., 2005a). W_{peak} and peripheral muscle strength have been demonstrated to be significantly lower in children with CF compared to healthy controls (Hussey et al., 2002). The results of *Inspire-CF* showed that the exercise intervention had no effect on peripheral lower limb muscle strength, despite improvements and progression of training reported by the personal trainers.

Ledger et al. (2013) reported a significant increase of 229m (95CI 18.8, 349.7, p<0.01) in distance covered and 2 levels (95%CI 0.8, 2.6, p=<0.01) completed, whilst Urquhart et al. (2012) reported an increase of 208m (95% CI 55.43, 360.57, p=0.04). CPET was also undertaken during the *Frequent Flyer Programme* and showed an increase in VO_{2peak} by 4.9 $ml{\cdot}kg{\cdot}min^{-1}$ (95%CI 1.9, 8.7, p=0.02) and

VO_{2peak} %pred. by 14% (95%CI 1.9, 25.8, p=0.03). All children maintained an SpO_2 >94% during testing and no arrhythmias were detected. These changes were achieved in supervised exercise programmes that ran over 12-months, in the sickest group of children with significant lung disease and lower initial exercise capacity. *Inspire-CF* demonstrated a significant change of >200m in the 10m-MSWT and change of 5 ml·kg·min^{-1}, which replicated the *Frequent Flyer Programme* results. However, children in *Inspire-CF* took 24-months, rather than 12-months, to achieve the same effect. This may suggest that once-per week supervised training sessions may not be a high enough dose of exercise for children with milder CF lung disease to elicit a change in VO_2peak and W_{peak}.

All 8 randomised controlled trials included CPET parameters of W_{peak} and/or VO_{2peak} but did not include a 10m-MSWT (Braggion et al., 1989, Cerny, 1989, Schneiderman-Walker et al., 2000, Selvadurai et al., 2002a, Klijn et al., 2004, Orenstein et al., 2004, Santana-Sosa et al., 2012, Santana-Sosa et al., 2014). In **Chapter 2** a comprehensive overview of these studies was undertaken. A tabulated summary of the changes in W_{peak} and VO_{2peak} from the randomised controlled trials are provided **Table 2-3** for ease of reference.

Braggion et al. (1989) reported there were no significant between-group differences in VO_{2peak} after a 16-week exercise intervention, whilst Cerny (1989) did not report VO_{2peak} and there was no significant between group difference in W_{peak}. Schneiderman-Walker et al. (2000) found no significant between group differences in VO_{2peak} and Wpeak %pred. at baseline and there was no change in either outcome after the 36-month exercise intervention. Relatively high fitness levels shown in VO_{2peak} measurements were suggested as the reason no changes were shown. *Inspire-CF* was a structured, 24-month supervised exercise programme, and both groups had lower than normal VO_{2peak} measurements at baseline, and both groups increased their VO_{2peak} by 10% over the 12-months. However, the analysis of VO_{2peak} was lower at baseline in *Inspire-CF*, but similar W_{peak} outcomes were achieved.

Table 7-9: Summary of change in W_{peak} and VO_{2peak} outcomes

				Work rate		VO_{2peak}	
Author	Groups	Interventions	n	ΔMean	*p*-value	ΔMean	*p*-value
Braggion et al. (1989)	Healthy controls CF	Aerobic	10	0.2 W·kg^{-1}	>0.05	2.1 ml·kg·min^{-1}	>0.05
		Strength	10	0.3 W·kg^{-1}	>0.05	2.1 ml·kg·min^{-1}	>0.05
Cerny (1989)	CF Control	Postural drainage	8	0.26 W·kg^{-1}	<0.01*	-	-
	CF	Aerobic	9	0.44 W·kg^{-1}	<0.02*	-	-
Schneiderman-Walker et al. (2000)	CF control	Control	36	-2.5 W_{peak} %.pred.	0.56	-1.9 ml·kg·min^{-1}	NR
	CF	Aerobic	36	-1.68 W_{peak} %pred.	0.56	-1.8 ml·kg·min^{-1}	
Selvaduri et al. (2002)	CF Control	Control	21	-	-	-1.2 ml·kg·min^{-1}	>0.05
	CF	Aerobic	21	-	-	7.3 ml·kg·min^{-1}	<0.01*
	CF	Strength	22	-	-	0.7 ml·kg·min^{-1}	>0.05
Klijn et al. (2004)	CF control	Control	9	-0.3 W·kg^{-1}	>0.05	-0.6 ml·kg·min^{-1}	>0.05
	CF	Anaerobic	11	1.4 W·kg^{-1}	<0.001*	1.5 ml·kg·min^{-1}	>0.05
Orenstein et al. (2014)	CF	Aerobic (at 6-months)	26	-	-	-1.9 ml·kg·min^{-1}	>0.05
	CF	Strength (at 6-months)	30	-	-	-2.2 ml·kg·min^{-1}	<0.01*
	CF	Aerobic (at 12-months)	25	-	-	-0.9 ml·kg·min^{-1}	>0.05
	CF	Strength (at 12-months)	28	-	-	-1.7 ml·kg·min^{-1}	>0.05
Santana Sosa et al. (2012)	CF control	Control	11	-	-	2.2 ml·kg·min^{-1}	>0.05
	CF	Aerobic + upper & lower body strength	11	-	-	3.9 ml·kg·min^{-1}	0.002*
Santana Sosa et al. (2012)	CF control	Control	10	-	-	-0.6 ml·kg·min^{-1}	>0.05
	CF	Aerobic + upper & lower body strength exercise + inspiratory muscle training	10	-	-	6.9 ml·kg·min^{-1}	<0.001*

NR = Not reported; A dash (-) indicates that this outcome was not recorded as an outcome; *statistically significant

Selvadurai et al. (2002a) compared a control group to strength and aerobic training groups in a 2-week in hospital intervention in children with CF and found that VO_{2peak} did not improve between baseline and end of study for the control group and strength training groups but did significantly improve for the aerobic training group. However, children in this study were being treated with IV-antibiotic treatment during the intervention, so comparison with *Inspire-CF* outcomes were not feasible, as IV-antibiotic treatment likely masked the true effects of the exercise programme.

Klijn et al. (2004) compared a control group to an anaerobic exercise group in a 12-week study and found no significant between group differences in baseline VO_{2peak}. VO_{2peak} decreased in the control group but significantly increase in the exercise group. This study included a standardised, 2-day per week, supervised exercise programme of 30–45-minute duration, which was 1-session more than the *Inspire-CF* exercise group. Physiological benefits of exercise were demonstrated after 3-months of regular exercise training in the (Klijn et al., 2004) study; although the exercise group increased their VO_{2peak} the between-group differences did not suggest the once-per week training session was as effective as 2-sessions.

Orenstein et al. (2004) reported no significant differences in VO_{2peak} between baseline and 12-months for either an aerobic exercise group or a strength training group. However, there was a significant increase in W_{peak} %pred. between baseline and 12-months for the aerobic and strength training groups. Adherence was poor, as children reported they were bored with the training programme as it was focused on two single pieces of exercise equipment. The *Inspire-CF* exercise programme attempted to provide variation in exercise modes, and motivation to exercise was maintained, with 34/37 children completing the exercise intervention, despite the wide variation in attendance.

The same research team conducted the final 2-studies, Santana-Sosa et al. (2012) and Santana-Sosa et al. (2014) implemented 8-week intrahospital weight and aerobic training exercise programmes, with 4-weeks of detraining. After 8-weeks there was a non-significant decrease in VO_{2peak} for the control group, however the exercise group significantly increase their $VO_{2peak,}$ but the effects of training were lost within 4-weeks of completing the study. These studies demonstrated that 3 x

weekly intensive aerobic and strength training had a significant impact on VO_{2peak}, but that the benefits were not maintained. The loss of exercise capacity after 4-weeks illustrated that regular exercise is important to be maintained in children with CF.

There is no consensus on a single standardised test to determine exercise capacity in children with CF (Radtke et al., 2009), however, there is agreement that exercise capacity should be measured and any physiological limitations to exercise identified (Hebestreit et al., 2015) as this is important when prescribing exercise in children with CF (Williams et al., 2010). The European Cystic Fibrosis Exercise Working Group (Hebestreit et al., 2015) has advocated CPET as the gold-standard exercise test for determining maximal exercise capacity in children with CF. However, there have been differences in opinion in the CPET protocol that should be used, with some research groups promoting the Godfrey (1970) cycle test (Hebestreit et al., 2015), whilst others have proposed a steep ramp test (Bongers et al., 2015), or a maximal incremental test followed by a supramaximal verification phase (Saynor et al., 2013a). *Inspire-CF* included CPET, using the Godfrey (1970) that is widely used in paediatric population (Takken and Hulzebos, 2013, Takken et al., 2017), however the incremental step increases were likely too steep for some children (particularly 6-8 year olds), and they either stopped cycling or could not maintain cycle cadence, and therefore true exercise capacity may not have been determined. Peripheral muscle weakness rather than respiratory limitations appeared to limit some children's' ability to perform CPET. Saynor et al. (2013a) have proposed supramaximal verification $VO2_{peak}$ post-traditional CPET, and this may be a more viable alternative in future studies. Nevertheless, consideration of modification of the rate of incremental increases in Watts should also be considered for children with CF.

Only 2 out of 16 (12.5%) of paediatric CF units in the UK have access to CPET laboratories (Stevens et al., 2010), and there are considerable costs associated with setting up a CPET laboratory. However, the advantage of CPET is that continuous measurement of changes in gas flow, oxygen consumption (VO_2), work rate (W), respiratory exchange ratio (RER), minute ventilation to carbon dioxide production (V_E/VCO_2), heart rate (HR) and peripheral oxygen saturation (SpO_2) can be undertaken, and electrocardiogram (ECG) monitoring can be used to determine arrythmias (Radtke et al., 2009,

Hebestreit et al., 2015). In the absence of CPET, and/or to add to understanding of a child's exercise capacity, a field-based test could be performed as they are no-cost or low-cost, and do not require a dedicated space. Functional field-based incremental tests such as the 10m-MSWT (Selvadurai et al., 2003) may provide sufficient information about sub-maximal exercise capacity and limitations to exercise in CF (Radtke et al., 2009, Urquhart, 2011). CPET has not been adopted as a routine annual exercise test at GOSH, despite CPET being advocated as the gold-standard exercise test in CF (Hebestreit et al., 2015). The physiotherapy team reported that they were more likely to adopt the 10m-MSWT as the primary exercise test at annual review, following the publication of results of *Inspire-CF*.

Inspire-CF was the first 24-month randomised controlled trial that provided an individually supervised exercise programme to children with a wide range of disease severity, with less than a 5% dropout rate. The field of knowledge around the understanding of exercise capacity has been extended, but the study has also provided foundation level knowledge of dose response to exercise, which will help clinicians prescribe exercise. **Chapter 6** illustrated that children needed to complete at least 52 weeks of training to realise an increase in FEV_1. Clinicians could use this minimum level of exercise to prescribe and educate children and parents and carers on the importance maintaining a regular exercise routine.

Transparent and comprehensive reporting of 10m-MSWT and CPET data, as suggested by the European consensus document (Hebestreit et al., 2015), will provide an opportunity for comparative analysis of data for future research. The *Inspire-CF* research team demonstrated that with carefully coordinated, collaborative working with cardiologists and laboratory clinicians, CPET could be integrated into CF annual review, which may pave the way towards permanent clinical integration. This was also the first study to incorporate the newly validated 25-level 10m-MSWT (Elkins et al., 2009), which provided an opportunity to study functional exercise capacity at a level beyond the 15-level 10m-MSWT (Bradley et al., 1999), which some of the children enrolled in the *Frequent Flyer Programme* had maximally achieved. The test was reportedly more relatable to children than CPET, as they had already undertaken bleep tests during school physical education sessions, and this

should be considered as the primary field-based, incremental exercise test in hospitals and clinical settings where CPET is not available.

CPET was not routinely performed by children prior to enrolling in *Inspire-CF*, and despite significant time dedicated to preparation for testing, as recommended by Saynor et al. (2013b), there were challenges. The *Inspire-CF* research team were limited to 60-minutes laboratory time per session, and so a series of short videos on both exercise tests were developed to show to children in advance of testing, and this enabled children to ask questions about the tests. The neoprene masks used by the laboratory induced a sense of claustrophobia in several children, and this required a period of desensitisation with the mask. Children were provided with a mask and silicon mouth-coupler, to practice fitting at home and to wear for up to 30-minutes, and in most cases, children were able to perform, and repeat, an optimal CPET. *Inspire-CF* did not include a specific strength measurement test for upper limb and lower limb. Integration of a functional strength test may have provided additional information on changes in peripheral muscle strength that was not achieved during CPET.

Wolff Parkinson White (WPW) syndrome is a heart condition in which there is an abnormal extra electrical pathway that can lead to episodes of rapid heart rate (Dalili et al., 2014). Individuals with WPW are at higher risk of sudden cardiac death than the general population, although this is rare. Risk for WPW syndrome is stratified by the persistence or loss of pre-excitation during episodes of increased heart rate, such as with exercise. Low risk is associated with a disappearance of the delta wave during exercise. The single case of WPW identified during CPET was asymptomatic and was only identified when an ECG was performed. Arrythmias are not widely reported in children with CF, however cardiac monitoring is inexpensive and could be considered at annual review (Douglas et al., 2015).

7.5. Summary

Inspire-CF has demonstrated that a 24-month individually supervised exercise programme could significantly increase functional exercise capacity as demonstrated by a 10m-MSWT. However, counterintuitively the same positive effects were not demonstrated in CPET outcomes of W_{peak} and VO_{2peak}, which are considered the primary outcomes for evaluating aerobic fitness in children with CF. W_{peak} was maintained in the exercise group despite strength training and demonstrating an increase in distance covered during the 10m-MSWT, and $VO2_{peak}$ increased in both groups. *Inspire-CF* did recruit children with a wide range of milder lung disease severity, when compared to children in the *Frequent Flyer Programme*, where children with more severe lung function and lower baseline exercise capacity, demonstrated significant improvements in VO_{2peak}. Children enrolled in *Inspire-CF* demonstrated VO_{2peak} and W_{peak} ranges that were comparable to healthy children, and this is important as children with CF compare themselves to their healthy peers. Comparison with 8 randomised controlled trials was difficult as these studies were confounded by multiple variables such as simultaneous IV-antibiotic treatment with exercise, smaller sample sizes, and shorter-durations. However, some studies did demonstrate significant improvements in VO_{2peak} and W_{peak}, and these studies included 2-3 weekly sessions of exercise. Once-weekly exercise may not be enough to elicit a change in VO_{2peak} in children with milder lung disease. The *Inspire-CF* individually supervised exercise programme did not demonstrate clearly defined physiological benefits of exercise on cardiac, pulmonary, and metabolic outcomes, which had been the programmes objectives.

8.

CHAPTER 8. THE EFFECTS OF SUPERVISED EXERCISE ON QUALITY OF LIFE

8.1. Hypothesis, aim and objectives

The primary hypothesis of **Chapter 8** was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of an increase in CFQ-R domains of physical functioning, respiratory symptoms and treatment burden.

The aim was to undertake an evaluation of the quality of life children enrolled in *Inspire-CF*.

The objectives of this chapter were to:

- Determine differences, if any, in quality of life
- Determine differences, if any, in parents/carers and children's perceptions of quality of life

8.2. Methods

The methodology related to the *Inspire-CF* population was described in **Chapter 3**. The methods of statistical analysis were described in **Chapter 3, Subheading 3.10, pg. 99**. Children completed age-appropriate versions of the CFQ-R and their parents or carers completed the associated parent/carer version. The 3 primary quality of domains of interest were related to respiratory function, physical functioning, and treatment burden. Statistical significance was accepted at $p \leq 0.05$, and all data are presented as mean±SD, 95%CI and p-values unless otherwise stated.

8.3. Results

8.3.1. Participants quality of life

All 71 children completed an age appropriate CFQ-R at baseline, and all but the 4 drop-outs (**Chapter 5, Subheading 5.3.3, pg. 122**), completed the CFQ-R at subsequent assessments. After discussion with the GOSH CF Units Clinical Psychologist, who had previously validated the United Kingdom English language version of the CFQ-R (Bryon et al., 2009), a decision was made such that children would complete the baseline version of the questionnaire at 12- and 24-month, as all versions included the primary domains of interest. There are no published thresholds for what constitutes a low, moderate or high quality of life, however the minimally clinically import difference of the CFQ-R is considered a change of 4.0 points in children with stable health status (Quittner et al., 2009).

At baseline, the exercise group generally perceived that they had a lower quality of life than the control group. There were no significant between-group differences in any of the domains except for treatment burden and social interaction. The exercise group perceived that they had a significantly lower ability to cope with treatment burden (-10; 95%CI -19, -1; p=0.04) and when interacting socially (-12; 95%CI -20, -5; p=0.001). There were no significant differences in all domains at 12- and 24-month assessments, except the exercise group still perceived that they had a lower ability to interact socially (-9; 95%CI -17, -2; p=0.02).

After adjusting for baseline differences and accounting for minimisation factors, at 24-month the exercise group reported higher perceptions of quality of life in all domains. The exercise group showed significant and clinically important improvements in their perceived ability to cope with treatment burden (13; 95%CI 3, 22; p=0.01). The exercise group also showed an increase in their perception of physical functioning (9; 95%CI -0.5, 18; p=0.06), which approached statistical significance, but the change of >4.0 points indicated this was also clinically important. There were also clinically important improvements in respiratory symptoms, social limitations, body image and the 14+ domains of health perception and weight. **Figure 8-1** shows the between-group differences in the 8 common domains of the CFQ-R.

Table 8-1: Analysis of between-group differences in CFQ domains

	Assessment	Control	Exercise	Mean diff. (95%CI)	*p*-value
Primary domains					
Physical functioning	baseline	89±11	84±15	-5 (-11, 2)	0.16
	12-month	87±15	85±16	-2 (-10, 5)	0.57
	24-month	85±15	88±16	3 (-5, 11)	0.43
Respiratory symptoms	baseline	82±11	80±17	-2 (-9, 4)	0.49
	12-month	84±12	80±13	-4 (-10, 2)	0.17
	24-month	78±16	81±16	3 (-5, 11)	0.40
Treatment burden	**baseline**	**77±18**	**67±20**	**-10 (-19, -1)**	**0.04***
	12-month	71±22	64±25	-7 (-18, 5)	0.23
	24-month	71±20	75±19	4 (-5, 14)	0.39
Secondary domains					
Emotional state	baseline	78±14	73±12	-5 (-11, 1)	0.11
	12-month	78±13	74±12	-4 (-10, 2)	0.20
	24-month	75±14	74±13	-2 (-8, 5)	0.62
Social limitations	**baseline**	**80±16**	**68±17**	**-12 (-20, -5)**	**0.001***
	12-month	**79±15**	**69±15**	**-9 (-17, -2)**	**0.02***
	24-month	77±16	71±16	-6 (-13, 2)	0.16
Eating disturbances	baseline	88±16	89±14	1 (-6, 8)	0.86
	12-month	86±21	88±16	2 (-7, 11)	0.40
	24-month	86±22	90±19	4 (-6, 14)	0.26
Body Image	baseline	86±19	87±19	1 (-8, 10)	0.86
	12-month	86±22	84±23	-2 (-12, 9)	0.80
	24-month	83±25	88±21	5 (-6, 16)	0.36
Digestive symptoms	baseline	80±20	73±22	-7 (-17, 3)	0.16
	12-month	74±19	79±24	5 (-6, 15)	0.38
	24-month	81±22	74±23	-7 (-18, 4)	0.20
Health perceptions	baseline	78±12	61±23	-17 (-36, 3)	0.08
	12-month	64±25	59±21	-5 (-31, 12)	0.99
	24-month	58±13	61±14	3 (-13, 18)	0.89
Role limitations	baseline	76±21	79±21	3 (-19, 25)	0.67
	12-month	81±14	79±22	-3 (-23, 18)	0.78
	24-month	72±18	78±19	6 (-16, 28)	0.56
Vitality	baseline	59±12	60±18	1 (-16, 18)	0.91
	12-month	55±13	49±9	-6 (-19, 6)	0.28
	24-month	53±13	49±6	-5 (-17, 8)	0.29
Weight perceptions	baseline	83±36	79±31	-4 (-40, 31)	0.65
	12-month	96±12	71±30	-24 (-53, 4)	0.06
	24-month	92±15	83±28	-8 (-34, 17)	0.63

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 8-2: Adjusted changes in CFQ domains

	Assessment	B	95%CI	*p*-value
Primary domains				
ΔPhysical functioning	baseline to 12-month	2	-7, 10	0.70
	baseline to 24-month	9ǂ	-0.5, 18	0.06
ΔRespiratory symptoms	baseline to 12-month	-1	-9, 7	0.78
	baseline to 24-month	6ǂ	-4, 17	0.21
ΔTreatment burden	baseline to 12-month	2	-8, 12	0.72
	baseline to 24-month	**13ǂ**	**3, 22**	**0.01***
Secondary domains				
ΔEmotional state	baseline to 12-month	2	-5, 9	0.63
	baseline to 24-month	3	-5, 11	0.49
ΔSocial limitations	baseline to 12-month	3	-6, 11	0.54
	baseline to 24-month	6ǂ	-3, 15	0.17
ΔEating disturbances	baseline to 12-month	1	-9, 10	0.87
	baseline to 24-month	4	-5, 14	0.38
ΔBody image	baseline to 12-month	-2	-12, 9	0.78
	baseline to 24-month	6ǂ	-5, 17	0.30
ΔDigestive symptoms	**baseline to 12-month**	**13ǂ**	**0, 26**	**0.05***
	baseline to 24-month	1	-14, 15	0.93
ΔHealth perceptions#	baseline to 12-month	20ǂ	-14, 54	0.22
	baseline to 24-month	20ǂ	-10, 49	0.16
ΔRole limitations#	baseline to 12-month	-7	-34, 21	0.60
	baseline to 24-month	4	-24, 33	0.73
ΔVitality#	baseline to 12-month	-7	-3, 19	0.55
	baseline to 24-month	-4	-13, 23	0.56
ΔWeight perceptions#	baseline to 12-month	-6	-53, 41	0.78
	baseline to 24-month	10ǂ	-55, 74	0.73

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$; ǂ Minimally clinically important increase achieved.

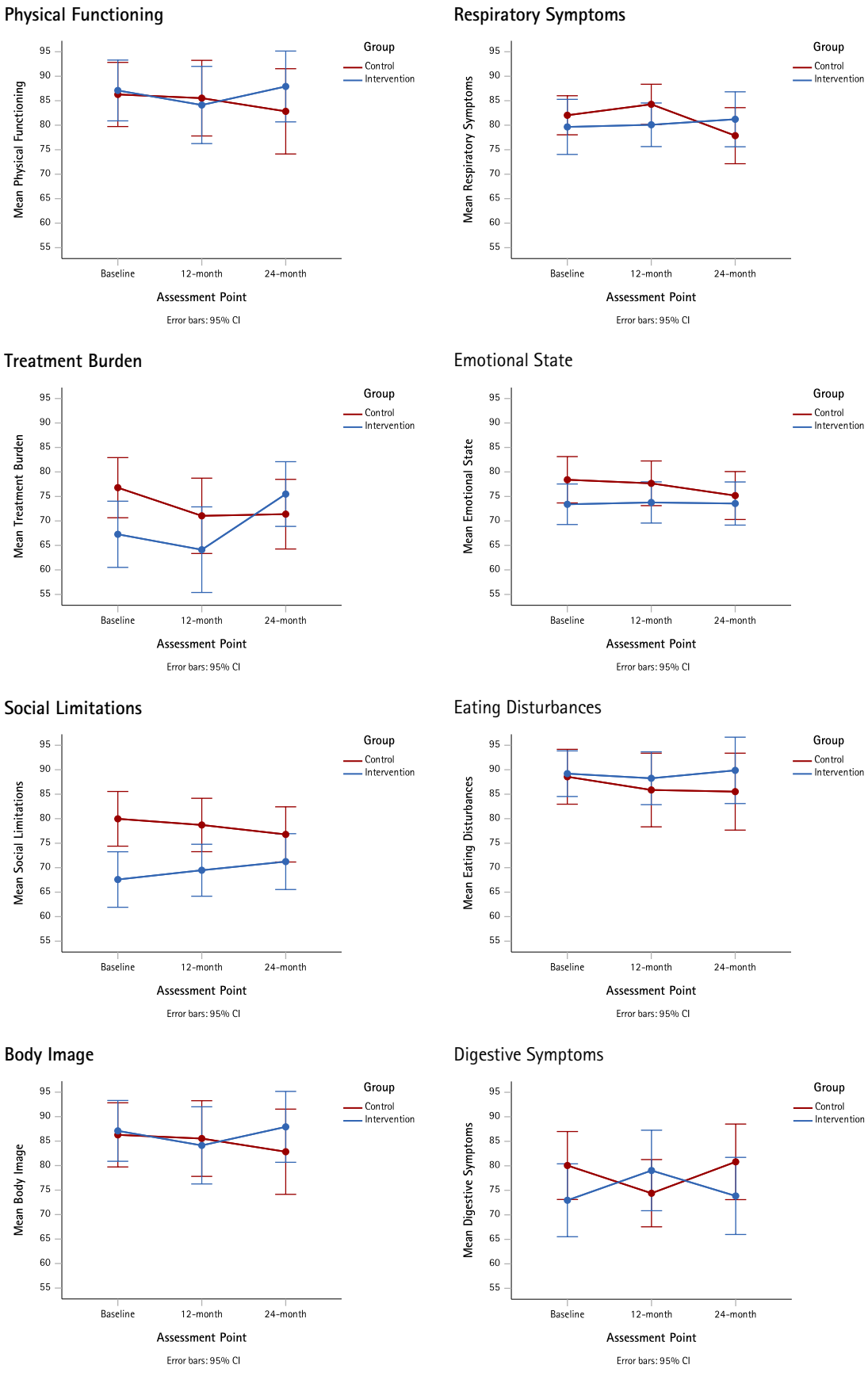

Figure 8-1: Between-group differences in the 8 common domains of the CFQ-R

8.3.2. Parent versus their child's perception of quality of life

Table 8-3 and **Table 8-4** show the results of analysis of between parent and child CFQ-R scores at baseline and 24-month. At baseline, both the control and intervention groups parents overestimated their child's physical functioning and respiratory symptoms, and significantly ($p \leq 0.05$) underestimated how children coped with their treatment burden. Both groups' parents also significantly overestimated ($p < 0.05$) their emotional state and significantly underestimated ($p < 0.05$) the impact of disturbances to eating. The control group parents significantly underestimated their child's perception of their body image.

After 24-months, children in the control group and their parents significantly ($p = 0.02$) differed in their perception of physical functioning, with parents overestimating their child's level of physical activity. However, the exercise group and their parents agreed on their perception of levels of physical functioning. Parents of the control group again overestimated their child's respiratory symptoms, whilst the exercise group's parents again agreed with their child's perception of their respiratory symptoms. Notably, both groups still significantly underestimated ($p < 0.05$) their child's ability to cope with their treatment burden. The between-group analysis of treatment burden in children in the control and exercise groups, had showed that the exercise group had significantly improve their perception of being able to manage their treatments burden. However, the significant widening of perception in treatment between the parents and children in the exercise group is difficult to interpret. Both groups' parents also significantly underestimated their children's perception of body image.

Figure 8-2 shows child and parent differences in perceptions of the 3 primary quality of domains of interest related to respiratory function, physical functioning, and treatment burden.

Table 8-3: Baseline differences in CFQ-R scores between parents and children

	Group	Child	Parent	Mean diff. (95%CI)	*p*-value
Primary domains					
Physical functioning	**Control**	**89±11**	**93±9**	**4 (0, 7)**	**0.03***
	Exercise	84±15	87±15	3 (-2, 8)	0.28
Respiratory symptoms	Control	82±11	83±14	1 (-3, 5)	0.66
	Exercise	80±17	82±18	3 (-2, 8)	0.26
Treatment burden	**Control**	**77±18**	**61±25**	**-16 (-25, -7)**	**0.001***
	Exercise	**67±20**	**60±21**	**-8 (-15, 0)**	**0.05***
Secondary domains					
Emotional state	**Control**	**78±14**	**85±14**	**6 (1, 11)**	**0.03***
	Exercise	**73±12**	**82±15**	**9 (3, 14)**	**0.003***
Social limitations	Control	80±16	77±20	-3 (-10, 5)	0.52
	Exercise	68±17	74±23	6 (-1, 14)	0.08
Eating disturbances	**Control**	**89±16**	**84±16**	**-5 (-9, -0.4)**	**0.03***
	Exercise	**89±14**	**81±24**	**-9 (-15, -2)**	**0.02***
Body image	**Control**	**86±19**	**73±22**	**-13 (-20, -6)**	**0.001***
	Exercise	87±19	83±23	-5 (-11, 2)	0.19
Digestive symptoms	Control	80±20	75±19	-5 (-11, 1)	0.10
	Exercise	73±22	73±22	0 (-9, 9)	0.95

Mean differences were calculated as exercise minus control group; *statistically significant $p \leq 0.05$

Table 8-4: 24-month differences in CFQ-R scores between parents and children

	Group	Child	Parent	Mean diff. (95%CI)	*p*-value
Primary Domains					
Physical functioning	**Control**	**85±15**	**91±11**	**6 (1,11)**	**0.02***
	Exercise	88±16	87±20	-1 (-6, 5)	0.79
Respiratory symptoms	Control	79±15	83±13	4 (-0.5, 9)	0.08
	Exercise	81±16	82±20	1 (-5, 6)	0.90
Treatment burden	**Control**	**72±20**	**64±20**	**-8 (-15, -2)**	**0.02***
	Exercise	**75±19**	**58±23**	**-17 (-26, -8)**	**0.0004***
Emotional state	**Control**	**76±14**	**82±13**	**6 (1, 12)**	**0.02***
	Exercise	74±13	78±17	6 (-2, 11)	0.17
Social limitations	Control	77±16	77±2	0 (-8, 9)	0.91
	Exercise	71±16	75±26	4 (-6, 13)	0.43
Eating disturbances	Control	86±22	82±22	-4 (-9, 2)	0.17
	Exercise	90±19	84±23	-6 (-13, 1)	0.11
Body image	**Control**	**83±25**	**73±25**	**-11 (-18, -4)**	**0.004***
	Exercise	**88±21**	**74±27**	**-14 (-23, -6)**	**0.002***
Digestive symptoms	Control	80±22	80±19	0 (-8, 8)	0.93
	Exercise	74±23	77±17	3 (-4, 11)	0.32

Mean differences were calculated as parent minus child; *Paired t-test test, statistically significant $p \leq 0.05$

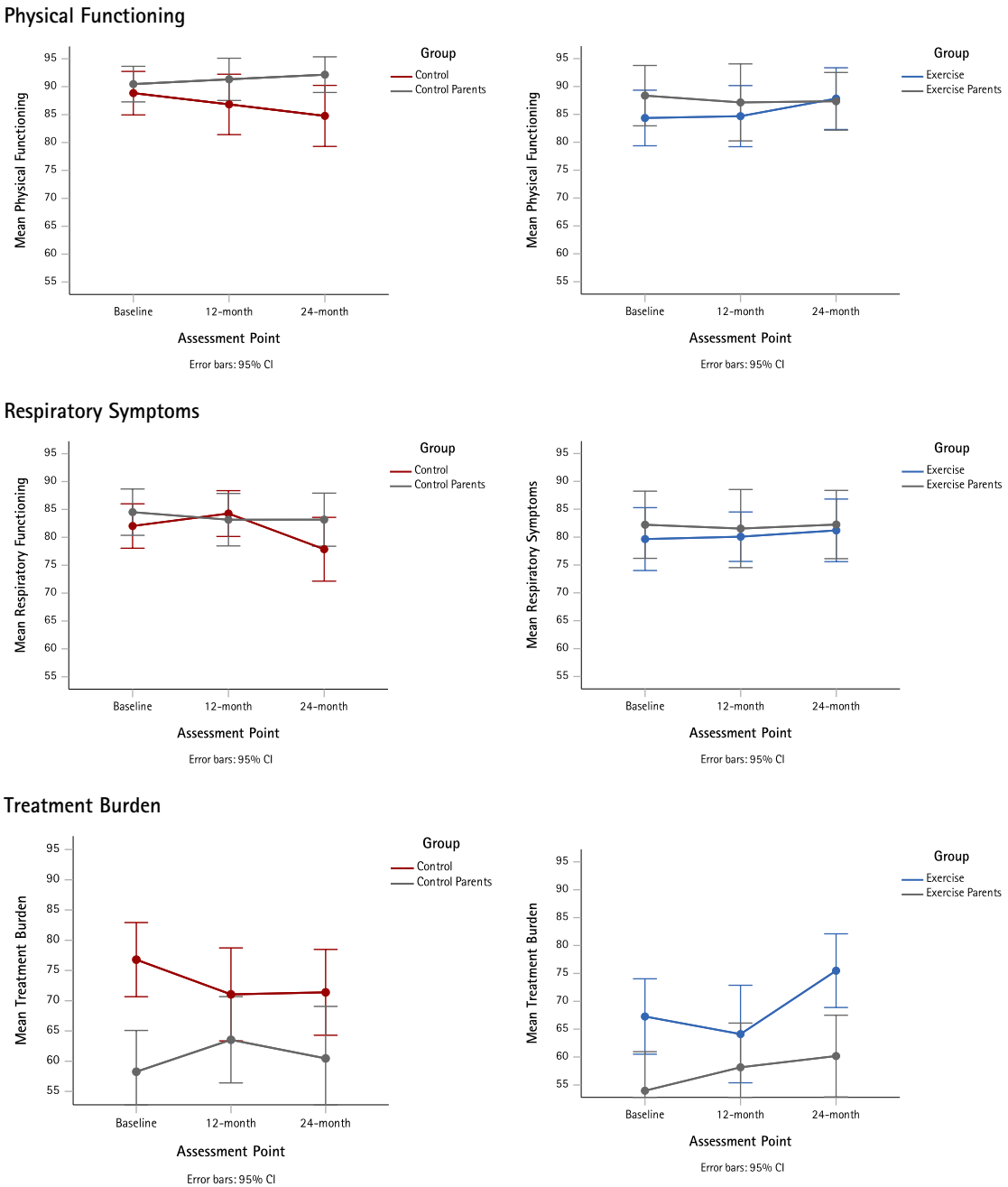

Figure 8-2: Differences between child and parent perceptions of physical functioning, respiratory symptoms, and treatment burden

8.4. Discussion

The primary hypothesis of *Inspire-CF* was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of an increase in CFQ-R domains of physical functioning, respiratory symptoms and treatment burden. This was not achieved for physical functioning or respiratory symptoms and therefore rejected; however, this hypothesis was achieved for perception of treatment burden, and the hypothesis should be accepted. At the start of *Inspire-CF*, the exercise group had a lower perception of their quality of life than the control group. Once weekly, individually supervised exercise training had a statistically and potentially clinically significant effect on the exercise groups perception of their treatment burden. This was unexpected. as the research team had theorised that the children in the exercise group may view the weekly exercise training sessions and contact with the personal trainer as additional burden. Additionally, the exercise group also demonstrated clinically significant improvements in their perceptions of physical functioning and respiratory symptoms, the two other primary domains of interest, and in perceptions of social limitations and body image. Children in the exercise group aged 14+ years also showed clinically important improvements in perceptions of their health and weight.

For the first time in a randomised controlled study in children with CF, positive and clinically significant changes in domains related to physical functioning, respiratory symptoms and treatment burden have been demonstrated, which suggested that individually supervised exercise had a positive effect on quality of life. Furthermore, all 8 common domains showed positive changes in the exercise group, as did 3 of the 4 domains common only to the 14+ age group.

Irrespective of age and disease severity, treatment burden is high in children with CF, as regimens may include regular airway clearance and inhaled mucolytic therapies, exercise, supplemental pancreatic enzyme replacement, gastrostomy tube feeding, diabetes maintenance, plus regular clinic appointments, hospital admissions and oral and IV-antibiotics (Sawicki and Tiddens, 2012). Adherence to daily treatment regimens is variable in both children (Prasad and Cerny, 2002) and this could have an adverse effect on health status, which in turn may impact on a quality of life.

Frequency of exacerbations of respiratory symptoms (Britto et al., 2002, Yi et al., 2004) changes in lung function and nutritional status (Bradley et al., 2001, Steinkamp and Wiedemann, 2002), age and gender (Gee et al., 2003), and exercise capacity and physical activity levels (Schneiderman et al., 2014) have all been associated with altered perception of health related quality of life.

Evaluation of health-related quality of life is therefore an important component of CF management (Orenstein et al., 1989, Quittner, 1998). Heath-related quality of life in CF was historically assessed using a non-disease specific questionnaire such as the Quality of Well-being Scale (Orenstein et al., 1989) as there were no disease specific quality of life questions. The Cystic Fibrosis Questionnaire (Henry et al., 2003) was subsequently developed, and has been translated into multiple languages, including United States English (Quittner et al., 2005), German (Wenninger et al., 2003) and Spanish (Olveira et al., 2010). The CFQ was revised (CFQ-R) to included age-appropriate versions, which are regularly completed at annual reviews in the UK (Bryon et al., 2009), to determine health-related quality of life in children. Parent or carers typically complete an associated version of the CFQ-R to the child version.

Comparisons of *Inspire-CF* results with 8 randomised controlled trials that evaluated the effects of exercise on quality of life in children with CF was difficult. This was primarily due to poor reporting of the outcomes or non-use of the disease specific CFQ-R in the previous trials. Nevertheless, good and very good quality of life as represented by the CFQ-R have been considered to be scores above 50 and 70 respectively (Santana-Sosa et al., 2012), and the *Inspire-CF* cohort reported scores above the very good range for all 8-common domains at each assessment point, though lower scores were reported in the health perception and vitality domains for children aged 14+. The *Inspire-CF* exercise group reported a clinically important change of 9 in perception of physical functioning, which was similar to the change of 12 reported by (Klijn et al., 2004). As was identified in **Chapter 2**, there were significant differences in the previous studies design, duration of study, level of supervision, and the structure of exercise prescription and training modes, when compared to *Inspire-CF*. These differences may have been the reason for between study differences in outcomes.

Schneiderman-Walker et al. (2000) created their own quality of life questionnaire, whilst Selvadurai et al. (2002a) and Orenstein et al. (2004) used the non-disease specific Quality of Life Scale (Kaplan et al., 1989), therefore direct comparisons with *Inspire-CF* were not feasible. Klijn et al. (2004) showed that after 12-weeks of interval type anaerobic training, the intervention group had a significant improvement (70±14 vs. 88±9; p,0.001) in CFQ-R physical functioning scores over the control group (83±19 vs. 87±18; p<0.2); but no changes in other domains. After 12-weeks of aerobic and strength training, Santana-Sosa et al. (2012) reported no change in CFQ-R domains; however in the same research groups later study of the same duration and exercise type, Santana-Sosa et al. (2014) found an overall trend (p=0.07) towards improved quality of life in the intervention group (629 vs. 688) but not in the control group (636 vs 638), on analysis of averaged CFQ-R scores. Reporting of averaged CFQ-R scores is not considered appropriate because the tool was designed such that researchers or clinicians could independently select the domains of interests (Quittner et al., 2005, Abbott et al., 2011). However, whilst domains could be prioritised, all domains should be reported, to allow for comparison to other studies.

Vitality, as a representative of energy and well-being in the 14+ age group did not improve, and reasons for this are not clear, but this may be due to children undertaking higher intensity of exercise but not with additional nutritional supplementation, as was required during the *Frequent Flyer Programme*. Hebestreit et al. (2014) reported similar findings and suggested that overload in intensity of exercise could be the reason why energy was decreased in this age group. Given that children in thee exercise group were under close supervision, and adaptations made as required to exercise intensity, it would seem less likely that this were the reason. Nevertheless, it is important that intensity and nutritional status be considered in future exercise-based studies.

One other randomised controlled trial that evaluated the effects of exercise on children with CF and included the CFQ-R as an outcome measure has been published since the conclusion of *Inspire-CF*. In a partially supervised 4-month study, Hommerding et al. (2015) used a graphically illustrated educational manual with instructions on how to perform a wide range of aerobic exercise such as jogging, swimming, walking, dancing, skipping and playing ball games, plus two-weekly telephone

calls to encourage children in their intervention group to exercise. There were no between-group differences in CFQ-R domains at baseline and after assessment at 1-month and 4-months there were again no improvements or differences between the two groups.

Children enrolled in the *Frequent Flyer Programme* (Ledger et al., 2013) showed clinically significant improvements in physical functioning (10; 95%CI -1, 21; p=0.07) and respiratory symptoms domains (6; 95%CI -9, 20; p+0.4) and these changes were comparable to the changes demonstrated in *Inspire-CF*. However, the *Frequent Flyer Programme* showed a worsening in perception of ability to cope with treatment burden (-4; 95%CI -20, 11; p=0.5), which was contrary to what was shown in *Inspire-CF*. This could be explained in part by the greater requirement for children with moderate-to-severe CF, to complete regular intensive home and hospital medical regimens. Urquhart et al. (2012) reported statistically and clinically significant improvements in the domains of physical functioning (59 to 83; p=0.001); respiratory symptoms (54 to 76; p=0.002) and treatment burden (41 to 61; p=0.002). These changes were higher than in both *Inspire-CF* and the *Frequent Flyer Programme* and may reflect the potentially positive impact of individually supervised exercise on quality of life as measured by the CFQ-R, in some sicker CF cohorts.

Parents and carers of children with CF have reported a lower perception of their children's quality of life (Thomas et al., 2006). In the 3 primary domains that were relevant in *Inspire-CF*, showed that parents in both groups, but more so in the parents of the control group, overestimated the physical functioning and respiratory symptoms of their children at baseline. The difference widened between parents and children in the control group, over the duration of the 24-months, whilst parents and children in the exercise group agreed in their scores. However, both sets of parents significantly underestimated their child ability to cope with treatment burden. The difference widened between parents and children in the exercise group, which was not expected. Children in the exercise group had reported a significant increase in the ability to cope with treatment burden over the duration of *Inspire-CF*. The reasons for this difference are unclear and difficult to interpret. Nevertheless, there were marked differences in parents and child perceptions of CFQ-R quality of life domains.

In line with published guidance on the reporting of quality of life measures (Abbott and Hart, 2005), *Inspire-CF*'s primary and secondary domains of interest were clearly identified and related directly to the exercise intervention. For standardisation, and to allow for comparison with future studies, all analyses at each assessment point were presented with both statistically and clinically significant results highlighted. Clinically important changes were indicated as these are considered important markers of clinical and health status and may be useful to clinicians.

Limitations of this analysis were that *Inspire-CF* was powered to show change in the primary endpoint of FEV_1 z-score over 24-months, therefore as the CFQ-R was a secondary endpoint, it was possible that the sample size for the study was not powered to clearly demonstrate statistically significant benefits of the exercise intervention on quality of life. Nevertheless, important clinical improvements were demonstrated. CF management guidelines recommend completion of a CFQ-R at annual review (Kerem et al., 2005, National Institute for Health & Care Excellence, 2017), and this was defined in the *Inspire-CF* protocol. All data for *Inspire-CF* were collected during periods of clinical stability (i.e., not within 2-weeks before or 2-weeks after IV-antibiotics or additionally prescribed oral antibiotics), and the CFQ-R was designed such that responses reflect the previous two weeks health status; therefore, it is plausible that the results reported by children do not reflect overall quality of life over the full 24-months periods.

8.5. Summary of Chapter 8

The results of Chapter 8 have shown that contrary to initial concerns, supervised exercise did not have a negative impact on the exercise groups perception of their ability to cope with their treatment burden. Children experienced clinically important increase in their health-related quality of life, which would suggest that once weekly, individually supervised exercise programme, does promote a sense of positive wellbeing. The CFQ-R domains account for the perception of quality of life in the 2-weeks prior to completion of the questionnaire, and therefore these results may not reflect the overall quality of life across the duration of the 24-months. There were wide differences in children and parents' perceptions of their quality of life, with either over or underestimation of children's quality of life, and clinicians should closely monitor for these differences. *Inspire-CF* demonstrated that exercise could positively impact on quality of life, and clinicians should continue to actively promote regular exercise as a mechanism to improve quality of life in children aged 6 years and over with CF.

9.

CHAPTER 9. THE EFFECTS OF SUPERVISED EXERCISE ON HEALTH ECONOMICS

9.1. Introduction

There are significant healthcare costs associated with maintaining optimal levels of CF medical treatment in the United Kingdom (Angelis et al., 2015). These healthcare costs, which exceeded £140 million between 2013-2014 and averaged £13,828 per patient excluding high cost drugs, were met by the NHS and were primarily related to acute hospitalisation and management of exacerbations (Department of Health, 2013).

Costs of care for adults and children with CF were individually categorised using an increasing complexity-adjusted structure that represented an NHS Commission on Specialised Services annual financial care package (**Table 9-1**). Categorisation of between Band 1 - Band 5 (**Table 9-2**) was based on an individual's annual therapy, hospitalisation, supplemental feeding, and CF-related complications requirements (Cystic Fibrosis Trust, 2012). The tariffs excluded high-cost drugs such as *Colomycin*®, *Tobramycin*®, *Dornase alfa*®, *Cayston*®, *Bronchitol*® and *Ivacaftor*® as these costs were met through bespoke negotiated agreements between the NHS and drug companies (Department of Health, 2013).

Specialist CF centres, such as GOSH, were paid a lump sum, and then used the tariff payments to meet all the healthcare costs for each child under their care, as well as costs incurred when care was provided by shared care hospitals (**Chapter 1, Subheading 1.8, pg. 36**). Any costs incurred over the allocated payment were borne by the specialist centres, and any surplus absorbed by the hospital. Annual reviews of the financial packages were undertaken in consultation with the Cystic Fibrosis Trust and the specialist CF centres, and an individual's banding may have been adjusted (increased or decreased) if their health status had changed.

Table 9-1: Banding tariffs for 2013-2014 with high-cost drugs excluded and adjusted for staff and cost changes and efficiency requirements.

		Children			Adults		
Band	Tariff	Proportion	No.	Cost in £	Proportion	No.	Cost in £
1	£5,210	21%	920	£4,795,440	10%	596	£3,102,555
1A	£7,707	6%	263	£2,026,787	1%	60	£458,952
2	£7,707	28%	1227	£9,458,339	13%	774	£5,966,374
2A	£12,457	22%	964	£12,011,787	35%	2084	£25,963,502
3	£19,067	20%	877	£16,714,132	30%	1787	£34,063,196
4	£34,388	2.70%	118	£4,069,510	8%	476	£16,382,443
5	£41,458	0.30%	13	£545,131	3%	179	£7,406,472
Total			4383*	£49,621,126#		5955*	£93,343,494#

*Patient numbers reported in the UK Cystic Fibrosis Registry Annual Data Report 2013 (Cystic Fibrosis Trust, 2014). Total cost of £142,949,620; #extrapolated using Department of Health (2013) banding tariffs; Average cost per UK patient of £13,828 excluding high cost drugs

Table 9-2: Cystic Fibrosis Banding Definitions Matrix

Banding definitions		Band						
		1	1A	2	2A	3	4	5
Therapies	Maximum number of total days of IV-antibiotics	0	14	28	56	84	112	≥113
	Nebulised antibiotics (*Pseudomonas aeruginosa* infection)		Yes					
	Long-term (>3 months) nebulised antibiotics or DNase			Yes				
	Long-term (>3 months) nebulised antibiotics and DNase				Yes			
Hospitalisations	Maximum numbers of days in hospital	0	7	14	14	57	112	≥113
Supplemental feeding	Nasogastric feeds				Yes			
	Gastrostomy					Yes		
Complications	CF Related Diabetes or *Allergic bronchopulmonary aspergillosis* w/o other complications				Yes			
	CF Related Diabetes and *Allergic bronchopulmonary aspergillosis*					Yes, and $FEV_1 \geq 60\%$	Yes, and $FEV_1 < 60\%$	
	Massive Haemoptysis or Pneumothorax					Yes, and $FEV_1 \geq 60\%$	Yes, and $FEV_1 < 60\%$	
	CF Related Diabetes and Gastrostomy					Yes, and $FEV_1 \geq 60\%$	Yes, and $FEV_1 < 60\%$	
	Nontuberculous mycobacterium treated or difficult to treat infections (e.g., *Methicillin-resistant Staphylococcus aureus* or *Burkholderia cepacia*) requiring other nebulised antibiotics e.g., *Meropenem®*, *Cayston®*, *Vancomycin®*.					Yes		

Adapted from: UK CF Registry Banding Matrix (Cystic Fibrosis Trust, 2012)

Despite the highest quality of medical management, admissions to hospital are associated with reductions in physical and social functioning (Yi et al., 2004) and quality of life (Britto et al., 2002). Admissions are also worrying and stressful periods for children and their families, who spend many days in isolated hospital rooms (Emerson et al., 2002). There is no consensus on specific length of stay required for IV-antibiotic therapy (Cystic Fibrosis Trust, 2009, Collaco et al., 2010), but mean length of stay has been previously reported as between 10-15 days (Agrawal et al., 2017, Cogen et al., 2017). However, length of stay depends on clinical status at admission, medications, intensity of therapy required and microbiology (Collaco et al., 2010), and all of these factors may impact on costs (Heimeshoff et al., 2012).

9.2. Hypothesis, aims and objectives

The primary hypothesis of **Chapter 9** was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of a decrease in hospital admissions, IV-antibiotic requirement, exacerbation of symptoms, and cost of healthcare.

The aim was to consider the number of, reasons for, and length of stay of admissions to hospital, the total IV-antibiotic requirement, and associated cost of healthcare in children enrolled in *Inspire-CF*. Understanding the cost of healthcare related to *Inspire-CF* may inform policy makers decisions, when considering the roll out of a similar programme into clinical practice. The objectives were to determine:

- Reasons for admission to hospital;
- Between-group differences, if any, in total number of annual admissions to hospital;
- Between-group differences, if any, in annual length of stay in hospital;
- Between-group differences, if any, in length of stay during routine admissions and for exacerbations of respiratory symptoms;
- Between-group differences, if any, in total IV-antibiotic requirement, and during to routine and exacerbation related admissions;
- Between-group differences, if any, in cost of healthcare.

9.3. Methods

9.3.1. Study perspective

Inspire-CF included an analysis of healthcare outcomes related to length of stay, IV-antibiotic requirements, and associated healthcare costs. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013) was used for the reporting of health economic outcomes.

9.3.2. Setting and location

All financial data related to children enrolled in *Inspire-CF* were received directly from the GOSH Financial Services Department following each annual audit. The reasons for admissions were collated from the GOSH Patient Information Management System.

9.3.3. Health outcomes

The following data were recorded for each participant:

- Reasons for admission to hospital, total number of admissions, length of stay, IV-antibiotic requirement (routine vs. exacerbation) and investigations related to endocrinology, gastroenterology and bronchoscopy, surgical procedures, sleeps studies and computed tomography (CT) scans.
- Healthcare costs related to staff resources (medical, nursing, pharmacy, therapies), ward admissions and outpatient clinics (including clinical supplies and overheads), surgical interventions, pathology, imaging, and high- and low-cost drugs.
- Costs related to the high-cost drug, *Ivacaftor*®.
- Spirometry and MBW costs.

9.3.4. Calculation of length of time in the study

Rolling admission was implemented for the study, therefore calculation of health economic outcomes was based on participants initial enrolment date into the study. The year preceding enrolment was defined as 365 days prior to each participant's baseline test. If the participant was already admitted to the hospital for IV-antibiotic treatment or any other reason at enrolment, a pragmatic decision was made to include the data for analysis if the patient had spent less than 7-days in hospital.

9.3.5. Data management

Healthcare costs were provided in the currency of British pounds (£) in a Microsoft Excel® spreadsheet, from the GOSH Financial Services Department. This data was cross referenced against participant data extracted from the GOSH Patient Information Management System. Any differences were flagged with the GOSH CF Unit Manager, who clarified any reasons for differences in coding or date inaccuracies, and where appropriate, these differences were reported to the financial services manager and updated in *Inspire-CF* databases.

9.3.6. Data analysis

Statistical processes were described in **Chapter 3, Subheading 3.10, pg. 99**. In brief, data were transferred for analysis into IBM® SPSS® Statistics 24 (Chicago, IL, USA), where independent t-tests were used to determine between-groups differences, and multiple linear regression was performed to model the changes in length of stay, IV-antibiotic requirements, and overall cost of healthcare. Relative risk was calculated to determine the likelihood of children to be admitted to hospital for an exacerbation of respiratory symptoms. Statistical significance was accepted at $p \leq 0.05$, and data are presented as mean±SD, 95%CI and p-values unless otherwise stated.

9.4. Results

9.4.1. Hospital admissions

At baseline, 41 of the 71 children (control=20 vs. exercise=21) had been admitted to hospital for at least 1-day in the 12-months preceding enrolment in *Inspire-CF*. Thirty children (control=14; exercise=16) had never been admitted to hospital, and of those, 13 children (control=4 vs. exercise=9) maintained a zero-admission status throughout the duration of the study. Therefore, the 58 children (control=30 vs. exercise=28) who had recorded at least 1 admission day were included in admission analysis.

9.4.2. Reasons for admissions

Table 9-3 shows the admission categories and total number of admissions to hospital for each group. There was a total of 241 individual hospital admissions to GOSH (n=227; 94.2%) and/or shared-care hospitals (n=14; 5.8%) during the 12-months preceding enrolment into *Inspire-CF*, and throughout the 24-month intervention period. In 97% of cases (n=236) children either started and/or ended their admission in GOSH. Planned IV-antibiotic treatment accounted for 49.0% of admissions (n=118), treatment of respiratory exacerbations accounted for 34.8% (n=84). All other categories accounted for the remaining 16.2% (n=39) of admissions. Seventeen children (control=10 vs. exercise=7) were admitted to hospital for the first time, and for at least one day, following enrolment into *Inspire-CF*.

Table 9-3: Descriptive statistics for admission category and number of admissions to hospital

		Control	Exercise	Total
Admission Type	Assessment	No. (%)	No. (%)	No. (%)
Routine	baseline	17 (65%)	9 (35%)	26 (11%)
	12-month	24 (57%)	18 (43%)	42 (17%)
	24-month	26 (52%)	24 (48%)	50 (21%)
Exacerbation (Respiratory)	baseline	19 (46%)	22 (55%)	41 (17%)
	12-month	11 (45%)	10 (55%)	21 (9%)
	24-month	12 (55%)	10 (45%)	22 (9%)
Exacerbation (Abdominal)	baseline	0 (0%)	0 (0%)	0 (0%)
	12-month	0 (0%)	1 (100%)	1 (0.4%)
	24-month	0 (0%)	0 (0%)	0 (0%)
Endocrinology	baseline	0 (0%)	0 (0%)	0 (0%)
	12-month	5 (83%)	1 (17%)	6 (2.5%)
	24-month	5 (71%)	2 (29%)	7 (3%)
Gastroenterology	baseline	1 (33%)	2 (67%)	3 (1.2%)
	12-month	1 (100%)	0 (0%)	1 (0.4%)
	24-month	1 (33%)	2 (67%)	3 (1.2%)
Bronchoscopy	baseline	2 (100%)	0 (0%)	2 (0.8%)
	12-month	1 (100%)	0 (0%)	1 (0.4%)
	24-month	0 (0%)	1 (100%)	1 (0.4%)
Surgical procedure	baseline	1 (100%)	0 (0%)	1 (0.4%)
	12-month	2 (50%)	2 (50%)	4 (1.7%)
	24-month	1 (100%)	0 (0%)	1 (0.4%)
Sleep Study	baseline	2 (100%)	0 (0%)	2 (0.8%)
	12-month	2 (50%)	2 (50%)	4 (1.7%)
	24-month	0 (0%)	1 (100%)	1 (0.4%)
CT scan	baseline	0 (0%)	0 (0%)	0 (0%)
	12-month	1 (100%)	0 (0%)	1 (0.4%)
	24-month	0 (0%)	0 (0%)	0 (0%)
Total		134 (56%)	107 (44%)	241 (100%)

9.4.4. Annual number of admissions to hospital for routine treatment and exacerbations

Table 9-4 and **Table 9-5** show the analysis of total number of annual admissions required to hospital for routine treatment and exacerbations of respiratory symptoms.

There were no significant between-group differences in the number of admissions required for routine IV-antibiotic treatment at baseline, 12- and 24-months assessments, however, each group did require more routine admissions between baseline and 24-months (**Figure 9-1: A**). After adjusting for minimisation factors, the exercise group were admitted to hospital slightly more often between baseline and 24-month assessments (0.2, 95% -0.3, 0.8; p=0.40), but this difference was not significant.

There were also no significant between-group differences in number of admissions for exacerbations at each assessment point, and each group required fewer admissions to hospital (**Figure 9-1: B**). The adjusted difference at 24-months, showed that the exercise group required slightly less admissions for exacerbations than the control group (-0.3; 95%CI -1.2, 0.5; 0.47), but this difference was not significant.

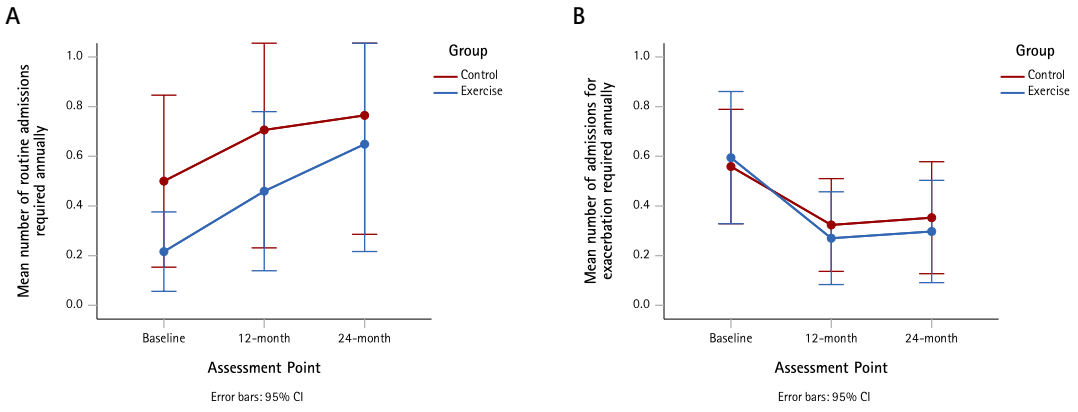

Figure 9-1: Mean number of admissions required annually for (A) routine treatment; and (B) exacerbation of respiratory symptoms

Table 9-4: Analysis of number of routine and hospital admissions annually

Variable	Assessment	Control	Total	Range	Exercise	Total	Range	Mean diff. (95%CI)	*p*-value
Number of hospital admissions per year									
Routine	baseline	0.9±1.2	17	0 - 4	0.6±0.6	8	0 - 2	-0.5 (-1.1, 0.1)	0.11
	12-month	1.0±1.6	24	0 - 5	0.8±1.2	17	0 - 3	-0.2 (-1.1. 0.6)	0.57
	24-month	1.2±1.6	26	0 - 4	1.1±1.5	26	0 - 4	-0.1 (-1.0, 0.9)	0.85
Exacerbations	baseline	1.2±0.4	19	1 - 2	1.5±0.5	22	1 - 2	0.3 (-0.1, 0.6)	0.10
	12-month	0.5±0.6	11	0 - 2	0.6±0.7	10	0 - 2	0.1 (-0.4, 0.5)	0.77
	24-month	0.6±0.8	12	0 - 2	0.6±0.8	10	0 - 2	0.0 (-0.6, 0.5)	0.86

Table 9-5: Adjusted differences in number of routine and hospital admissions annually

Variable	Duration	B	95%CI	*p*-value
ΔNumber of hospital admissions per year				
ΔRoutine	baseline to 12-month	0.1	-0.2, 0.4	0.60
	baseline to 24-month	0.2	-0.3, 0.8	0.40
ΔExacerbations	baseline to 12-month	-0.3	-1.0, 0.5	0.48
	baseline to 24-month	-0.3	-1.2, 0.5	0.47

9.4.5. Length of stay

The total number of days all children had spent in hospital was 2443 days (control=1302; vs. exercise=1141) and there was a wide range of total days spent in hospital each year (control=1 to 136 days vs. exercise=1 to 69 days). The shortest lengths of stay in hospital were related to 1-day admissions for starting of IV-antibiotics, before children were discharged to finish the course at home and day-case procedures or tests. The longest lengths of stay were related to exacerbation of respiratory symptoms.

Table 9-6 and **Table 9-7** show the analysis of total number days spent in hospital annually, average length of stay during all admissions, and average length of stay during admissions for routine treatment and exacerbations of respiratory symptoms.

9.4.6. Annual length of stay in hospital

At baseline the control group had spent an average of 21.5±18.6 days in hospital in the year preceding enrolment into *Inspire-CF*, whilst the exercise group had spent 20.6±13.5 days in hospital each year, but this difference was not significant (0.9 days; 95%CI -11.3, 9.4; p=0.85) (**Figure 9-2: A**). After 24-months of exercise, the exercise group (18.1±18.2 days) were spending less time in hospital annually than the control group (20.3±29.8 days), but these differences were not significant (-2 days; 95%CI -17.2, 9.8; p=0.67). After adjusting for minimisation factors the exercise group were spending less time in hospital but again, this difference was not significant (-3.3 days ; 95%CI –13.0, 6.4; p=0.50).

9.4.7. Length of stay during all admissions

There were no significant between-group differences in average length of stay of all admissions, at baseline, 12- and 24-month assessments. However, after adjusting for minimisation factors, the exercise group had spent less time in hospital during all admissions than the control group between baseline and 12-month assessments (-4.1 days; 95%CI -9.0, 0.9; p=0.10), and significantly less time between baseline and 24-month assessments (-4.7 days; -9.5, -0.02; p=0.05), and this difference is illustrated in **Figure 9-2: B**.

Table 9-6: Analysis of length of stay in hospital

Variable	Assessment	Control	Total	Range	Exercise	Total	Range	Mean diff. (95%CI)	*p*-value
Length of stay in hospital annually (in days)									
All admissions	baseline	21.5±18.6	430	0 - 67	20.6±13.5	432	0 – 62	-0.9 (-11.3, 9.4)	0.85
	12-month	19.3±19.6	406	0 - 60	18.2±16.0	346	0 - 69	-1.1 (-12.7, 10.4)	0.85
	24-month	20.3±29.8	466	0 - 136	18.1±18.2	363	0 - 56	-2.2 (-17.2, 13.0)	0.78
Length of stay during admissions (in days)									
All admission types	baseline	12.2±5.4	231	0 - 28	14.8±7.3	297	3 - 35	2.7 (-1.5, 6.8)	0.20
	12-month	11.4±4.2	182	0 - 17	12.3±3.8	185	4 -19	1.0 (-2.0, 3.9)	0.50
	24-month	10.6±4.8	181	0 - 23	9.8±4.4	156	2 - 14	-0.9 (-4.1, 2.4)	0.59
Routine	baseline	12.4±2.3	218	0 - 49	13.6±0.7	109	0 - 27	1.2 (-0.7, 3.2)	0.20
	12-month	13.2±1.8	320	0 - 70	12.3±2.3	213	10 - 42	-1.0 (-3.0, 1.1)	0.33
	24-month	12.2±2.7	328	0 - 57	13.2±1.4	317	10 - 54	1.0 (-1.0, 3.0)	0.24
Exacerbations	baseline	15.1±5.5	283	10 - 31	16.2±4.6	356	13 -62	1.0 (-2.7, 4.8)	0.57
	12-month	13.0±3.7	146	0 - 32	14.4±2.6	161	0 - 28	1.5 (-1.8, 4.5)	0.37
	24-month	17.2±10.2	231	0 – 88	12.2±0.7	123	0 - 26	-5.0 (-12.9, 1.20)	0.08

Mean differences were calculated as exercise minus control group

Table 9-7: Adjusted differences in length of stay in hospital

Variable	Duration	B	95%CI	*p*-value
Δ Length of stay in hospital annually (in days)				
ΔAll admissions	baseline to 12-month	-1.1	-8.2, 6.0	0.76
	baseline to 24-month	-3.3	-13.0, 6.4	0.50
Δ Length of stay during admissions (in days)				
ΔAll admission types	baseline to 12-month	-4.1	-9.0, 0.9	0.10
	baseline to 24-month	**-4.7**	**-9.5, -0.02**	**0.05***
ΔRoutine	baseline to 12-month	-0.2	-11.2, 10.8	0.96
	baseline to 24-month	1.9	-4.4, 8.2	0.56
ΔExacerbations	baseline to 12-month	-2.4	-12.9, 8	0.51
	baseline to 24-month	-6.5	-39.5, 26.5	0.24

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

9.4.8. Length of stay during routine admissions and admissions for exacerbations

There were no significant between-group differences in average length of stay of all routine admissions, at baseline, 12- and 24-month assessments. However, **Figure 9-2: C** shows the variability in both groups over the 24-month intervention period. After adjusting for minimisation factors, the exercise group had spent slightly less time in hospital between baseline and 12-month assessments (-0.2 days; 95%CI -11.2, 10.8; p=0.96), but 1.9 days (95%CI -4.4, 8.2; p=0.56) more in hospital between baseline and 24-months, however these differences were not significant. Similarly, there were no significant between-group differences in average length of stay during exacerbations, at baseline, 12- and 24-month assessments, although the exercise group had spent between 1.0 and1.5 days more in hospital at baseline and 12-months respectively. However as is illustrated in **Figure 9-2: D**, at 24-months the exercise group were spending less time in hospital (-5 days; 95%CI -12.9, 1.2; p=0.08) than the control group and this difference approached statistical significance. After adjusting for minimisation factors, this difference remained but was not significant (-6.5 days; 95%CI -39.5, 26.5; p=0.24).

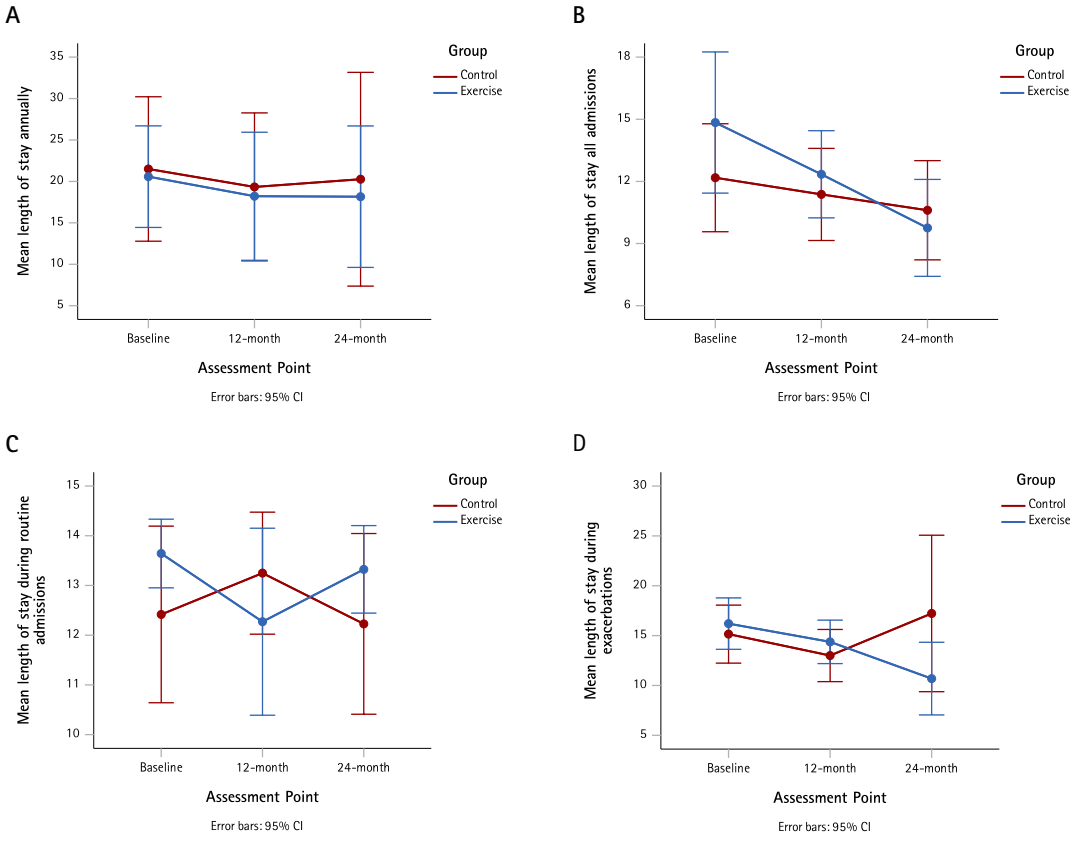

Figure 9-2: Mean length of stay in days in hospital (A) annually; (B) during all admissions; (C) during routine admissions; and (D) during admissions for exacerbation of respiratory symptoms.

9.5. Total IV-antibiotic requirement

Thirty-one children (control=15 vs. intervention=16) had not required any IV-antibiotic treatment in the 12-months preceding enrolment in *Inspire-CF*, and 22 of these children (control=8 vs. intervention=14) maintained this status throughout the duration of the study. Nine children (control=6 vs. intervention=3) who had not required any IV-antibiotic treatment in the 12-months preceding enrolment in *Inspire-CF* received IV-antibiotic treatment during the subsequent 24-months. A total of 49 children (control=26 vs. exercise=23) who had received IV-antibiotic treatment in the 12-months preceding enrolment and/or during the 24-month intervention period were included in analysis. IV-antibiotics were mostly delivered in hospital, but some children (control=10 vs. exercise=10) did complete parenteral IV-antibiotics at home.

Table 9-8 and **Table 9-9** show the analysis of total IV antibiotic, and the requirements during routine admission and during admissions for exacerbations.

At baseline the exercise group had spent more time on IV-antibiotics than the control group, however these differences were not statistically significant (1.8; 95%CI –1.9, 5.4; p=0.33). There were no between group differences at 12-month assessments (-0.1; 95%CI -1.9, 1.6; 0.86). At 24-month assessment the exercise group had spent less time (-1.4; 95%CI -3.7, 0.9; p=0.23) on IV-antibiotics than the control group, but this difference was not significant. However, after adjusting for minimisation factors, there was a significant decrease in the exercise groups total IV-antibiotic requirement at both 12-month (-4.8, -9.6, -0.02; p=0.05) and 24-month assessments (-5.0; -9.5, -0.5; p=0.03).

Table 9-8: Analysis of IV-antibiotic requirement

Variable	Assessment	Control	Total	Range	Exercise	Total	Range	Mean diff. (95%CI)	*p*-value
Total IV-antibiotics (During admissions and home)	Baseline	14.5±5.1	276	8 - 28	16.3±6.0	326	12 - 35	1.8 (-1.9, 5.4)	0.33
	12-month	13.3±1.9	213	9 – 17	13.2±2.8	197	8 - 19	-0.1 (-1.9, 1.6)	0.86
	24-month	13.4±3.3	241	5 - 23	12.0±3.3	191	0 - 14	-1.4 (-3.7, 0.9)	0.23
Routine	baseline	12.4±2.3	112	8 – 16	13.6±0.7	96	12 - 14	1.2 (-0.7, 3.2)	0.20
	12-month	13.2±1.8	146	10 -17	12.3±2.3	98	8 - 14	-1.0 (-3.1, 1.1)	0.33
	24-month	12.2±2.7	135	5 -14	13.3±1.1	120	11 -15	1.1 (-0.8, 3.0)	0.24
Exacerbation	baseline	15.2±5.5	243	10 - 28	16.2±4.7	243	12 - 31	1.0 (-2.7, 4.8)	0.57
	12-month	13.0±3.7	130	7 - 19	14.4±2.6	115	11 - 19	1.4 (-1.8, 4.5)	0.37
	24-month	17.2±10.2	155	10 - 44	12.2±0.7	86	11 - 13	-5.0 (-12.9, 2.8)	0.18

Mean differences were calculated as exercise minus control group; *Statistically significant $p \leq 0.05$

Table 9-9: Adjusted-differences in IV-antibiotic requirement

Variable	Duration	B	95%CI	*p*-value
ΔTotal IV-antibiotics (During admissions and home)	**baseline to 12-month**	**-4.8**	**-9.6, -0.02**	**0.05***
	baseline to 24-month	**-5.0**	**-9.5, -0.5**	**0.03***
ΔRoutine	baseline to 24-month	-0.2	-11.2, 10.8	0.96
	baseline to 24-month	1.9	-4.4, 8.2	0.44
ΔExacerbation	baseline to 12-month	-2.4	-12.9, 8.0	0.51
	baseline to 24-month	-6.5	-39.5, 26.5	0.24

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status. *Statistically significant $p \leq 0.05$

9.5.1. Comparison of routine IV-antibiotic requirements

Sixteen children (control=9 vs. exercise=7) had received IV-antibiotic treatment during a planned admission. Twelve of these children (control=8 vs. intervention=4) were on a regular regimen of 3, 4 or 6-monthly admissions for prophylactic IV-antibiotic treatment, typically pre-scheduled as a 14-day admission, and these regimens were maintained for the duration of *Inspire-CF*. Seven children (control=3 vs. exercise=4) were admitted for routine IV-antibiotics for the first time after enrolment. A total of 25 children (control=11 vs. exercise=14) had been admitted for at least one planned set of IV-antibiotics and were included in analysis.

Total IV-antibiotic requirement decreased in both groups (**Figure 9–1: A**), and there were no significant between-group differences in IV-antibiotic requirement during routine admissions, at baseline, 12- and 24-month assessments. However, **Figure 9–3: B** shows the variability in both groups over the 24-month intervention period. After adjusting for minimisation factors, the exercise group had spent slightly less time in hospital between baseline and 12-month assessments (-0.2; -11.2, 10.8; 0.96), and 1.9 days (95%CI -4.4, 8.2; 0.44) more in hospital between baseline and 24-months, however these differences were not significant.

9.5.2. Comparison of IV-antibiotic requirements during exacerbations

A total of 42 children (22=control vs. exercise=20) had received treatment for at least one exacerbation and were included in analysis. There were no significant between-group differences in IV-antibiotic requirement during exacerbations, at baseline, 12- and 24-month assessments, although the exercise group had spent 1-1.4 days on IV-antibiotics at baseline and 12-months. However as is illustrated in **Figure 9–3: C,** the exercise group required less IV-antibiotics at 24-months (-5; 95%CI -12.9, 2.8; p=0.88) than the control group, but this difference was not significant. However, after adjusting for minimisation factors, the exercise group had required few IV-antibiotic days between baseline and 12-months (-2.4; -12.9, 8.0; p=0.81) and between baseline and 24-months (-6.5; -39.5, 26.5; p=0.24), but again these differences were not significant.

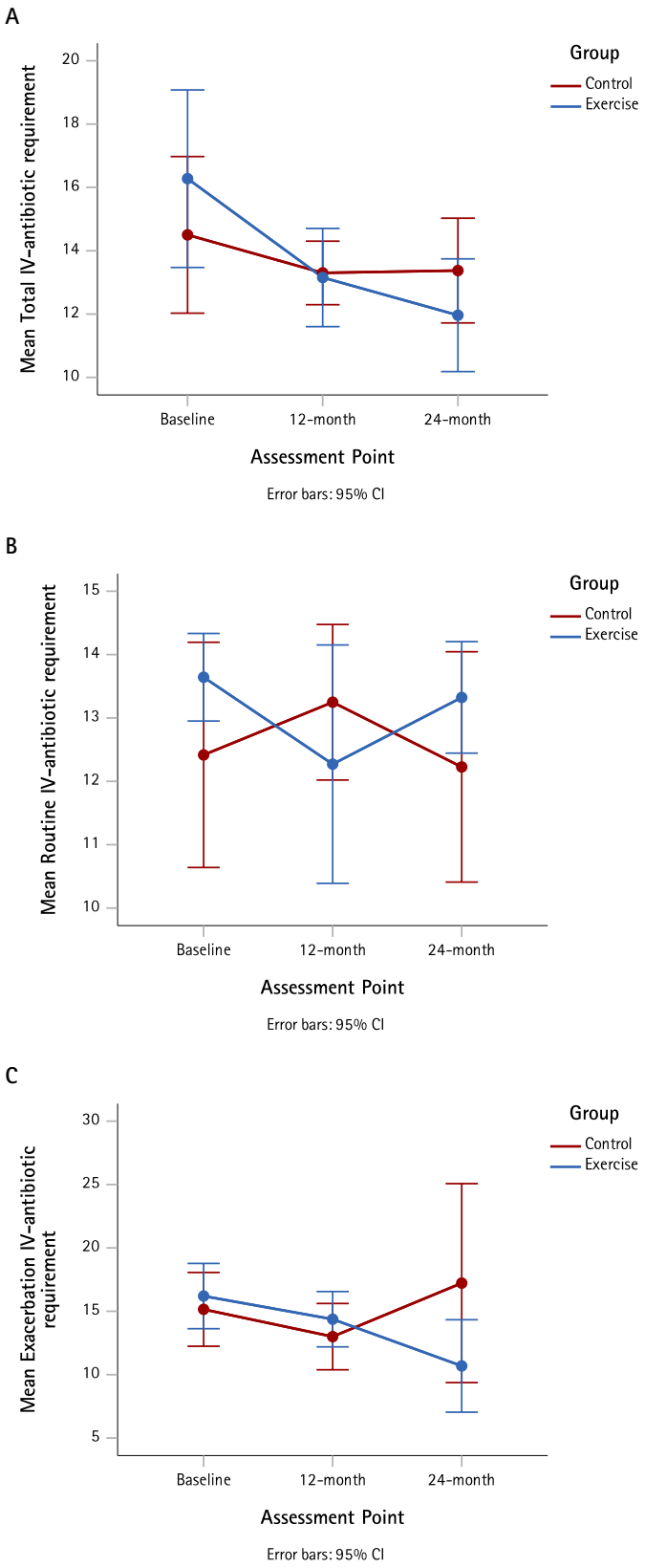

Figure 9-3: Mean of the (A) total IV-antibiotic requirement; (B) during routine admissions; and (C) during admissions for exacerbations of respiratory symptoms

9.5.3. Similarity of length of stay and IV-antibiotic requirements

The results of analysis of total length of stay and total IV-antibiotic requirement were similar, as would be expected, given that children were typically admitted to hospital to complete a course of 14-days of IV-antibiotics. The slight variation in outcomes may be because some children completed part of their IV-antibiotic course at home. This would also be true of the analysis of routine admissions and admissions for exacerbations.

9.5.4. Relative risk for respiratory exacerbation

At baseline, 30 of the 71 children (control=15 vs. intervention=15) had received IV-antibiotic treatment for an exacerbation of respiratory symptoms in the 12-months preceding enrolment in *Inspire-CF*. The relative risk (1.0; 95%CI 0.53, 1.66) suggested that both groups were just as likely to have been hospitalised for an exacerbation in the year preceding enrolment, and this result was not significant.

During the 24-months programme, 28 children (control=15 vs. exercise=13) were admitted for a respiratory exacerbation, of which 12 children (control=7 vs. exercise=5) were admitted for their first time. At 24-month assessment, the relative risk for requiring hospitalisation for an exacerbation after enrolment in *Inspire-CF* was lower in the exercise group (0.82; 95%CI 0.46, 1.47) though this was not significant. The relative risk of requiring hospitalisation for a first-time exacerbation was lower in the exercise group (0.66; 95%CI 0.23, 1.87), but again this was not significant.

9.5.6. Overall health care costs

Overall cost of care for the 71 children enrolled in *Inspire-CF* was £5,028,015 (control=£2,532,213 vs. exercise=£2,495,802) that included £464,852 (control=£156,730 vs. exercise=£308,122) in costs related to *Ivacaftor*®. There was an adjustment to the GOSH accounting algorithms in the first 12-months of the study, such that ward overheads were included in cost allocations. Consequently, there was a steep increase in costs for both groups at 12-month assessments.

No children were prescribed *Ivacaftor*® at baseline, however 3 children (control=1 vs. exercise=2) were prescribed and subsequently started the drug in the first 12-months of the study. One child (female; aged 15 years) in the exercise group who had been prescribed *Ivacaftor*®, dropped-out of *Inspire-CF* at 12-months. The total cost of the drug was £464,852, with allocated costs between baseline and 12-month assessment of £385,328 (control=£106,872 vs. exercise=£278,456) and between 12- and 24-month assessment of £79,524 (control=£49,857 vs. exercise=£29,666).

Figure 9-4: A illustrates the total annual cost of care for each group including *Ivacaftor*® costs, and **Figure 9-4: B** illustrates the total cost of care for each group excluding *Ivacaftor*® costs.

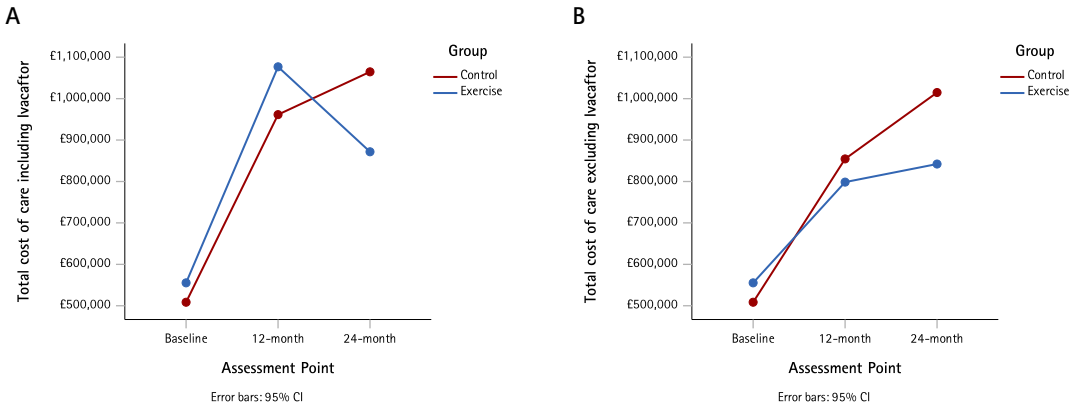

Figure 9-4: Total annual costs per group including (A) Ivacaftor® costs and (B) excluding Ivacaftor® costs

Table 9-10: Total costs of healthcare

	Staffing				Setting		Clinical		Intervention			Drugs			
Assessment	Medical	Nursing	Pharmacy	Therapies	Ward	Outpatients	Supplies	Overheads	Surgical	Imaging	Pathology	Lo-cost	Hi-cost	Ivacaftor	Total Cost
Baseline	£292,237	£177,026	£11,837	£86,962	£247,369	£16,854	£62,902	£15,084	£43,538	£18,422	£33,530	£40,426	£17,791	£0	£1,063,978
Control	£150,290	£82,451	£4,262	£40,270	£123,477	£8,008	£22,382	£0	£21,431	£7,817	£18,899	£20,763	£8,545	£0	£508,595
Exercise	£141,948	£94,575	£7,575	£46,691	£123,892	£8,846	£40,520	£15,084	£22,107	£10,605	£14,631	£19,663	£9,246	£0	£555,383
12-month	£212,688	£245,478	£20,399	£113,580	£257,098	£19,800	£217,016	£18,221	£17,320	£11,785	£36,162	£61,375	£421,040	£385,328	£2,037,289
Control	£116,503	£146,817	£12,533	£63,373	£149,335	£10,608	£133,888	£10,645	£8,534	£5,775	£19,423	£40,484	£136,581	£106,872	£961,369
Exercise	£96,185	£98,662	£7,867	£50,207	£107,763	£9,192	£83,128	£7,576	£8,786	£6,010	£16,739	£20,890	£284,459	£278,456	£1,075,920
24-month	£225,833	£264,392	£41,844	£213,257	£375,839	£15,852	£152,287	£251,840	£28,397	£21,804	£51,192	£72,518	£132,169	£79,524	£1,926,748
Control	£113,806	£139,587	£25,506	£117,149	£207,803	£8,302	£77,708	£149,494	£11,512	£12,674	£27,032	£37,729	£84,089	£49,857	£1,062,249
Exercise	£112,027	£124,805	£16,338	£96,108	£168,036	£7,549	£74,578	£102,346	£16,885	£9,130	£24,160	£34,789	£48,080	£29,666	£864,499
Total	£730,758	£686,896	£74,080	£413,799	£880,306	£52,506	£432,205	£285,145	£89,254	£52,011	£120,884	£174,319	£571,000	£464,852	£5,028,015

9.5.7. Average cost per child

In the year preceding enrolment into the study, the average cost of the exercise group (£15,010±20,750) was more than the control group (£14,959±16,619) was but this difference was not statistically significant (-£52; 95%CI -£8,819, £8923; p=0.99). At 12-month assessment the exercise group (£29,103±£66,285) cost more than the control group (£28,276±£45,719), but this difference was also not statistically significant (£827; 95%CI -£25,991, £27,645; p=95). At 24-month assessment the exercise group (£23,559±£30,0027) cost less than the control group (£31,313±£43,832), but this difference (-£7,754; 95%CI -£25,4758, £10,249; p=0.39) was not statistically significant (**Figure 9-5: A).** After adjusting for minimisation factors, the difference in cost since baseline at 12-month assessment was more (£5353; 95%CI -£22,675, £33,381; p=0.70) in the exercise group, but less at 24-months (-£4099; 95%CI -£20,218, £12,021; p=0.61) in the exercise group, and the adjusted differences were not statistically significant.

The 3 children who were prescribed *Ivacaftor®* were identified as outliers, however adjusting for the cost of *Ivacaftor®* did not have a significant effect on the model (**Figure 9-5: B**). There were no significant between-group differences in annual costs, but the exercise group cost less than the control group at both 12-month assessment (-£3556; 95%CI -£19,558, £12,813; p=0.66) and 24-month assessment points (-£5,399; 94%CI -£23,653, £12,854; p=0.57).

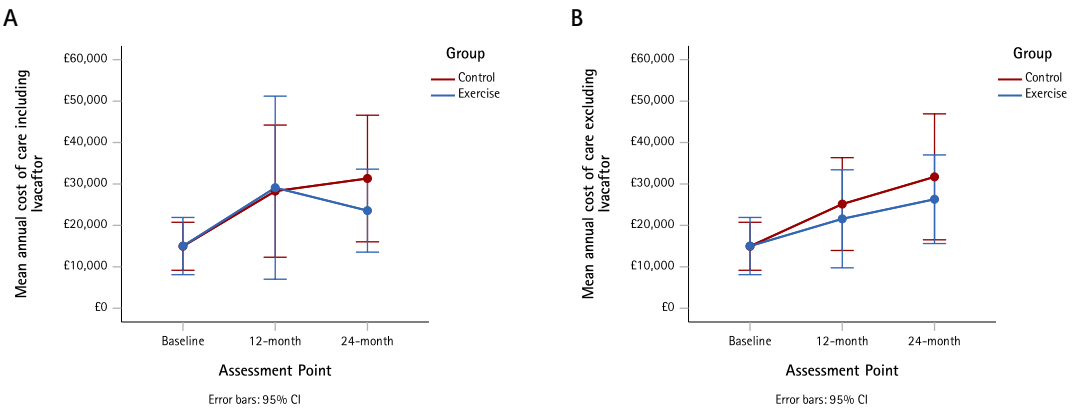

Figure 9-5: Mean annual cost of care (A) including Ivacaftor and (B) excluding Ivacaftor

Table 9-11: Between-group differences in total cost of healthcare

Variable	Assessment	Control	Total	Range	Exercise	Total	Range	Mean diff. (95%CI)	*p*-value
Total Cost	baseline	£14,959±16,619	£508,894	£663 - £66,909	£15,010±20,750	£555,382	£1,444 - £115,048	-£52 (95%CI -£8,819, £8923)	0.99
	12-month	£28,276±£45,719	£961, 368	£1976 - £243,819	£29,103±£66,285	£1,076,791	£858 - £326,455	£827 (95%CI -£25,991, £27,645)	0.95
	24-month	£31,313±£43,832	£1,064,642	£1372 - $172,955	£23,559±£30,0027	£871,670	£467 - £100,633	-£7751 (95%CI -£25,758, £10,249)	0.39

Mean differences were calculated as exercise minus control group

Table 9-12: Adjusted difference in total cost of healthcare

Variable	Duration	B	95%CI	*p*-value
ΔTotal Cost	baseline to 12-month	£5353	-£22,675, £33,381	0.70
	baseline to 24-month	-£4099	-£20,218, £12,021	0.61

B is the model co-efficient (average change in the variable, reflected as assessment point minus baseline data) after adjusting for minimisation factors of gender, disease severity, Area lived in, and Nuffield membership status.

9.5.8. Average cost per admission

When each child was admitted to hospital for IV-antibiotic treatment, they would have been prescribed an individualised regimen of IV-antibiotics treatment, and/or oral antibiotic therapy, and/or nebulised antibiotic therapy, plus additional supplementary medications e.g., nebulised mucolytics such as hypertonic saline and/or recombinant human DNase (*Dornase alfa* or *Pulmozyme*®, Genentech, Roche, USA), vitamins, and pancreatic enzymes (Creon™), therefore it was likely that there would be differences in average cost per admission. Average costs per admission were based on the cumulative cost at the end of each admission. **Table 9–13** shows the analysis of average costs and daily costs for admissions for routine treatment and exacerbation of symptoms.

9.5.9. Average cost per routine admissions

The average cost per routine admission at baseline was higher for the exercise group (£10,951±£12,495) than the control group (£5800±£2404), however this difference was not significant (£5151; 95%CI -£1356, £11,658; p=0.12). At 12-month assessment the difference had narrowed (£177; 95CI -£3869, £4221; p=0.92) with the cost of admission similar between exercise group (£8532±£3366) and control group (£8355±4999). Analysis of average cost per routine admission at 24-month assessments, showed that the control group (£17,547±15,862) cost more than the exercise group (£15,076±£8541), however this difference (-£2472; 95%CI-£18,885, £10,941; p=0.69) was not statistically significant.

9.5.10. Average cost per admissions for exacerbations of respiratory symptoms

The average cost of admissions for exacerbation of symptoms were higher in the control group (£9691±£6549) when compared to the exercise group (£5586±£3537) at baseline, but this difference was not significant (£-4106; 95%CI-£9647, £1437; p=0.12). Again, at 12-month assessment, the control group (£16,857±£9680) cost more than the exercise group (£10,150±7156), and this difference approached significance (-£6708; 95%CI -£14,631, £1215; p=0.09). At 24-month assessment the exercise group (£24,774±12,105) cost slightly more than the control group (£23,747±14,198), but again this difference was not significant (£1027; 95%CI -£11,775, £13,830; p=0.87).

Table 9-13: Cost per admission and daily costs per admissions for routine admissions and for exacerbation of respiratory symptoms

Variable	Assessment	Control	Range	Exercise	Range	Mean diff. (95%CI)	*p*-value
Cost per admission							
Routine	baseline	£5800±£2404	£1672 - £12,357	£10,951±£12,495	£1732 – £53,595	£5151 (-£1356, £11,658)	0.12
	12-month	£8355±4999	£2422 - £17,366	£8532±£3366	£1057 - £11,638	£177 (-£3869, £4221)	0.92
	24-month	£17,547±15,862	£3177 - £52,495	£15,076±£8541	£4102 - £26,303	-£2472 (-£18,885, £10,941)	0.69
Exacerbation	baseline	£9691±£6549	£3325 - £21,261	£5586±£3537	£1218 - £12, 396	£-4106 (-£9647, £1437)	0.12
	12-month	£16,857±£9680	£1510, £29526	£10,150±£7156	£2707 - £20482	-£6708 (-£14,631, £1215)	0.09
	24-month	£24,774±12,105	£2572 - £44,576	£23,747±14,198	£11,906 - £24,773	-£1027 (-£11,775, £13,830)	0.97
Cost per day per admission							
Routine	baseline	£483±£200	£139 - £1030	£782±£893	£124 - £3828	£299 (-£169, 767)	0.20
	12-month	£643±£385	£186 - £1356	£710±£281	£88 - £970	£68 (-£250, £386)	0.66
	24-month	£1462±£1321	£265 - £4375	£1160±£657	£316 - £2023	-£302 (-£1402, £797)	0.56
Exacerbation	baseline	£646±£437	£222 - £1417	£349±£221	£76 - £775	-£297 (-£661, £68)	0.10
	12-month	£1297±£745	£116 - £2271	£725±£511	£193 - £1463	-£572 (-£1165, £22)	0.06
	24-month	£1397±£835	£151 - 2622	£2065±£1008	£992 - 3954	£678 (-£273, £1608)	0.15

Mean differences were calculated as exercise minus control group

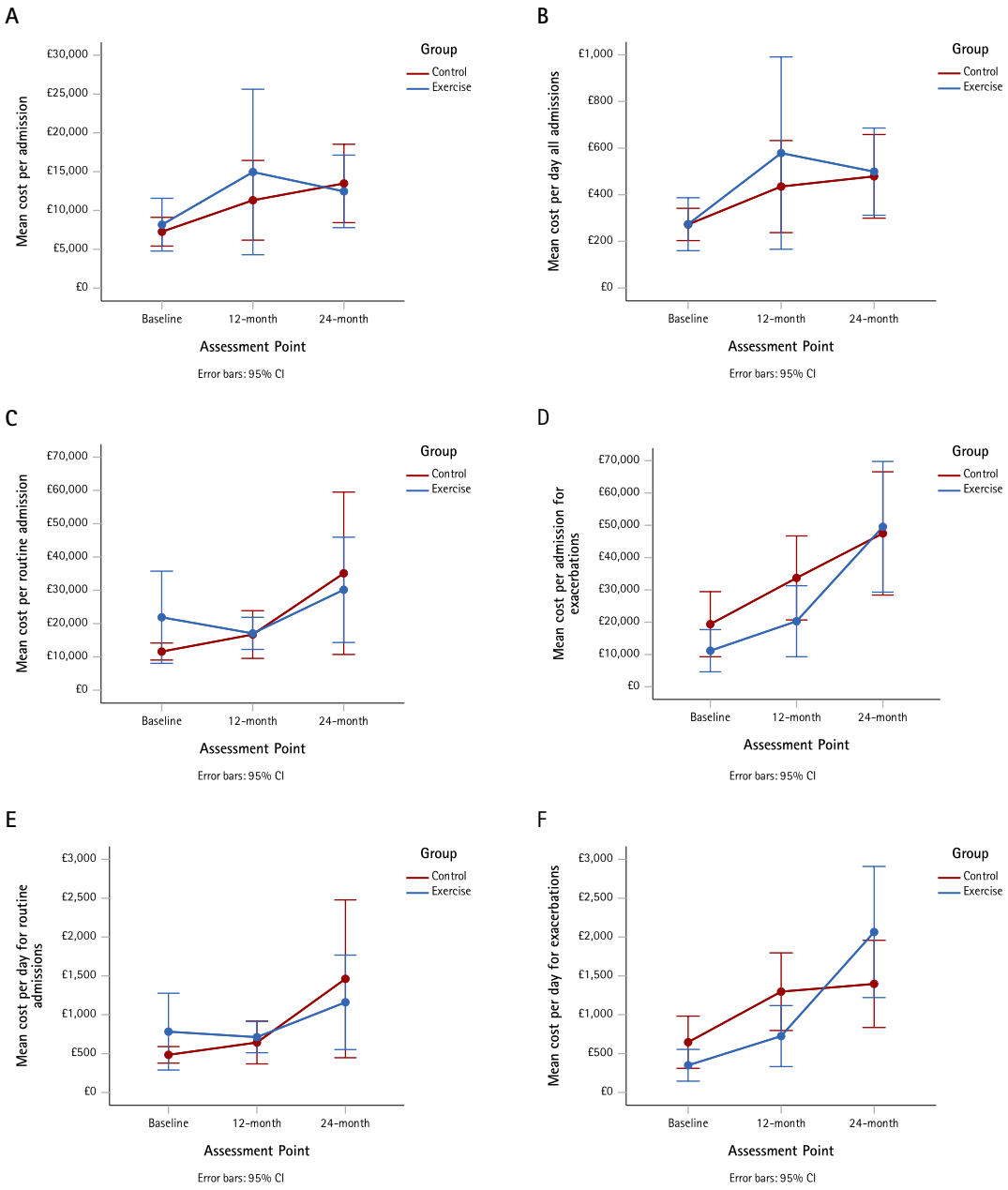

Figure 9-6: Mean cost (A) all admissions and (B) daily cost of all admissions; Mean costs of (C) routine admissions and (D) admissions for exacerbations; Mean daily cost of (E) routine admissions and (F) admissions for exacerbations

9.5.11. Shared care banding costs

Eighteen children (control=6 vs exercise=12) were identified as being treated under confidential, shared-care hospital agreements. It was not possible to identify how the shared-care centres allocated the finances or if they were used. The payments to the shared-care hospital were not included in the cost analysis as they were not reflected in each child's financial records, but are provided for transparency, with total payments being £190,089 (control= £54,477 vs. exercise £135,612).

9.5.12. Lung function test costs

Comprehensive spirometry and MBW costs were not allocated to individual financial records, as these costs were covered in internal GOSH financial arrangements. In the year that the study ended, these costs were highlighted by the finance team to be included in future cost allocations. For transparency, GOSH charges for spirometry were £209 per test and £872 per MBW. Therefore, had the costs for every test performed by each child been included (i.e., at outpatient clinics, annual reviews, during bronchodilator reversibility tests, and during admissions to hospital), the total costs would have been £232,948 (control=£121,492 vs. exercise=£111,456).

9.5.13. Heterogeneity

There was heterogeneity in all outcomes and across both groups. This was expected due to the wide range of disease severity in the children, and this has been previously reported in research related to genetic variation (Drumm et al., 2012), response to treatment for exacerbation (Robinson et al., 2009a), and impact on health economic analyses in clinical populations (Marshall and Hux, 2009).

9.6. Discussion

The primary hypothesis of **Chapter 9** was that a 24-month, individually supervised exercise intervention would elicit a between-group difference, in favour of the exercise group, of a decrease in hospital admissions, IV-antibiotic requirement, exacerbation of symptoms, and cost of healthcare. The results presented in this chapter do not support this hypothesis and therefore it must be rejected.

9.6.1. Length of stay and IV-antibiotic requirements

After 24-months of supervised exercise, the exercise group had spent a significant 5 days less in hospital during overall admissions than the control group and required significantly less IV-antibiotics (5 days) over the 24-month intervention period. Although not statistically significant, the exercise group had spent nearly 7 days less in hospital and on IV-antibiotic during admissions for exacerbation of respiratory symptoms, but 2 days longer in hospital during routine admissions and on IV-antibiotics. These results may be considered clinically important as children spent less days in hospital annually and less time on IV-antibiotics, which meant that they were able to spend more time with family, at school and with friends.

The exercise group had spent slightly more combined time on IV-antibiotics during admissions and at whilst completing a course home and had also spent slightly more time on IV-antibiotics during exacerbations during routine admissions at baseline. However, by the end of the study, children who exercised were spending less time on IV-antibiotics, particularly if they were admitted for an exacerbation. This might be explained by earlier identification of changes in clinical status using the pre-exercise checklist (**Appendix J**) In these cases, the trainers would have referred the child for earlier assessment at an outpatient clinic, where oral IV-antibiotics may have been started or a planned admission may have been scheduled.

During the *Frequent Flyer Programme*, all members of the CF clinical team knew that the children were enrolled in the pilot study, with weekly review of airway clearance regimens and attending weekly exercise training. The pilot programme lead physiotherapist attended bi-monthly clinical team meetings and provided an overview of each child's progress. Decisions related to bringing

forward admissions due to exacerbation or postponement due to improvements in clinical status were discussed at these CF clinical team meetings. However, the random allocation of children to *Inspire-CF* groups was not shared with the CF clinical team, and the research team were not involved in the review of children at any clinics or in decisions related to admissions.

There were 8 cases where a trainer had identified that a child's health status had deteriorated, and after review at an outpatient clinic, the medical team made the decision to bring forward a planned admission. It is possible that these admissions may still have been recorded in the GOSH Patient Information Management System as a planned admission, despite exacerbation of symptoms. Similarly, in 5 cases a decision was made by the medical team to push back a planned admission due to stable clinical status. There were no reported deteriorations in health status in any child that had a planned admission pushed back.

In a large retrospective multi-centre cross-sectional study of 17,312 children aged ≤18 years, Cogen et al. (2017) reported that the average number of exacerbations was 3.8 per year, with 37% of those being a single exacerbation, whilst 46% experienced between 2 - 6 exacerbations per year. Throughout the duration of *Inspire-CF*, the average number of exacerbations recorded in each group were < 1 per year with a range of 0 - 2 per year. It was pleasing to note that both *Inspire-CF* groups required less admissions to hospital for exacerbations than have been previously reported in children within the same age range.

9.6.2. Cost of healthcare

There were considerable healthcare costs identified in both groups throughout the duration of the study. The control group cost 47.2% more at 12-month assessment and 62.8% more at 24-month assessment compared to baseline, and the exercise group cost 35.6% and 40.0% more at 12- and 12-month assessments respectively. The annual increase in costs could be attributed to inclusion of overhead costs and a substantial increase in the costs related to high-cost drugs.

In the year preceding enrolment into *Inspire-CF*, the between group differences showed that the exercise group had cost 4.3% more than the control group. At 12-month assessment this difference had increased to 5.6% however, at 24-month assessment the exercise group cost 10.3% less than the control group, The overall cost (excluding baseline cost) showed that the exercise group cost 2% less (£79,281) throughout the duration of the study. However, although analysis showed that the exercise group were costing an average of £7751 less than the control group, after 24-months intervention, this difference was not statistically significant, and it is therefore not possible to conclude that this difference was as response to the exercise intervention. The average cost per admissions for exacerbations and routine admissions was also lower in the exercise group after 24-months intervention, but again these differences were not significant. There is wide variation in type, number and cost of IV-antibiotic drugs prescribed based on bacterial colonisation and lung function on admission, therefore number of days spent in hospital and on IV-antibiotics is likely more relevant to clinicians.

The annual banding of children is likely to also have also impacted on the way in which costs were allocated. The system was introduced in 2013/2014 and the research team were made aware of ongoing upgrades to the financial software systems used at GOSH. These upgrades would have included changes related to banding structures that would allow for absolute costs of care to be calculated for each child, and to ensure that the hospital was receiving appropriate levels of funding.

9.6.3. Comparison to pilot studies

Ledger et al. (2013) demonstrated a 22% decrease in overall IV-antibiotic requirements and direct cost savings of £220,338, with an average cost per patient in the *Frequent Flyer Programme* of £46,472 in 16 children (FEV_1 z-score -3±1.6), whilst Urquhart et al. (2012) reported a 17% reduction in overall IV-antibiotic requirement and a direct cost saving of £66,384 in 12 children (FEV_1 z-score -2.7±1.9). The *Inspire-CF* control group (FEV_1 z-score -1.3±1.0) showed an overall increase in IV-antibiotic requirement of 10.9%, whist the exercise group (FEV_1 z-score -0.9±1.3) showed a decrease of 8.7% after 24-month, which may be an important clinical change. It is difficult to make an appropriate comparison of average cost per patients to those in the *Inspire-CF* groups as all the

children in the observational studies were prone to exacerbation and deterioration in clinical status, and chronically colonised with one or more bacterium, that required defined protocols of 3–4 monthly routine IV-antibiotics. In *Inspire-CF*, both groups cost around £15,00 at baseline but this had increased to £31,313 in the control group and £23,559 in the exercise group after 24-months intervention.

9.6.4. Comparison to broader literature

Robson et al. (1992) first attempted to quantify the costs related to CF care in 119 adults CF patients in the UK that cost £980,646 over a 12-month period and at an average of £8241 per patient. Since then, there have been a multitude of health economic cost-analyses completed (Lieu et al., 1999, Baumann et al., 2003, Grieve et al., 2003, Krauth et al., 2003, Balinsky and Zhu, 2004, Rosenberg and Farrell, 2005, Hollmeyer et al., 2011, Colombo et al., 2013, van Gool et al., 2013, Whiting et al., 2014, Gu et al., 2015, Chevreul et al., 2016, Agrawal et al., 2017, Sharma et al., 2018, Vadagam and Kamal, 2018) in a wide range of contexts. However, the comparison to the broader literature will relate to reporting of general outcomes, as apart from the observational studies, no other studies have evaluated the effects of exercise on health economics.

Healthcare in the USA is primarily funded by private health insurance, self-pay, Medicare, and Medicaid, and in Europe healthcare is funded differently depending on country, for example Germany is funded using statutory contributions, whilst taxes fund the Spanish system, and taxes and social security contribution fund Portuguese health care. This makes it difficult to directly compare to the UK's NHS which is a free publicly funded healthcare system, however some comparisons can be drawn. During the *Inspire-CF* research programme the British £ to American $ conversion rate was ~£1.00/$1.43, and the British £ to Euro € conversion rate was ~£1.00/€1.15.

Cogen et al. (2017) recently reported that median length of stay was 10.0 days (interquartile range 6-14 days) during exacerbations in 4827 children (aged <18 years) in the USA, however they did not report on cost of care. In another USA based study, Agrawal et al. (2017) evaluated adult CF-related hospitalisations (n=8328; 18 years and over) between 2003 and 2013 and found that admissions for

exacerbations accounted for 72% of admissions in 2003 and increased to 89% in 2013. The average length of stay remained stable at 10.2 days over the 10-year period, however costs per patient increased 57.7% from £41,993 ($60,051) to £66,199 ($94,664). Vadagam and Kamal (2018) reported on children's admissions to hospital (n=3142; age 0-10 years) in the USA using 2012 data and found that average length of stay was 10.3 days, but 13.1 days in children with 2-3 comorbidities. There was a wide range of cost per patient of £20,938 - £21,158 ($29,942 - $30,256) in patients without insurance and £57234 - £68,364 ($81,845 - $97,760) in patients with insurance. In a follow up report by Ramphul et al. (2019) based on 2016 data in children (n=3429; mean age 12-years), the average length of stay was 10.1 days, and total cost per patient was £75,416 ($107,845). This data did not include *Ivacaftor*® as the drug was only approved for used in children in 2015.

In an evaluation of CF costs in 138 German children (aged 0-18 years), Baumann et al. (2003) reported an average cost per patient of £20,860 (€23,989). No details of average length of stay were reported. A comprehensive comparison of costs associated with CF care in adults (n=399) and children (n=506) across Europe was conducted by Chevreul et al. (2016), who reported average costs per patients of £19,387 (€22,295) in Bulgaria, £24,733 (€28,443) in France, £19,440 (€22,356) in Germany, £25.974 (€29,870) in Italy, £ 28,618 (€32,911) in Spain, £40,604 (€46,694) in Sweden and £42,264 (€48,603) in the UK. No details of average length of stay were reported in any of these studies.

In the studies that reported on average length of stay, there was a notable similarity in average length of stay of 14 days which was comparable to *Inspire-CF*. The importance of this finding was that children appeared to be spending the same length of time in hospital, and not more, as their peers in other countries. However, there was wide variation in average cost per patient per year, with the USA reporting substantially higher costs than the rest of the world, particularly for those patients who are self-funded. There was variation in costs across Europe, and this is likely due to size of the CF population and the differences in funding and structure of healthcare between nations. High-cost drugs are the primary driver of costs, followed by admissions and medical and therapy

staff. The average cost per UK patient of £13,828 (Department of Health, 2013), was exceeded in all years of *Inspire-CF*, however these results may be a more realistic representation of costs incurred.

Variability in the reporting of costs was evident across studies, however generally direct costs allocated to capital costs (e.g., buildings and equipment), services (e.g., energy, cleaning, estate management, catering, water, and sewage), departmental costs (e.g., radiography, pharmacy, physiotherapy, pathology, haematology, immunology), and direct staff costs were accounted for. Indirect costs (e.g., medical illustration, medical record, administration, linen, and laundry, time off school, travel time) were less well-reported. *Inspire-CF* costs were only related to direct costs and direct data reporting, however this was comparable to the vast majority of 28 healthcare cost studies that were evaluated in a review by Hollin and Robinson (2016). Indirect costs should be considered, (Krauth et al., 2003) however these costs are very difficult to calculate and rely on individual patient reporting which is highly susceptible to bias.

9.6.5. Strengths

This is the first comprehensive analysis of health economic outcomes in a longitudinal prospective randomised controlled trial that included supervised exercise as an intervention. This study has further increased the knowledge base around hospital admissions and cost of care in children with CF in a large specialist hospital. There are significant challenges in performing a healthcare economic evaluation at it depends on an institutions willingness to share the substantial amount of information required, and robust recording and reporting of the data (Husereau et al., 2013). A strength of *Inspire-CF* was that the clinical and health economic data provided was considered robust, as the research team were able to cross-reference across electronic datasets and GOSH shared the data transparently. Additional information has been provided on *Ivacaftor*®, spirometry and MBW costs for transparency. The results of analysis therefore provided a comprehensive summary of health economic data related to all admissions and direct costs recorded during the study.

9.6.6. Limitations

The primary limitation of this economic analysis was that the analysis of cost was only related to direct reported costs as received from the GOSH financial department. Each singular item cost, for example individual drug prescriptions and associated costs were not defined. It is possible, that some of the data received was miscategorised, for example a routine vs. exacerbation admission, however this was identified and corrected where possible. It was also not possible to calculate direct costs related to the shared-care hospitals. Whilst the results may be more generalised to a UK population, there were similarities in length of stay to other countries, and the cost analysis included comparable outcomes as were reported in American and European studies.

9.6.7. Summary

Inspire-CF has demonstrated that a 24-month individually supervised exercise programme could significantly reduce overall length of time in hospital annually and reduce the length of time spent on IV-antibiotics during exacerbations of respiratory symptoms. Early-detection of changes in health status may have been beneficial to children as they were likely started on oral antibiotics or admitted to hospital before they deteriorated. Cost of health care increased year on year for both groups but there was no significant indication that the 24-month exercise intervention reduced cost of healthcare, despite the exercise group spending less time in hospital and on IV-antibiotics.

10.

CHAPTER 10. SUMMARY AND SYNTHESIS

Inspire-CF was a fully funded, single centre, randomised controlled trial, focused on once-weekly supervised exercise in children aged 6-15 years with CF. This thesis addressed the following 2 research questions:

1. Does a weekly supervised, individually tailored exercise training programme, provided in addition to current specialist CF care, produce significant improvements in lung function, exercise capacity, and quality of life, in children aged 6-15 years, with a wide range of lung disease severity?
2. Is there a health-economic benefit associated with the provision of a weekly supervised, individually tailored exercise training programme in children aged 6-15 years with CF, and a wide range of lung disease severity?

10.1. Main findings

The primary research hypothesis was that if there were no between-group differences in FEV_1 z-score at baseline, the 24-month individually supervised exercise programme would elicit an increase in FEV_1 z-score by 0.7 (80% power; p=0.05). The main finding of *Inspire-CF* is that the exercise intervention had no significant effect on the primary outcome measure of FEV_1 z-score, and therefore this hypothesis must be rejected. An annual deterioration of ~1.5% in FEV_1 %pred. was recorded in both the control and exercise groups. This was disappointing as the disease specific exercise programme had been designed to progressively increase exercise capacity, and it was anticipated that this would produce a positive effect on lung function. Previous randomised controlled trials of relatively short duration conducted in children with CF also reported no significant change in FEV_1, irrespective of the modes (i.e., aerobic, anaerobic and strength) of delivery. The two studies that have reported a significant increase in lung function following an

exercise programme, were both confounded by consecutive administration of IV-antibiotics, which likely masked the true effects of the exercise intervention.

However, there did appear to be a dose-related effect of exercise on lung function. Children who attended at least 52, fortnightly exercise sessions that included HIIT and strength training, over the duration of the study could expect an increase of as much as 7.5% in FEV_1 annually. This effect was not realised in children who did not attend regular exercise sessions. The clinical implication of this finding is that exercise should continue to be actively encouraged for all children with CF, irrespective of lung disease severity, but physiotherapists should emphasise that sporadic and inconsistent participation in exercise is unlikely to preserve or slow the deterioration of lung function.

Functional aerobic fitness significantly improved in the exercise group, with children saying they felt more 'normal' because they could run further, and at the same level or even higher, than their healthy peers. However, these results were not reflected in the gold standard CPET outcomes of W_{peak} and VO_{2peak}, and sub-maximal measurements at the GET, which showed no significant effect of the exercise programme. These findings were difficult to explain, except that all the other randomised controlled trials that demonstrated significant improvements in VO_{2peak} and W_{peak}, had included more than one training session per week. It is therefore possible that once-weekly exercise is not intensive enough to elicit a change in VO_{2peak} and W_{peak} in children who recorded comparatively normal ranges of VO_{2peak} and W_{peak} at baseline.

Medical and physiotherapy regimens are time consuming and considered boring by children with CF, and consequently adherence is poor. The *Inspire-CF* team were concerned that regular interaction with the exercise group may increase the burden of treatment, however children reported a significant increase in their perception of coping with their treatment regimens. Despite the overall impression of improved quality of life, the analysis of the CFQ-R should be considered with caution as the domains only account for the perception of quality of life in the 2-weeks prior to completion of the questionnaire. Therefore, the overall quality of life across the duration of the 24-months may

not be truly reflected. There was a significant difference in parent and child perception of their quality of life, with parents either over or underestimating quality of life. More regular completion of the CFQ-R in both child and parents, followed up by a face-to-face discussion with both child and parent may reveal more about the perceived quality of life of children with CF.

The health economic analysis provided a comprehensive, longitudinal overview of the significant time that children with CF spend in hospital on IV-antibiotics and the considerable costs associated with their management and treatment. Although the exercise group spent significantly less time in hospital annually, the between-group differences in routine admissions and admissions for exacerbation of respiratory symptoms did not demonstrate that the exercise intervention had any impact on reducing time in hospital or IV-antibiotic requirements, for either of the admission types. Costs of healthcare increased year on year, which was primarily related to high-cost drugs and the prescription of *Ivacaftor*® in the latter stages of the study.

Inspire-CF was complex and challenging to implement, and there were significant costs associated with the setup and running of the study. Consequently, it would be unlikely that healthcare policy decision makers would consider implementing a similar programme into clinical practice. However, the merits of the *Frequent Flyer Programme* should not be forgotten, as supervised exercise may still be an important consideration for sicker children with moderate-to-severe lung disease.

The advantage of providing supervised exercise to sicker groups of children with CF, is that personal trainers aim to continuously motivate the children to exercise by trying to keep exercise fun and interesting. Observational studies, like the *Frequent Flyer Programme,* demonstrated significant improvements in exercise capacity and a slowing in the rate of deterioration in lung function in children with moderate-to-severe lung disease. These studies also showed that providing supervised exercise could be cost-neutral, or even cost-saving. However, they were observational studies, and their results should not be over-interpreted, as there were no comparisons to a control group. *Inspire-CF* was not able to reproduce these findings in a cohort of children with a wide range of milder lung disease, therefore it is plausible that a Hawthorne effect (Franke and Kaul, 1978) was

observed in the *Frequent Flyer Programme* such that it was the closer monitoring rather than the exercise intervention that led to improved outcomes.

10.2. Update on published evidence related to exercise since Inspire-CF concluded

Inspire-CF concluded in June 2016, and since then there has been a substantial increase in the knowledge base related to exercise in CF. As such it is important to consider this new evidence and where appropriate draw comparisons to the results documented in this thesis.

10.2.1. Survival and trajectory of lung function in children with cystic fibrosis since 2014

Since 2014, the number of adults and children registered with the disease in the UK CF Registry has increased from 10,338, with a median predicted survival age of 36.6 years (Cystic Fibrosis Trust, 2014) to 10,908, with a median life expectancy of 38.0 years (Cystic Fibrosis Trust, 2022). Importantly, there has been an increase in mean FEV_1 %pred. between 2013 and 2021 (**Table 10-1**), and this is primarily due to prescription of CFTR modulator drugs (**Chapter 10, Subheading 10.3, pg. 233**) being widely available on the NHS and in particular, has significantly improved lung function in those aged 12-19 years of age, where rapid deterioration in FEV_1 was previously documented.

Table 10-1: Comparison of mean FEV_1%pred. for male and female children aged 6-19 years based in the UK between 2013 and 2021

	Age groups			
Year	6-7 yr.	8-11 yr.	12-15 yr.	16-19 yr.
2013 mean FEV_1%pred.	91.0	88.0	79.8	74.3
2021 mean FEV_1%pred.	93.8	92.2	92.3	87.8
Difference (2013-2021)	2.8	4.2	12.5	13.5

FEV_1 %pred. based on Global Lung Initiative equations (Quanjer et al., 2012b) as reported in the UK Cystic Fibrosis Registry Annual Data Report 2013 (Cystic Fibrosis Trust, 2014) and UK Cystic Fibrosis Registry Annual Data Report 2022 (Cystic Fibrosis Trust, 2022).

Schluter et al. (2022) have recently published a comparison of UK (n=3055) and USA (n=9463) longitudinal lung function data in children aged 6-18 years. The results of the analysis showed that FEV_1 %pred. declined at a significantly faster rate in the UK (-1.6%; 95%CI -1.72, -1.50) compared with the USA (-1.41%; 95%CI -1.47, -1.36). This equates to a ~0.2% (95%CI 0.08, 0.32) faster rate in UK.

Inspire-CF showed that children in both control and exercise groups demonstrated an annual rate of deterioration of -1.5% in FEV_1 annually, which is in line with this most recent data. It is reasonable to speculate that children enrolled in *Inspire-CF* may have since benefitted from the prescription of CFTR modular drugs, and that they have demonstrated improvements in FEV_1, and that annual rates of deterioration have slowed.

10.2.2. Lung clearance index as a primary endpoint for exercise-based interventions

MBW was undertaken annually by children treated by the GOSH CF Unit, and LCI was included as a secondary outcome measure in *Inspire-CF*. The results of analysis of LCI outcomes in **Chapter 6, Subheading 6.3.4 , pg. 145** demonstrated that LCI in the exercise group did not increase (worsen) as much as the control group, although the between-group differences were not statistically significant. One of the speculated reasons for this difference was that children who exercised regularly may have reduced dynamic lung hyperinflation (Stevens et al., 2013, Vendrusculo et al., 2019).

It is interesting to note that since the completion of *Inspire-CF*, MBW has still not been fully integrated into clinical practice (Subbarao et al., 2015) primarily due to uncertainty of the exact clinical utility of the test in monitoring for changes in CF lung disease (Perrem et al., 2018). However, MBW has been demonstrated to be highly sensitive to changes within the small airways in children with normal FEV_1 (Subbarao et al., 2015) and detecting early lung disease (Hoo et al., 2012), therefore the recent, proposals by Hatziagorou et al. (2021) and Gambazza et al. (2022) for LCI to become a primary endpoint in exercise-based interventional studies would be recommended.

10.2.3. Exercise as a substitute for airway clearance therapy in cystic fibrosis

At the start of *Inspire-CF* there were early reports of children and adults substituting exercise for airway clearance therapy sessions (Dwyer et al., 2011). This was identified as a top 10 research priority by a partnership of people with CF and healthcare providers (Rowbotham et al., 2018), with the aim of reducing the burden of physiotherapy treatment regimens. Since then, there have been several studies (Ward et al., 2018, Vendrusculo et al., 2019, Ward et al., 2019, Ward et al., 2021) and reviews (Chapman et al., 2021, Dwyer, 2021, Heinz et al., 2022, Rowbotham and Daniels, 2022,

Saynor et al., 2022) that have determined that exercise is a viable replacement for airway clearance therapy. As airway clearance regimens are commonly reported as burdensome (Davies et al., 2020), these new findings are highly relevant.

Inspire-CF did not specifically investigate exercise as an alternative to airway clearance therapy, but children were actively encouraged to maintain a regimen throughout the time they were enrolled in the study and performed huffs and coughs during exercise sessions when required. The personal training team used the 6-point checklist questionnaire (**Appendix J**) to determine if children were completing prescribed airway clearance and nebulised therapy regimens, and if they were not, this was flagged with the GOSH specialist CF physiotherapy team. It was noted during *Inspire-CF* that some children, particularly those aged 12-15 years, were reporting poor adherence to their regimens so it is reassuring that exercise may have been assisting in maintenance of children's lung health. *Inspire-CF* showed that treatment burden was not increased by participation in regular exercise, so these more recent findings will likely be welcomed by children and their parents/carers, who are always looking to reduce treatment burden.

10.2.4. Current evidence for the effects of exercise on lung function, exercise capacity and quality of life in children with cystic fibrosis

Since the systematic review that was documented in **Chapter 2**, Radtke et al. (2022) have published a comprehensive Cochrane Review on the effects of physical activity and exercise training in CF. Meta-analysis of 24 randomised controlled trials that included 875 children under the age of years and with a wide range of lung disease severity, concluded that programmes that included at least 6-months of physical activity, likely had a positive effect on VO_{2peak} (1.60 ml·min^{-1}; 95%CI 0.16, 3.05; p=0.03) when compared to children who did not undertake physical activity. However, physical activity was unlikely to have a positive effect on FEV_1 %pred. (2.41; 95%CI 0.49 to 5.31; p=0.06). Analysis of the CFQ-R physical functioning (2.19; -3.42, 7.80; p=0.18) and respiratory (-0.05; 95%CI -3.61, 3.51; p=0.62) domains, also demonstrated that exercise may not have a positive effect on quality of life. Additionally, regular exercise may not reduce the likelihood of repeat exacerbations of respiratory symptoms within 6-months (incidence rate ratio 1.28; 95%CI 0.85, 1.94; p=0.24).

The findings of *Inspire-CF* are currently in preparation for publication and will likely echo the conclusion of this review. However, it reasonable to speculate that the unique contribution that future systematic reviews may comment on, is the dose-related effect of the *Inspire-CF* exercise programme, such that sustained and regular moderate-to-high intensity exercise may have a positive impact on FEV_1.

10.2.5. Developments in standardisation of cardiopulmonary exercise tests and collaborative work to further understand the effects of exercise on physiological markers

Inspire-CF exercise testing protocols and reporting of outcomes was based on the Hebestreit et al. (2015) consensus statement, and was carried out in a very busy clinical laboratory. There were significant time limitations and scheduling pressures that have been previously outlined. It is therefore pleasing to note that there remains a continued focus for CPET to be implemented clinically as the primary, CF annual review exercise test, and that a new statement on the standardisation of CPET has been published (Radtke et al., 2019). It is also pleasing that leading research teams, continue to collaborate (Williams et al., 2022), and that more work has been undertake to identify key prognostic information to further validate the importance of CPET (Hebestreit et al., 2019). These publications are of particular importance to physiotherapists and the wider MDT considering the adoption of CPET at annual review.

10.2.6. Advocacy for high intensity interval training programmes

Inspire-CF employed HIIT and muscle strength training, and the full protocol will be published as a supplement in future. Recently published articles on the potential benefits of HIIT in CF and other chronic respiratory conditions confirmed the potential benefits of HIIT (Sawyer et al., 2020a, Sawyer et al., 2020b). Although children in the *Inspire-CF* exercise group initially struggled with HIIT, children tolerated the protocol well and were able to independently replicate their training sessions on a weekly basis. As such, physiotherapists and other clinicians recommending exercise to people with CF, should advocate for the use of HIIT, supplemented by strength training.

10.2.7. ACTIVATE-CF

At the same time as *Inspire-CF* was enrolling participants, a trial called ACTIVATE-CF had also started enrolling participants, and the results of that study have recently been published and present an opportunity for comparison of outcomes with *Inspire-CF* (Hebestreit et al., 2022). ACTIVATE-CF was a fully funded, international, multicentre randomised controlled trial that evaluated the effects of vigorous physical activity in children and adults with CF. The study recruited 117 participants (control=57; exercise=60) to the study, but this was only 40% of their anticipated sample size. Participants had low levels of physical activity at baseline (≤ 4-hours per week) and were required to undertake 30 minutes of strength training and 2-hours of aerobic exercise per week, for 6-months, and were followed up at 12-months. The results of the study showed that the exercise group had significantly increased their levels of physical activity at 6-months and had maintained some of the increased exercise capacity at 12-month assessments. However, counterintuitively the control group significantly increased their lung function, whilst the exercise groups lung function decreased.

Inspire-CF and ACTIVATE-CF were the 2 most recent longitudinal randomised controlled trials, and despite the significant experience in both research teams on drawing on the best available evidence, to develop structured, disease specific exercise interventions, both studies failed to demonstrate a positive effect on lung function. It is interesting that exercise capacity was maintained after 6-months in the ACTIVATE-CF group, as this phenomenon has not been achieved in previous short-term studies. *Inspire-CF* and ACTIVATE-CF both demonstrated significant increases in functional physical activities, however *Inspire-CF* did not replicate the changes in $VO2_{peak}$ and W_{peak} that were demonstrated in ACTIVATE-CF. A higher weekly dose of physical activity was prescribed in ACTIVATE-CF, and baseline exercise capacity was lower than in *Inspire-CF*. These may be the reasons that an increase in VO_{2peak} was reported in the ACTIVATE-CF trial. The ACTIVATE-CF research group did suggest that the intervention may have been too intensive initially for participants with low activity levels, and this may have negatively impacted on the exercise groups enthusiasm for exercising.

10.3. Impact of CFTR modulator therapy

The single most significant development that has positively impacted the lives of people with CF is the new generation of CFTR modulator drugs like *Ivacaftor*® (Kalydeco®), combination drug *Lumacaftor/Ivacaftor (Orkambi®)*, and triple combination *Elexacaftor/Tezacaftor/Ivacaftor* (*Trikafta*®). The drugs target CFTR mutations such as the *p.Phe508del* and *p.Gly551Asp*, and correct basic molecular and cellular defects, and have been widely available on the NHS since the completion of *Inspire-CF*. These drugs have been life-changing for children and adults with CF, and significantly improved lung function and growth parameters. Medical treatment for CF remains focused on improving lung function, and these drugs have been demonstrated to help achieve this goal, but at a significant cost to the NHS.

When *Inspire-CF* was started, CFTR modulator drugs were not immediately available for prescription on the NHS, however 3 participants (control=1; exercise=2) with at least one *p.Gly551Asp* mutation were prescribed *Ivacaftor*® (Kalydeco®) in the first 12-months of the study. There were no published data on the effects of the drug on exercise capacity. Since then, a range of studies have reported improved aerobic capacity, as well as lung function and growth outcomes, when CFTR modulator drugs have been prescribed (Saynor et al., 2014, Whiting et al., 2014, Edgeworth et al., 2017, Wilson et al., 2021, Causer et al., 2022, Rysgaard et al., 2022). Most recently, Caterini et al. (2022) have published a significant review of the potential role of CFTR modulators may have on exercise intolerance in CF, and have proposed a range of potential research routes to help clinicians better understand the effects of the drugs on clinical and health outcomes. It will be interesting to track these research developments in the next few years.

10.4. Future Research

Dose-related effects of exercise in CF have not been previously explored, and this opens a new opportunity for future research. *Inspire-CF* considered the dose-related effect of HIIT and strength training on lung function, and in future studies other modes of exercise should be considered. Future studies should also explore the dose-related effect of exercise on VO_{2peak} and W_{peak}, and other common secondary outcomes. The linear relationship, if any, between exercise training and dose effect should also be explored.

Gabel et al. (2022) recently highlighted that some people are gaining weight excessively since being prescribed a CFTR modular drug, and this presents as an important consideration for physiotherapists and other clinicians advocating for continued promotion of exercise in CF. This opens an unexpected area of research for physiotherapists and dieticians to collaborate. The *Frequent Flyer Programme* highlighted some of the negative impact of moderate-to-high intensity exercise in children with moderate to severe lung disease, such that some children lost body mass. Future studies should aim to repeat the *Frequent Flyer Programme* intervention in a similar cohort of children who are prescribed CFTR modulator drugs.

10.5. Conclusions

When *Inspire-CF* was started, it was anticipated that the exercise intervention would increase exercise capacity and improve lung function, however this objective was not achieved. The dose-related effect of exercise on FEV_1 is an important finding, particularly as *Orkambi*® was approved for prescription after demonstrating an increase of 2.6 to 4.0 in FEV_1 %pred., so exercise should continue to be advocated in children with CF. The wider health benefits of exercise, including maintenance of a good quality of life, should be advocated. A routine of exercise, structured sport and physical activity should be actively encouraged, especially in children with CF who have normal lung function and are not eligible for prescription of the latest pharmaceutical CFTR modulator therapies.

REFERENCES

ABBOTT, J. & HART, A. 2005. Measuring and reporting quality of life outcomes in clinical trials in cystic fibrosis: a critical review. *Health Qual Life Outcomes,* 3**,** 19.

ABBOTT, J., HART, A., HAVERMANS, T., MATOSSIAN, A., GOLDBECK, L., BARRETO, C., BERGSTEN-BRUCEFORS, A., BESIER, T., CATASTINI, P., LUPI, F. & STAAB, D. 2011. Measuring health-related quality of life in clinical trials in cystic fibrosis. *J Cyst Fibros,* 10 Suppl 2**,** S82-5.

AGRAWAL, A., AGARWAL, A., MEHTA, D., SIKACHI, R. R., DU, D. & WANG, J. 2017. Nationwide trends of hospitalizations for cystic fibrosis in the United States from 2003 to 2013. *Intractable Rare Dis Res,* 6**,** 191-198.

AINSWORTH, B. E., HASKELL, W. L., HERRMANN, S. D., MECKES, N., BASSETT, D. R., JR., TUDOR-LOCKE, C., GREER, J. L., VEZINA, J., WHITT-GLOVER, M. C. & LEON, A. S. 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc,* 43**,** 1575-81.

AMERICAN THORACIC SOCIETY & AMERICAN COLLEGE OF CHEST PHYSICIANS. 2003. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med,* 167**,** 211-77.

AMIN, R., LAM, M., DUPUIS, A. & RATJEN, F. 2011. The effect of early Pseudomonas aeruginosa treatment on lung function in pediatric cystic fibrosis. *Pediatr Pulmonol,* 46**,** 554-558.

ANGELIS, A., TORDRUP, D. & KANAVOS, P. 2015. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. *Health Policy,* 119**,** 964-79.

ASHLOCK, M. A., BEALL, R. J., HAMBLETT, N. M., KONSTAN, M. W., PENLAND, C. M., RAMSEY, B. W., VAN DALFSEN, J. M., WETMORE, D. R. & CAMPBELL, P. W. 2009. A pipeline of therapies for cystic fibrosis. *Semin Respir Crit Care Med,* 30**,** 611-26.

AURORA, P. 2010. Multiple-breath inert gas washout test and early cystic fibrosis lung disease. *Thorax,* 65**,** 373-4.

AURORA, P., BUSH, A., GUSTAFSSON, P., OLIVER, C., WALLIS, C., PRICE, J., STROOBANT, J., CARR, S., STOCKS, J. & LONDON CYSTIC FIBROSIS COLLABORATION 2005a. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med,* 171**,** 249-56.

AURORA, P., GUSTAFSSON, P., BUSH, A., LINDBLAD, A., OLIVER, C., WALLIS, C. E. & STOCKS, J. 2004. Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. *Thorax,* 59**,** 1068-73.

AURORA, P., KOZLOWSKA, W. & STOCKS, J. 2005b. Gas mixing efficiency from birth to adulthood measured by multiple-breath washout. *Respir Physiol Neurobiol,* 148**,** 125-39.

BALDWIN, D. R., HILL, A. L., PECKHAM, D. G. & KNOX, A. J. 1994. Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. *Respir Med,* 88**,** 49-53.

BALINSKY, W. & ZHU, C. W. 2004. Pediatric cystic fibrosis: evaluating costs and genetic testing. *J Pediatr Health Care,* 18**,** 30-4.

BALLMANN, M. & VON DER HARDT, H. 2002. Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis. *J Cyst Fibros,* 1**,** 35-7.

BAQUET, G., GUINHOUYA, C., DUPONT, G., NOURRY, C. & BERTHOIN, S. 2004. Effects of a short-term interval training program on physical fitness in prepubertal children. *J Strength Cond Res,* 18**,** 708-13.

BAR-OR, O. 1987. The Wingate anaerobic test. An update on methodology, reliability and validity. *Sports Med,* 4, 381-94.

BAUMANN, U., STOCKLOSSA, C., GREINER, W., VON DER SCHULENBURG, J. M. & VON DER HARDT, H. 2003. Cost of care and clinical condition in paediatric cystic fibrosis patients. *J Cyst Fibros,* 2, 84-90.

BEHM, D. G., FAIGENBAUM, A. D., FALK, B. & KLENTROU, P. 2008. Canadian Society for Exercise Physiology position paper: resistance training in children and adolescents. *Appl Physiol Nutr Metab,* 33, 547-61.

BENSON, A. C., TORODE, M. E. & FIATARONE SINGH, M. A. 2008. Effects of resistance training on metabolic fitness in children and adolescents: a systematic review. *Obes Rev,* 9, 43-66.

BLACK, R., TALLIS, M., URQUHART, D., HARRIS, M., COOPER, D. & DAKIN, C. 2009. Intensive out-patient physiotherapy - an approach to optimising lung health in childhood cystic fibrosis. *Pediatr Pulmonol,* 44, 391–392.

BLAIR, S. N., KOHL, H. W., GORDON, N. F. & PAFFENBARGER, R. S. J. 1992. How much physical activity is good for health? *Annu Rev Public Health,* 13, 99-126.

BONGERS, B. C., VAN BRUSSEL, M., HULZEBOS, E. & TAKKEN, T. 2014a. *Pediatric norms for cardiopulmonary exercise testing in relation to sex and age,* Utrecht, Netherlands, Uitgeverij BOXPress, 's-Hertogenbosch.

BONGERS, B. C., WERKMAN, M. S., ARETS, H. G., TAKKEN, T. & HULZEBOS, H. J. 2015. A possible alternative exercise test for youths with cystic fibrosis: the steep ramp test. *Med Sci Sports Exerc,* 47, 485-92.

BONGERS, B. C., WERKMAN, M. S., TAKKEN, T. & HULZEBOS, E. H. 2014b. Ventilatory response to exercise in adolescents with cystic fibrosis and mild-to-moderate airway obstruction. *Springerplus,* 3, 696.

BOUCHER, G. P., LANDS, L. C., HAY, J. A. & HORNBY, L. 1997. Activity levels and the relationship to lung function and nutritional status in children with cystic fibrosis. *Am J Phys Med Rehabil,* 76, 311-5.

BOWLER, I. M., GREEN, J. H., WOLFE, S. P. & LITTLEWOOD, J. M. 1993. Resting energy expenditure and substrate oxidation rates in cystic fibrosis. *Archives of Disease in Childhood,* 68, 754-759.

BRADLEY, J., HOWARD, J., WALLACE, E. & ELBORN, S. 1999. Validity of a modified shuttle test in adult cystic fibrosis. *Thorax,* 54, 437-9.

BRADLEY, J., MCALISTER, O. & ELBORN, S. 2001. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. *Eur Respir J,* 17, 712-5.

BRADLEY, J. & MORAN, F. 2008. Physical training for cystic fibrosis. *Cochrane Database Syst Rev,* CD002768.

BRAGGION, C., CORNACCHIA, M., MIANO, A., SCHENA, F., VERLATO, G. & MASTELLA, G. 1989. Exercise tolerance and effects of training in young patients with cystic fibrosis and mild airway obstruction. *Pediatr Pulmonol,* 7, 145-52.

BRITTO, M. T., KOTAGAL, U. R., HORNUNG, R. W., ATHERTON, H. D., TSEVAT, J. & WILMOTT, R. W. 2002. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest,* 121, 64-72.

BRUCE, R. A., LOVEJOY, F. W. J., PEARSON, R., YU, P. N. G., BROTHERS, G. B. & VELASQUEZ, T. 1949. Normal respiratory and circulatory pathways of adaptation in exercise. *J Clin Invest,* 28, 1423-30.

BRYON, M., BUU, A. & DAVIS, M. 2009. CFQ-UK: Cystic Fibrosis Questionnaire, a health-related quality of life measure (English UK, Version 1).

BRYON, M. & WALLIS, C. 2011. Parents as equal partners in the paediatric cystic fibrosis multidisciplinary team. *J R Soc Med,* 104 Suppl 1**,** S30-5.

BUCHHEIT, M. & LAURSEN, P. B. 2013. High-intensity interval training, solutions to the programming puzzle: Part I: cardiopulmonary emphasis. *Sports Med,* 43**,** 313-38.

BUTCHER, S. J. & JONES, R. L. 2006. The Impact of Exercise Training Intensity on Change in Physiological Function in Patients with Chronic Obstructive Pulmonary Disease. *Sports Medicine,* 36**,** 307-325.

CAINE, D., DIFIORI, J. & MAFFULLI, N. 2006. Physeal injuries in children's and youth sports: reasons for concern? *Br J Sports Med,* 40**,** 749-60.

CASPERSEN, C. J., POWELL, K. E. & CHRISTENSON, G. M. 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep,* 100**,** 126-31.

CATERINI, J. E., RATJEN, F., BARKER, A. R., WILLIAMS, C. A., RENDALL, K., SCHNEIDERMAN, J. E. & WELLS, G. D. 2022. Exercise intolerance in cystic fibrosis-the role of CFTR modulator therapies. *J Cyst Fibros,* 21**,** 282-292.

CAUSER, A. J., SHUTE, J. K., CUMMINGS, M. H., SHEPHERD, A. I., WALLBANKS, S. R., PULSFORD, R. M., BRIGHT, V., CONNETT, G. & SAYNOR, Z. L. 2022. Elexacaftor-Tezacaftor-Ivacaftor improves exercise capacity in adolescents with cystic fibrosis. *Pediatr Pulmonol*.

CERNY, F. J. 1989. Relative effects of bronchial drainage and exercise for in-hospital care of patients with cystic fibrosis. *Phys Ther,* 69**,** 633-9.

CERNY, F. J., PULLANO, T. P. & CROPP, G. J. 1982. Cardiorespiratory adaptations to exercise in cystic fibrosis. *Am Rev Respir Dis,* 126**,** 217-20.

CHAPMAN, N., WATSON, K., HATTON, T., CAVALHERI, V., WOOD, J., GUCCIARDI, D. F., SMITH, E. F. & HILL, K. 2021. Methods Used to Evaluate the Immediate Effects of Airway Clearance Techniques in Adults with Cystic Fibrosis: A Systematic Review and Meta-Analysis. *J Clin Med,* 10.

CHATHAM, K., IONESCU, A. A., NIXON, L. S. & SHALE, D. J. 2004. A short-term comparison of two methods of sputum expectoration in cystic fibrosis. *Eur Respir J,* 23**,** 435-9.

CHÉRON, G., PARADIS, K., STÉRU, D., DEMAY, G. & LENOIR, G. 1984. Cardiac involvement in cystic fibrosis revealed by a ventricular arrhythmia. *Acta Paediatr Scand,* 73**,** 697-700.

CHEVREUL, K., MICHEL, M., BRIGHAM, K. B., LOPEZ-BASTIDA, J., LINERTOVA, R., OLIVA-MORENO, J., SERRANO-AGUILAR, P., POSADA-DE-LA-PAZ, M., TARUSCIO, D., SCHIEPPATI, A., ISKROV, G., PENTEK, M., VON DER SCHULENBURG, J. M., KANAVOS, P., PERSSON, U., FATTORE, G. & BURQOL-RD RESEARCH NETWORK 2016. Social/economic costs and health-related quality of life in patients with cystic fibrosis in Europe. *Eur J Health Econ,* 17 Suppl 1**,** 7-18.

COGEN, J., EMERSON, J., SANDERS, D. B., REN, C., SCHECHTER, M. S., GIBSON, R. L., MORGAN, W., ROSENFELD, M. & EPIC STUDY GROUP 2015. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. *Pediatr Pulmonol,* 50**,** 763-70.

COGEN, J. D., ORON, A. P., GIBSON, R. L., HOFFMAN, L. R., KRONMAN, M. P., ONG, T. & ROSENFELD, M. 2017. Characterization of Inpatient Cystic Fibrosis Pulmonary Exacerbations. *Pediatrics,* 139.

COLLACO, J. M., GREEN, D. M., CUTTING, G. R., NAUGHTON, K. M. & MOGAYZEL, P. J. J. 2010. Location and duration of treatment of cystic fibrosis respiratory exacerbations do not affect outcomes. *Am J Respir Crit Care Med,* 182**,** 1137-43.

COLLINS, F. S. 1992. Cystic fibrosis: molecular biology and therapeutic implications. *Science,* 256**,** 774-9.

COLOMBO, C., DACCO, V., ALICANDRO, G., LOI, S., MAZZI, S., LUCIONI, C. & RAVASIO, R. 2013. Cost of cystic fibrosis: analysis of treatment costs in a specialized center in northern Italy. *Adv Ther,* 30**,** 165-75.

COREY, M. 2007. Power considerations for studies of lung function in cystic fibrosis. *Proc Am Thorac Soc,* 4**,** 334-7.

COREY, M., LEVISON, H. & CROZIER, D. 1976. Five- to seven-year course of pulmonary function in cystic fibrosis. *Am Rev Respir Dis,* 114**,** 1085-92.

CRITICAL APPRAISAL SKILLS PROGRAMME UK. 2014. *Critical Appraisal Skills tool for the evaluation of quality of evidence in research* [Online]. Critical Appraisal Skills Programme UK. [Accessed 2014].

CROPP, G. J., PULLANO, T. P., CERNY, F. J. & NATHANSON, I. T. 1982. Exercise tolerance and cardiorespiratory adjustments at peak work capacity in cystic fibrosis. *Am Rev Respir Dis,* 126**,** 211-6.

CYSTIC FIBROSIS TRUST 2009. Antibiotic treatment for cystic fibrosis. 3rd ed. London, United Kingdom: Cystic Fibrosis Trust.

CYSTIC FIBROSIS TRUST 2011a. Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK. 2nd ed. London, United Kingdom: Cystic Fibrosis Trust.

CYSTIC FIBROSIS TRUST 2011b. Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. Second edition ed. London, United Kingdom: Cystic Fibrosis Trust.

CYSTIC FIBROSIS TRUST 2012. UK CF Registry: Banding matrix definitions. London: Cystic Fibrosis Trust.

CYSTIC FIBROSIS TRUST. 2013. *Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis* [Online]. London, United Kingdom: Cystic Fibrosis Trust. Available: http://www.cysticfibrosis.org.uk/media/448939/cd-standards-of-care-dec-2011.pdf [Accessed 25.11.2013 2013].

CYSTIC FIBROSIS TRUST 2014. UK Cystic Fibrosis Registry Annual Data Report 2013. London, United Kingdom: Cystic Fibrosis Trust.

CYSTIC FIBROSIS TRUST 2022. UK Cystic Fibrosis Registry 2021 Annual Data Report. London, United Kingdom: Cystic Fibrosis Trust.

DAHAB, K. S. & MCCAMBRIDGE, T. M. 2009. Strength training in children and adolescents: raising the bar for young athletes? *Sports Health,* 1**,** 223-6.

DALILI, M., VAHIDSHAHI, K., AARABI-MOGHADDAM, M. Y., RAO, J. Y. & BRUGADA, P. 2014. Exercise testing in children with Wolff-Parkinson-White syndrome: what is its value? *Pediatr Cardiol,* 35**,** 1142-6.

DANIELS, T., GOODACRE, L., SUTTON, C., POLLARD, K., CONWAY, S. & PECKHAM, D. 2011. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. *Chest,* 140**,** 425-432.

DANKERT-ROELSE, J. E. & TE MEERMAN, G. J. 1995. Long term prognosis of patients with cystic fibrosis in relation to early detection by neonatal screening and treatment in a cystic fibrosis centre. *Thorax,* 50**,** 712-8.

DAVIES, G., ROWBOTHAM, N. J., SMITH, S., ELLIOT, Z. C., GATHERCOLE, K., RAYNER, O., LEIGHTON, P. A., HERBERT, S., DUFF, A. J., CHANDRAN, S., DANIELS, T., NASH, E. F. & SMYTH, A. R. 2020. Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. *J Cyst Fibros,* 19**,** 499-502.

DAVIES, J. C., EBDON, A. M. & ORCHARD, C. 2014. Recent advances in the management of cystic fibrosis. *Arch Dis Child,* 99**,** 1033-6.

DE BOECK, K., WILSCHANSKI, M., CASTELLANI, C., TAYLOR, C., CUPPENS, H., DODGE, J., SINAASAPPEL, M. & DIAGNOSTIC WORKING GROUP 2006. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax,* 61, 627-35.

DE MEER, K., GULMANS, V. A. & VAN DER LAAG, J. 1999. Peripheral muscle weakness and exercise capacity in children with cystic fibrosis. *Am J Respir Crit Care Med,* 159, 748-54.

DEL CORRAL, T., GOMEZ SANCHEZ, A. & LOPEZ-DE-URALDE-VILLANUEVA, I. 2020. Test-retest reliability, minimal detectable change and minimal clinically important differences in modified shuttle walk test in children and adolescents with cystic fibrosis. *J Cyst Fibros,* 19, 442-448.

DEPARTMENT OF HEALTH 2013. NHS: Payment by results guidance for 2013-2014. Leeds, United Kingdom: Department of Health Results Team, Department of Health.

DODD, M. E. & PRASAD, S. A. 2005. Physiotherapy management of cystic fibrosis. *Chron Respir Dis,* 2, 139-49.

DONALDSON, S. H., BENNETT, W. D., ZEMAN, K. L., KNOWLES, M. R., TARRAN, R. & BOUCHER, R. C. 2006. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med,* 354, 241-50.

DORING, G., FLUME, P., HEIJERMAN, H., ELBORN, J. S. & CONSENSUS STUDY GROUP 2012. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros,* 11, 461-79.

DORING, G., HOIBY, N. & CONSENSUS STUDY GROUP 2004. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. *J Cyst Fibros,* 3, 67-91.

DOUGLAS, H., LEDGER, S., RAND, S., GIARDINI, A. & MAIN, E. 2015. Routine ECG monitoring for patients with cystic fibrosis: physiotherapists be aware! *Physiotherapy,* 101, e932-e933.

DRUMM, M. L., ZIADY, A. G. & DAVIS, P. B. 2012. Genetic variation and clinical heterogeneity in cystic fibrosis. *Annu Rev Pathol,* 7, 267-82.

DUNHAM, C. & HARMS, C. A. 2012. Effects of high-intensity interval training on pulmonary function. *Eur J Appl Physiol,* 112, 3061-8.

DWYER, T. 2021. Huff and puff of exercise for airway clearance in cystic fibrosis: how clear is the evidence? *Thorax,* 76, 746.

DWYER, T. J., ALISON, J. A., MCKEOUGH, Z. J., DAVISKAS, E. & BYE, P. T. P. 2011. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest,* 139, 870-877.

EDGEWORTH, D., KEATING, D., ELLIS, M., BUTTON, B., WILLIAMS, E., CLARK, D., TIERNEY, A., HERITIER, S., KOTSIMBOS, T. & WILSON, J. 2017. Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. *Clin Sci (Lond),* 131, 2037-2045.

ELBORN, J. S., BELL, S. C., MADGE, S. L., BURGEL, P. R., CASTELLANI, C., CONWAY, S., DE RIJCKE, K., DEMBSKI, B., DREVINEK, P., HEIJERMAN, H. G., INNES, J. A., LINDBLAD, A., MARSHALL, B., OLESEN, H. V., REIMANN, A. L., SOLE, A., VIVIANI, L., WAGNER, T. O., WELTE, T. & BLASI, F. 2016. Report of the European Respiratory Society/European Cystic Fibrosis Society task force on the care of adults with cystic fibrosis. *Eur Respir J,* 47, 420-8.

ELKINS, M. R., DENTICE, R. L. & BYE, P. T. 2009. Validation of the MST-25: an extension of the modified shuttle test. *J Cyst Fibros,* 8, S70.

ELKINS, M. R., LANE, T., GOLDBERG, H., PAGLIUSO, J., GARSKE, L. A., HECTOR, E., MARCHETTO, L., ALISON, J. A. & BYE, P. T. 2005. Effect of airway clearance techniques on the efficacy of the sputum induction procedure. *Eur Respir J,* 26**,** 904-8.

EMERSON, J., ROSENFELD, M., MCNAMARA, S., RAMSEY, B. & GIBSON, R. L. 2002. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol,* 34**,** 91-100.

ENG, P. A., MORTON, J., DOUGLASS, J. A., RIEDLER, J., WILSON, J. & ROBERTSON, C. F. 1996. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol,* 21**,** 77-83.

ERICKSON, M. L., SEIGLER, N., MCKIE, K. T., MCCULLY, K. K. & HARRIS, R. A. 2015. Skeletal muscle oxidative capacity in patients with cystic fibrosis. *Exp Physiol,* 100**,** 545-52.

EUROPEAN MEDICINES AGENCY COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE. 2009. Guideline for the clinicial development of medicinal products for the treatment of cystic fibrosis, EMEA/CHMP/EWP/9147/2008. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017055.pdf.

FAIGENBAUM, A. D., KRAEMER, W. J., BLIMKIE, C. J., JEFFREYS, I., MICHELI, L. J., NITKA, M. & ROWLAND, T. W. 2009. Youth resistance training: updated position statement paper from the national strength and conditioning association. *J Strength Cond Res,* 23**,** S60-79.

FAIGENBAUM, A. D., LLOYD, R. S. & MYER, G. D. 2013. Youth resistance training: past practices, new perspectives, and future directions. *Pediatr Exerc Sci,* 25**,** 591-604.

FAIGENBAUM, A. D., MCFARLAND, J. E., HERMAN, R. E., NACLERIO, F., RATAMESS, N. A., KANG, J. & MYER, G. D. 2012. Reliability of the one-repetition-maximum power clean test in adolescent athletes. *J Strength Cond Res,* 26**,** 432-7.

FAIGENBAUM, A. D. & MYER, G. D. 2010a. Pediatric resistance training: benefits, concerns, and program design considerations. *Curr Sports Med Rep,* 9**,** 161-8.

FAIGENBAUM, A. D. & MYER, G. D. 2010b. Resistance training among young athletes: safety, efficacy and injury prevention effects. *Br J Sports Med,* 44**,** 56-63.

FARRELL, P. M., WHITE, T. B., REN, C. L., HEMPSTEAD, S. E., ACCURSO, F., DERICHS, N., HOWENSTINE, M., MCCOLLEY, S. A., ROCK, M., ROSENFELD, M., SERMET-GAUDELUS, I., SOUTHERN, K. W., MARSHALL, B. C. & SOSNAY, P. R. 2017. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr,* 181S**,** S4-S15 e1.

FLUME, P. A., MOGAYZEL, P. J., JR., ROBINSON, K. A., GOSS, C. H., ROSENBLATT, R. L., KUHN, R. J., MARSHALL, B. C. & CLINICAL PRACTICE GUIDELINES FOR PULMONARY THERAPIES COMMITTEE 2009a. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med,* 180**,** 802-8.

FLUME, P. A., ROBINSON, K. A., O'SULLIVAN, B. P., FINDER, J. D., VENDER, R. L., WILLEY-COURAND, D. B., WHITE, T. B., MARSHALL, B. C. & CLINICAL PRACTICE GUIDELINES FOR PULMONARY THERAPIES COMMITTEE 2009b. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care,* 54**,** 522-37.

FRANKE, R. H. & KAUL, J. D. 1978. The Hawthorne Experiments: First Statistical Interpretation. *American Sociological Review,* 43**,** 623-643.

FUCHS, S. I. & GAPPA, M. 2011. Lung clearance index: clinical and research applications in children. *Paediatr Respir Rev,* 12**,** 264-70.

GABEL, M. E., FOX, C. K., GRIMES, R. A., LOWMAN, J. D., MCDONALD, C. M., STALLINGS, V. A. & MICHEL, S. H. 2022. Overweight and cystic fibrosis: An unexpected challenge. *Pediatr Pulmonol,* 57 Suppl 1**,** S40-S49.

GAMBAZZA, S., MARIANI, A., BRIVIO, A., CARTA, F., BLARDONE, C., LISIERO, S., RUSSO, M. & COLOMBO, C. 2022. Time Free From Hospitalization in Children and Adolescents With Cystic Fibrosis: Findings From FEV1, Lung Clearance Index and Peak Work Rate. *Front Pediatr,* 10**,** 926248.

GAMELIN, F. X., BAQUET, G., BERTHOIN, S., THEVENET, D., NOURRY, C., NOTTIN, S. & BOSQUET, L. 2009. Effect of high intensity intermittent training on heart rate variability in prepubescent children. *Eur J Appl Physiol,* 105**,** 731-8.

GEE, L., ABBOTT, J., CONWAY, S. P., ETHERINGTON, C. & WEBB, A. K. 2003. Quality of life in cystic fibrosis: the impact of gender, general health perceptions and disease severity. *J Cyst Fibros,* 2**,** 206-213.

GIBSON, R. L., BURNS, J. L. & RAMSEY, B. W. 2003. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med,* 168**,** 918-51.

GODFREY, S. 1970. Physiological response to exercise in children with lung or heart disease. *Arch Dis Child,* 45**,** 534-8.

GODFREY, S., DAVIES, C. T., WOZNIAK, E. & BARNES, C. A. 1971. Cardio-respiratory response to exercise in normal children. *Clin Sci,* 40**,** 419-31.

GODFREY, S. & MEARNS, M. 1971. Pulmonary function and response to exercise in cystic fibrosis. *Arch Dis Child,* 46**,** 144-51.

GRIEVE, R., THOMPSON, S., NORMAND, C., SURI, R., BUSH, A. & WALLIS, C. 2003. A cost-effectiveness analysis of rhDNase in children with cystic fibrosis. *Int J Technol Assess Health Care,* 19**,** 71-9.

GROEN, W. G., HULZEBOS, H. J., HELDERS, P. J. & TAKKEN, T. 2010. Oxygen uptake to work rate slope in children with a heart, lung or muscle disease. *Int J Sports Med,* 31**,** 202-6.

GRUBER, W., ORENSTEIN, D. M. & BRAUMANN, K. M. 2011a. Do responses to exercise training in cystic fibrosis depend on initial fitness level? *Eur Respir J,* 38**,** 1336-42.

GRUBER, W., ORENSTEIN, D. M., BRAUMANN, K. M., PAUL, K. & HULS, G. 2011b. Effects of an exercise program in children with cystic fibrosis: are there differences between females and males? *J Pediatr,* 158**,** 71-6.

GRUET, M., TROOSTERS, T. & VERGES, S. 2017. Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions. *J Cyst Fibros,* 16**,** 538-552.

GU, Y., GARCIA-PEREZ, S., MASSIE, J. & VAN GOOL, K. 2015. Cost of care for cystic fibrosis: an investigation of cost determinants using national registry data. *Eur J Health Econ,* 16**,** 709-17.

GULMANS, V. A., DE MEER, K., BRACKEL, H. J., FABER, J. A., BERGER, R. & HELDERS, P. J. 1999. Outpatient exercise training in children with cystic fibrosis: physiological effects, perceived competence, and acceptability. *Pediatr Pulmonol,* 28**,** 39-46.

GULMANS, V. A., DE MEER, K., BRACKEL, H. J. & HELDERS, P. J. 1997. Maximal work capacity in relation to nutritional status in children with cystic fibrosis. *Eur Respir J,* 10**,** 2014-7.

GUSTAFSSON, P. M., AURORA, P. & LINDBLAD, A. 2003. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J,* 22**,** 972-9.

HANKINSON, J. L., ODENCRANTZ, J. R. & FEDAN, K. B. 1999. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med,* 159**,** 179-87.

HATZIAGOROU, E., KAMPOURAS, A., AVRAMIDOU, V., TOULIA, I., CHRYSOCHOOU, E. A., GALOGAVROU, M., KIRVASSILIS, F. & TSANAKAS, J. 2021. Toward the Establishment of New Clinical Endpoints for Cystic Fibrosis: The Role of Lung Clearance Index and Cardiopulmonary Exercise Testing. *Front Pediatr,* 9**,** 635719.

HEBESTREIT, H., ARETS, H. G., AURORA, P., BOAS, S., CERNY, F., HULZEBOS, E. H., KARILA, C., LANDS, L. C., LOWMAN, J. D., SWISHER, A., URQUHART, D. S. & EUROPEAN CYSTIC FIBROSIS EXERCISE WORKING GROUP 2015. Statement on Exercise Testing in Cystic Fibrosis. *Respiration,* 90**,** 332-51.

HEBESTREIT, H., HULZEBOS, E. H. J., SCHNEIDERMAN, J. E., KARILA, C., BOAS, S. R., KRIEMLER, S., DWYER, T., SAHLBERG, M., URQUHART, D. S., LANDS, L. C., RATJEN, F., TAKKEN, T., VARANISTKAYA, L., RÜCKER, V., HEBESTREIT, A., USEMANN, J. & RADTKE, T. 2019. Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis. *Am J Respir Crit Care Med,* 199**,** 987-995.

HEBESTREIT, H., KIESER, S., JUNGE, S., BALLMANN, M., HEBESTREIT, A., SCHINDLER, C., SCHENK, T., POSSELT, H. G. & KRIEMLER, S. 2010. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. *Eur Respir J,* 35**,** 578-83.

HEBESTREIT, H., KRIEMLER, S., SCHINDLER, C., STEIN, L., KARILA, C., URQUHART, D. S., ORENSTEIN, D. M., LANDS, L. C., SCHAEFF, J., EBER, E., RADTKE, T. & ON BEHALF OF THE ACTIVATE-CF STUDY WORKING GROUP 2022. Effects of a Partially Supervised Conditioning Program in Cystic Fibrosis: An International Multicenter, Randomized Controlled Trial (ACTIVATE-CF). *Am J Respir Crit Care Med,* 205**,** 330-339.

HEBESTREIT, H., SCHMID, K., KIESER, S., JUNGE, S., BALLMANN, M., ROTH, K., HEBESTREIT, A., SCHENK, T., SCHINDLER, C., POSSELT, H. G. & KRIEMLER, S. 2014. Quality of life is associated with physical activity and fitness in cystic fibrosis. *BMC Pulm Med,* 14**,** 26.

HEIJERMAN, H., WESTERMAN, E., CONWAY, S., TOUW, D., DORING, G. & CONSENSUS WORKING GROUP 2009. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. *J Cyst Fibros,* 8**,** 295-315.

HEIMESHOFF, M., HOLLMEYER, H., SCHREYOGG, J., TIEMANN, O. & STAAB, D. 2012. Cost of illness of cystic fibrosis in Germany: results from a large cystic fibrosis centre. *Pharmacoeconomics,* 30**,** 763-77.

HEINZ, K. D., WALSH, A., SOUTHERN, K. W., JOHNSTONE, Z. & REGAN, K. H. 2022. Exercise versus airway clearance techniques for people with cystic fibrosis. *Cochrane Database Syst Rev,* 6**,** CD013285.

HELGERUD, J., HØYDAL, K., WANG, E., KARLSEN, T., BERG, P., BJERKAAS, M., SIMONSEN, T., HELGESEN, C., HJORTH, N., BACH, R. & HOFF, J. 2007. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc,* 39**,** 665-71.

HENRY, B., AUSSAGE, P., GROSSKOPF, C. & GOEHRS, J. M. 2003. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res,* 12**,** 63-76.

HIGGINS, L. W., ROBERTSON, R. J., KELSEY, S. F., OLSON, M. B., HOFFMAN, L. A., REBOVICH, P. J., HAILE, L. & ORENSTEIN, D. M. 2013. Exercise intensity self-regulation using the OMNI scale in children with cystic fibrosis. *Pediatr Pulmonol,* 48**,** 497-505.

HILLS, A. P., MOKHTAR, N. & BYRNE, N. M. 2014. Assessment of physical activity and energy expenditure: an overview of objective measures. *Front Nutr,* 1**,** 5.

HOLLIN, I. L. & ROBINSON, K. A. 2016. A Scoping Review of Healthcare Costs for Patients with Cystic Fibrosis. *Appl Health Econ Health Policy,* 14**,** 151-9.

HOLLMEYER, H., SCHREYOGG, J., WAHN, U. & STAAB, D. 2011. Staff costs of hospital-based outpatient care of patients with cystic fibrosis. *Health Econ Rev,* 1**,** 10.

HOMMERDING, P. X., BAPTISTA, R. R., MAKAREWICZ, G. T., SCHINDEL, C. S., DONADIO, M. V., PINTO, L. A. & MAROSTICA, P. J. 2015. Effects of an educational intervention of physical activity for children and adolescents with cystic fibrosis: a randomized controlled trial. *Respir Care,* 60**,** 81-7.

HOO, A. F., THIA, L. P., NGUYEN, T. T., BUSH, A., CHUDLEIGH, J., LUM, S., AHMED, D., BALFOUR LYNN, I., CARR, S. B., CHAVASSE, R. J., COSTELOE, K. L., PRICE, J., SHANKAR, A., WALLIS, C., WYATT, H. A., WADE, A., STOCKS, J. & LONDON CYSTIC FIBROSIS COLLABORATION 2012. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. *Thorax,* 67**,** 874-81.

HULZEBOS, H. J., SNIEDER, H., VAN DER ET, J., HELDERS, P. J. & TAKKEN, T. 2011. High-intensity interval training in an adolescent with cystic fibrosis: a physiological perspective. *Physiother Theory Pract,* 27**,** 231-7.

HULZEBOS, H. J., WERKMAN, M. S., VAN BRUSSEL, M. & TAKKEN, T. 2012. Towards an individualized protocol for workload increments in cardiopulmonary exercise testing in children and adolescents with cystic fibrosis. *J Cyst Fibros,* 11**,** 550-4.

HUSEREAU, D., DRUMMOND, M., PETROU, S., CARSWELL, C., MOHER, D., GREENBERG, D., AUGUSTOVSKI, F., BRIGGS, A. H., MAUSKOPF, J., LODER, E. & ISPOR HEALTH ECONOMIC EVALUATION PUBLICATION GUIDELINES - CHEERS GOOD REPORTING PRACTICES TASK FORCE 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) - explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health,* 16**,** 231-50.

HUSSEY, J., GORMLEY, J., LEEN, G. & GREALLY, P. 2002. Peripheral muscle strength in young males with cystic fibrosis. *J Cyst Fibros,* 1**,** 116-21.

IONESCU, A., IONESCU, A. A., PAYNE, N., OBIETA-FRESNEDO, I., FRASER, A. & SHALE, D. 2001. Subclinical Right Ventricular Dysfunction in Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine,* 163**,** 1212-1218.

JONES, S. R., CARLEY, S. & HARRISON, M. 2003. An introduction to power and sample size estimation. *Emerg. Med.,* 20**,** 453.

KAPLAN, R. M., ANDERSON, J. P., WU, A., MATHEWS, C., KOZIN, F. & ORENSTEIN, D. 1989. The quality of well being scale. *Med Care,* 27**,** 27-42.

KARILA, C., DE BLIC, J., WAERNESSYCKLE, S., BENOIST, M. R. & SCHEINMANN, P. 2001. Cardiopulmonary exercise testing in children: an individualized protocol for workload increase. *Chest,* 120**,** 81-7.

KARLSON, C. W. & RAPOFF, M. A. 2009. Attrition in randomized controlled trials for pediatric chronic conditions. *J Pediatr Psychol,* 34**,** 782-93.

KENDRICK, A. H. 2006. Airway clearance techniques in cystic fibrosis. *Eur Respir J,* 27**,** 1082-3.

KENT, L., REIX, P., INNES, J. A., ZIELEN, S., LE BOURGEOIS, M., BRAGGION, C., LEVER, S., ARETS, H. G. M., BROWNLEE, K., BRADLEY, J. M., BAYFIELD, K., O'NEILL, K., SAVI, D., BILTON, D., LINDBLAD, A., DAVIES, J. C., SERMET, I. & DE BOECK, K. 2014. Lung clearance index: Evidence for use in clinical trials in cystic fibrosis. *J Cyst Fibros,* 13**,** 123-138.

KEOCHKERIAN, D., CHLIF, M., DELANAUD, S., GAUTHIER, R., MAINGOURD, Y. & AHMAIDI, S. 2005. Timing and driving components of the breathing strategy in children with cystic fibrosis during exercise. *Pediatr Pulmonol,* 40**,** 449-56.

KEREM, E., CONWAY, S., ELBORN, S., HEIJERMAN, H. & CONSENSUS COMMITTEE 2005. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros,* 4**,** 7-26.

KEREM, E., VIVIANI, L., ZOLIN, A., MACNEILL, S., HATZIAGOROU, E., ELLEMUNTER, H., DREVINEK, P., GULMANS, V., KRIVEC, U., OLESEN, H. & ECFS PATIENT REGISTRY STEERING GROUP 2014. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. *Eur Respir J,* 43**,** 125-33.

KIM, C. S., GREENE, M. A., SANKARAN, S. & SACKNER, M. A. 1986. Mucus transport in the airways by two-phase gas-liquid flow mechanism: continuous flow model. *J Appl Physiol (1985),* 60**,** 908-17.

KIM, C. S., IGLESIAS, A. J. & SACKNER, M. A. 1987. Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *J Appl Physiol (1985),* 62**,** 959-71.

KIRKWOOD, B. R. & STERNE, J. A. C. 2012. Calculation of Required Sample Size. *Essential Medical Statistics, 2nd Edition.* 2nd ed. London, United Kingdom: Wiley-Blackwell.

KLIJN, P. H., OUDSHOORN, A., VAN DER ENT, C. K., VAN DER NET, J., KIMPEN, J. L. & HELDERS, P. J. 2004. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest,* 125**,** 1299-305.

KLIJN, P. H., VAN DER NET, J., KIMPEN, J. L., HELDERS, P. J. & VAN DER ENT, C. K. 2003. Longitudinal determinants of peak aerobic performance in children with cystic fibrosis. *Chest,* 124**,** 2215-9.

KONSTAN, M. W., MORGAN, W. J., BUTLER, S. M., PASTA, D. J., CRAIB, M. L., SILVA, S. J., STOKES, D. C., WOHL, M. E., WAGENER, J. S., REGELMANN, W. E., JOHNSON, C. A. & SCIENTIFIC ADVISORY GROUP AND THE INVESTIGATORS AND COORDINATORS OF THE EPIDEMIOLOGIC STUDY OF CYSTIC FIBROSIS 2007. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr,* 151**,** 134-9, 139 e1.

KONSTAN, M. W., WAGENER, J. S., VANDEVANTER, D. R., PASTA, D. J., YEGIN, A., RASOULIYAN, L. & MORGAN, W. J. 2012. Risk factors for rate of decline in FEV_1 in adults with cystic fibrosis. *J Cyst Fibros,* 11**,** 405-11.

KOTHA, K. & CLANCY, J. P. 2013. Ivacaftor treatment of cystic fibrosis patients with the G551D mutation: a review of the evidence. *Ther Adv Respir Dis,* 7**,** 288-96.

KRAUTH, C., JALILVAND, N., WELTE, T. & BUSSE, R. 2003. Cystic fibrosis: cost of illness and considerations for the economic evaluation of potential therapies. *Pharmacoeconomics,* 21**,** 1001-24.

KRIEMLER, S., KIESER, S., JUNGE, S., BALLMANN, M., HEBESTREIT, A., SCHINDLER, C., STUSSI, C. & HEBESTREIT, H. 2013. Effect of supervised training on FEV_1 in cystic fibrosis: a randomised controlled trial. *J Cyst Fibros,* 12**,** 714-20.

LABOMBARDA, F., SALOUX, E., BROUARD, J., BERGOT, E. & MILLIEZ, P. 2016. Heart involvement in cystic fibrosis: A specific cystic fibrosis-related myocardial changes? *Respir Med,* 118**,** 31-38.

LAO, O., ANDRES, A. M., MATEU, E., BERTRANPETIT, J. & CALAFELL, F. 2003. Spatial patterns of cystic fibrosis mutation spectra in European populations. *Eur J Hum Genet,* 11**,** 385-94.

LAURENT, C. M., VERVAECKE, L. S., KUTZ, M. R. & GREEN, J. M. 2014. Sex-specific responses to self-paced, high-intensity interval training with variable recovery periods. *J Strength Cond Res,* 28**,** 920-7.

LEDGER, S. J., OWEN, E., PRASAD, S. A., GOLDMAN, A., WILLAMS, J. & AURORA, P. 2013. A pilot outreach physiotherapy and dietetic quality improvement initiative reduces IV antibiotic requirements in children with moderate-severe cystic fibrosis. *J Cyst Fibros,* 12**,** 766-72.

LEGER, L. A., MERCIER, D., GADOURY, C. & LAMBERT, J. 1988. The multistage 20 metre shuttle run test for aerobic fitness. *J Sports Sci,* 6**,** 93-101.

LESTER, M. K. & FLUME, P. A. 2009. Airway-clearance therapy guidelines and implementation. *Respir Care,* 54**,** 733-50; Discussion 751-3.

LIEU, T. A., RAY, G. T., FARMER, G. & SHAY, G. F. 1999. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics,* 103**,** e72.

LIOU, T. G., ELKIN, E. P., PASTA, D. J., JACOBS, J. R., KONSTAN, M. W., MORGAN, W. J. & WAGENER, J. S. 2010. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros,* 9**,** 250-6.

LOPES-PACHECO, M. 2016. CFTR Modulators: Shedding light on precision medicine for cystic fibrosis. *Front. Pharmacol.,* 7**,** 275-275.

LUM, S., GUSTAFSSON, P., LJUNGBERG, H., HULSKAMP, G., BUSH, A., CARR, S. B., CASTLE, R., HOO, A. F., PRICE, J., RANGANATHAN, S., STROOBANT, J., WADE, A., WALLIS, C., WYATT, H., STOCKS, J. & LONDON CYSTIC FIBROSIS COLLABORATION 2007. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. *Thorax,* 62**,** 341-7.

LUM, S., STOCKS, J., STANOJEVIC, S., WADE, A., ROBINSON, P., GUSTAFSSON, P., BROWN, M., AURORA, P., SUBBARAO, P., HOO, A. F. & SONNAPPA, S. 2013. Age and height dependence of lung clearance index and functional residual capacity. *Eur Respir J,* 41**,** 1371-7.

LUMLEY, T., DIEHR, P., EMERSON, S. & CHEN, L. 2002. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health,* 23**,** 151-69.

LYCZAK, J. B., CANNON, C. L. & PIER, G. B. 2002. Lung infections associated with cystic fibrosis. *Clin Microbiol Rev,* 15**,** 194-222.

MARCOTTE, J. E., CANNY, G. J., GRISDALE, R., DESMOND, K., COREY, M., ZINMAN, R., LEVISON, H. & COATES, A. L. 1986. Effects of nutritional status on exercise performance in advanced cystic fibrosis. *Chest,* 90**,** 375-9.

MARIN, V. B., VELANDIA, S., HUNTER, B., GATTAS, V., FIELBAUM, O., HERRERA, O. & DIAZ, E. 2004. Energy expenditure, nutrition status, and body composition in children with cystic fibrosis. *Nutrition,* 20**,** 181-6.

MARSHALL, D. A. & HUX, M. 2009. Design and analysis issues for economic analysis alongside clinical trials. *Med Care,* 47**,** S14-20.

MARTIN, N. D., SMITH, W. R., COLE, T. J. & PREECE, M. A. 2007. New height, weight and head circumference charts for British children with Williams syndrome. *Arch Dis Child,* 92**,** 598-601.

MAYELL, S. J., MUNCK, A., CRAIG, J. V., SERMET, I., BROWNLEE, K. G., SCHWARZ, M. J., CASTELLANI, C., SOUTHERN, K. W. & EUROPEAN CYSTIC FIBROSIS SOCIETY NEONATAL SCREENING WORKING GROUP 2009. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. *J Cyst Fibros,* 8**,** 71-8.

MCCOOL, F. D. & ROSEN, M. J. 2006. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. *Chest,* 129**,** 250S-259S.

MCKONE, E. F., BARRY, S. C., FITZGERALD, M. X. & GALLAGHER, C. G. 1999. Reproducibility of maximal exercise ergometer testing in patients with cystic fibrosis. *Chest,* 116**,** 363-8.

MEHTA, G., MACEK, M., JR., MEHTA, A. & EUROPEAN REGISTRY WORKING GROUP 2010. Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries. *J Cyst Fibros,* 9 Suppl 2**,** S5-S21.

MERKUS, P. J., TIDDENS, H. A. & DE JONGSTE, J. C. 2002. Annual lung function changes in young patients with chronic lung disease. *Eur Respir J,* 19**,** 886-91.

MILLA, C. E. 2004. Association of nutritional status and pulmonary function in children with cystic fibrosis. *Curr Opin Pulm Med,* 10**,** 505-9.

MILLER, M. R., HANKINSON, J., BRUSASCO, V., BURGOS, F., CASABURI, R., COATES, A., CRAPO, R., ENRIGHT, P., VAN DER GRINTEN, C. P., GUSTAFSSON, P., JENSEN, R., JOHNSON, D. C., MACINTYRE, N., MCKAY, R., NAVAJAS, D., PEDERSEN, O. F., PELLEGRINO, R., VIEGI, G., WANGER, J. & ATS ERS TASK FORCE 2005. Standardisation of spirometry. *Eur Respir J,* 26**,** 319-38.

MOORCROFT, A. J., DODD, M. E. & WEBB, A. K. 1997. Long-term change in exercise capacity, body mass, and pulmonary function in adults with cystic fibrosis. *Chest,* 111**,** 338-43.

MOORCROFT, A. J., DODD, M. E. & WEBB, A. K. 1998. Exercise limitations and training for patients with cystic fibrosis. *Disabil Rehabil,* 20**,** 247-53.

MOSER, C., TIRAKITSOONTORN, P., NUSSBAUM, E., NEWCOMB, R. & COOPER, D. M. 2000. Muscle size and cardiorespiratory response to exercise in cystic fibrosis. *Am J Respir Crit Care Med,* 162**,** 1823-7.

NATIONAL INSTITUTE FOR HEALTH & CARE EXCELLENCE. 2017. Cystic fibrosis: diagnosis and management. NG78. Available: https://www.nice.org.uk/guidance/ng78 [Accessed 5/1/2018].

NGUYEN, T. T., THIA, L. P., HOO, A. F., BUSH, A., AURORA, P., WADE, A., CHUDLEIGH, J., LUM, S., STOCKS, J. & LONDON CYSTIC FIBROSIS COLLABORATION 2014. Evolution of lung function during the first year of life in newborn screened cystic fibrosis infants. *Thorax,* 69**,** 910-7.

NIXON, P. A., ORENSTEIN, D. M., KELSEY, S. F. & DOERSHUK, C. F. 1992. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med,* 327**,** 1785-8.

O' NEILL, P. A., DODDS, M., PHILLIPS, B., POOLE, J. & WEBB, A. K. 1987. Regular exercise and reduction of breathlessness in patients with cystic fibrosis. *Br J Dis Chest,* 81**,** 62-9.

O'DONOHOE, R. & FULLEN, B. M. 2014. Adherence of subjects with cystic fibrosis to their home program: a systematic review. *Respir Care,* 59**,** 1731-46.

O'NEILL, P. A., DODDS, M., PHILLIPS, B., POOLE, J. & WEBB, A. K. 1987. Regular exercise and reduction of breathlessness in patients with cystic fibrosis. *Br J Dis Chest,* 81**,** 62-9.

O'SULLIVAN, B. P. & FREEDMAN, S. D. 2009. Cystic fibrosis. *Lancet,* 373**,** 1891-1904.

OLVEIRA, G., OLVEIRA, C., GASPAR, I., CRUZ, I., CRUZ, I., DORADO, A., PEREZ-RUIZ, E., PORRAS, N. & SORIGUER, F. 2010. Validation of the Spanish version of the Revised Cystic Fibrosis Quality of Life Questionnaire in adolescents and adults (CFQR 14+ Spain). *Arch Bronconeumol,* 46**,** 165-175.

OPARA, J., KUCIO, C., MAŁECKI, A. & PILCH, J. 2013. Methods of blinding clinical trials in physiotherapy. *Physiotherapy,* 21.

ORENSTEIN, D. M., HOVELL, M. F., MULVIHILL, M., KEATING, K. K., HOFSTETTER, C. R., KELSEY, S., MORRIS, K. & NIXON, P. A. 2004. Strength vs aerobic training in children with cystic fibrosis: a randomized controlled trial. *Chest,* 126**,** 1204-14.

ORENSTEIN, D. M., NIXON, P. A., ROSS, E. A. & KAPLAN, R. M. 1989. The quality of well-being in cystic fibrosis. *Chest,* 95**,** 344-7.

PAN, H. & COLE, T. J. 2011. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Version 2.74. Available: http://www.healthforallchildren.co.uk/.

PARANJAPE, S. M., BARNES, L. A., CARSON, K. A., VON BERG, K., LOOSEN, H. & MOGAYZEL, P. J. J. 2012. Exercise improves lung function and habitual activity in children with cystic fibrosis. *J Cyst Fibros,* 11**,** 18-23.

PARAZZI, P. L., MARSON, F. A., RIBEIRO, M. A., DE ALMEIDA, C. C., MARTINS, L. C., PASCHOAL, I. A., TORO, A. A., SCHIVINSKI, C. I. & RIBEIRO, J. D. 2015. Ventilatory abnormalities in patients with cystic fibrosis undergoing the submaximal treadmill exercise test. *BMC Pulm Med,* 15**,** 63.

PARKINS, M. D. & FLOTO, R. A. 2015. Emerging bacterial pathogens and changing concepts of bacterial pathogenesis in cystic fibrosis. *J Cyst Fibros,* 14**,** 293-304.

PATEL, S., ABRAHAMSON, E., GOLDRING, S., GREEN, H., WICKENS, H. & LAUNDY, M. 2015. Good practice recommendations for paediatric outpatient parenteral antibiotic therapy (p-OPAT) in the UK: a consensus statement. *J Antimicrob Chemother,* 70**,** 360-73.

PENAFORTES, J. T., GUIMARAES, F. S., MOCO, V. J., ALMEIDA, V. P., MENEZES, S. L. & LOPES, A. J. 2013. Relationship between body balance, lung function, nutritional status and functional capacity in adults with cystic fibrosis. *Braz J Phys Ther,* 17**,** 450-7.

PEREZ, M., GROENEVELD, I. F., SANTANA-SOSA, E., FIUZA-LUCES, C., GONZALEZ-SAIZ, L., VILLA-ASENSI, J. R., LOPEZ-MOJARES, L. M., RUBIO, M. & LUCIA, A. 2014. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. *Pediatr Pulmonol,* 49**,** 641-9.

PERREM, L., RAYMENT, J. H. & RATJEN, F. 2018. The lung clearance index as a monitoring tool in cystic fibrosis: ready for the clinic? *Curr Opin Pulm Med,* 24**,** 579-585.

PETERSON, M. L., JACOBS, D. R., JR. & MILLA, C. E. 2003. Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. *Pediatrics,* 112**,** 588-92.

PIANOSI, P., LEBLANC, J. & ALMUDEVAR, A. 2005a. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax,* 60**,** 50-4.

PIANOSI, P., LEBLANC, J. & ALMUDEVAR, A. 2005b. Relationship between FEV_1 and peak oxygen uptake in children with cystic fibrosis. *Pediatr Pulmonol,* 40**,** 324-9.

PLOWMAN, S. 2001a. Children Aren't Miniature Adults: Similarities and Differences in Physiological Responses to Exercise: Part 1. *ACSM's Health & Fitness Journal,* 5**,** 11-17.

PLOWMAN, S. 2001b. Children Aren't Miniature Adults: Similarities and Differences in Physiological Responses to Exercise: Part 2. *ACSM s Health & Fitness Journal,* 5**,** 13-18.

PRASAD, S. A. & CERNY, F. J. 2002. Factors that influence adherence to exercise and their effectiveness: application to cystic fibrosis. *Pediatr Pulmonol,* 34**,** 66-72.

QUANJER, P. H., BORSBOOM, G. J., BRUNEKREEF, B., ZACH, M., FORCHE, G., COTES, J. E., SANCHIS, J. & PAOLETTI, P. 1995. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol,* 19**,** 135-42.

QUANJER, P. H., HALL, G. L., STANOJEVIC, S., COLE, T. J., STOCKS, J. & ERS GLOBAL LUNG FUNCTION INITIATIVE 2012a. Age and height based prediction bias in spirometry reference equations. *Eur Respir J,* 40**,** 190-7.

QUANJER, P. H., STANOJEVIC, S., COLE, T. J., BAUR, X., HALL, G. L., CULVER, B. H., ENRIGHT, P. L., HANKINSON, J. L., IP, M. S., ZHENG, J., STOCKS, J. & ERS GLOBAL LUNG FUNCTION INITIATIVE 2012b. Multi-ethnic reference values for spirometry for the 3-95 yr age range: the global lung function 2012 equations. *Eur Respir J,* 40**,** 1324-43.

QUANJER, P. H., STANOJEVIC, S., COLE, T. J. & STOCKS, S. 2013. GLI-2012 Desktop Software for Large Data Sets. 1.3.4, Build 3, 7 April 2013 ed.

QUE, C., CULLINAN, P. & GEDDES, D. 2006. Improving rate of decline of FEV_1 in young adults with cystic fibrosis. *Thorax,* 61**,** 155-7.

QUINTON, P. M. 1999. Physiological basis of cystic fibrosis: a historical perspective. *Physiol Rev,* 79**,** S3-S22.

QUITTNER, A. L. 1998. Measurement of quality of life in cystic fibrosis. *Curr Opin Pulm Med,* 4**,** 326-31.

QUITTNER, A. L., BUU, A., MESSER, M. A., MODI, A. C. & WATROUS, M. 2005. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest,* 128**,** 2347-54.

QUITTNER, A. L., MODI, A. C., WAINWRIGHT, C., OTTO, K., KIRIHARA, J. & MONTGOMERY, A. B. 2009. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest,* 135**,** 1610-1618.

QUITTNER, A. L., MODI, A. C., WATROUS, M. & MESSER, M. A. 2002. Cystic Fibrosis questionnaire-revised: A health-related quality of life measure. CFQ-R Scoring calculator. 2.0 ed. Miami, USA: Cystic Fibrosis Foundation.

RADTKE, T., CROOK, S., KALTSAKAS, G., LOUVARIS, Z., BERTON, D., URQUHART, D. S., KAMPOURAS, A., RABINOVICH, R. A., VERGES, S., KONTOPIDIS, D., BOYD, J., TONIA, T., LANGER, D., DE BRANDT, J., GOERTZ, Y. M. J., BURTIN, C., SPRUIT, M. A., BRAEKEN, D. C. W., DACHA, S., FRANSSEN, F. M. E., LAVENEZIANA, P., EBER, E., TROOSTERS, T., NEDER, J. A., PUHAN, M. A., CASABURI, R., VOGIATZIS, I. & HEBESTREIT, H. 2019. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev,* 28.

RADTKE, T., NOLAN, S. J., HEBESTREIT, H. & KRIEMLER, S. 2015. Physical exercise training for cystic fibrosis. *Cochrane Database Syst Rev,* 6**,** CD002768.

RADTKE, T., SMITH, S., NEVITT, S. J., HEBESTREIT, H. & KRIEMLER, S. 2022. Physical activity and exercise training in cystic fibrosis. *Cochrane Database Syst Rev,* 8**,** CD002768.

RADTKE, T., STEVENS, D., BENDEN, C. & WILLIAMS, C. A. 2009. Clinical exercise testing in children and adolescents with cystic fibrosis. *Pediatr Phys Ther,* 21**,** 275-81.

RAMPHUL, K., MEJIAS, S. G. & JOYNAUTH, J. 2019. An update on admissions of cystic fibrosis children in the United States based on national databases. *Hosp Pract (1995),* 47**,** 111-112.

RAND, S., HILL, L. & PRASAD, S. A. 2013. Physiotherapy in cystic fibrosis: optimising techniques to improve outcomes. *Paediatr Respir Rev,* 14**,** 263-9.

RAND, S. & PRASAD, S. A. 2012. Exercise as part of a cystic fibrosis therapeutic routine. *Expert Rev Respir Med,* 6**,** 341-51; quiz 352.

RAND, S., PRASAD, S. A. & MAIN, E. 2015. New incremental field step-test (iSTEP) is valid and feasible in measuring near maximal exercise performance in children with cystic fibrosis. *Physiotherapy,* 101**,** e931-e932.

RASCH, D. & GUIARD, V. 2004. The robustness of parametric statistical methods. *Psychol Sci.,* 46**,** 175-208.

RATJEN, F. & DORING, G. 2003. Cystic fibrosis. *Lancet,* 361**,** 681-9.

RIORDAN, J. R., ROMMENS, J. M., KEREM, B., ALON, N., ROZMAHEL, R., GRZELCZAK, Z., ZIELENSKI, J., LOK, S., PLAVSIC, N. & CHOU, J. L. 1989. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science,* 245**,** 1066-73.

RISSER, W. L. 1991. Weight-training injuries in children and adolescents. *Am Fam Physician,* 44**,** 2104-8.

ROBERTSON, R. J., GOSS, F. L., ANDREACCI, J. L., DUBE, J. J., RUTKOWSKI, J. J., SNEE, B. M., KOWALLIS, R. A., CRAWFORD, K., AARON, D. J. & METZ, K. F. 2005. Validation of the children's OMNI RPE scale for stepping exercise. *Med Sci Sports Exerc,* 37**,** 290-8.

ROBERTSON, R. J., GOSS, F. L., BELL, J. A., DIXON, C. B., GALLAGHER, K. I., LAGALLY, K. M., TIMMER, J. M., ABT, K. L., GALLAGHER, J. D. & THOMPKINS, T. 2002. Self-regulated cycling using the Children's OMNI Scale of Perceived Exertion. *Med Sci Sports Exerc,* 34**,** 1168-75.

ROBERTSON, R. J., GOSS, F. L., BOER, N. F., PEOPLES, J. A., FOREMAN, A. J., DABAYEBEH, I. M., MILLICH, N. B., BALASEKARAN, G., RIECHMAN, S. E., GALLAGHER, J. D. & THOMPKINS, T. 2000. Children's OMNI scale of perceived exertion: mixed gender and race validation. *Med Sci Sports Exerc,* 32**,** 452-8.

ROBINSON, P. D., COOPER, P., VAN ASPEREN, P., FITZGERALD, D. & SELVADURAI, H. 2009a. Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis. *Pediatr Pulmonol,* 44**,** 733-42.

ROBINSON, P. D., GOLDMAN, M. D. & GUSTAFSSON, P. M. 2009b. Inert Gas Washout: Theoretical Background and Clinical Utility in Respiratory Disease. *Respiration,* 78**,** 339-355.

ROBSON, M., ABBOTT, J., WEBB, K., DODD, M. & WALSWORTH-BELL, J. 1992. A cost description of an adult cystic fibrosis unit and cost analyses of different categories of patients. *Thorax,* 47**,** 684-9.

ROCA, J., WHIPP, B. J., AGUSTÍ, A. G. N., ANDERSON, S. D., CASABURI, R., COTES, J. E., DONNER, C. F., ESTENNE, M., FOLGERIN, H., HIGENBOTTAM, T. W., KILLIAN, K. J., PALANGE, P., PATESSIO, A., PREFAUT, C., SERGYSELS, R., WAGNER, P. D., WEISMAN, I. & ON BEHALF OF THE EUROPEAN RESPIRATORY SOCIETY TASK FORCE ON STANDARDIZATION OF CLINICAL EXERCISE TESTING 1997. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. *Eur Respir J,* 10**,** 2662-89.

ROSENBERG, M. A. & FARRELL, P. M. 2005. Assessing the cost of cystic fibrosis diagnosis and treatment. *J Pediatr,* 147**,** S101-5.

ROSENSTEIN, B. J. & CUTTING, G. R. 1998. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr,* 132**,** 589-95.

ROSENTHAL, M., BAIN, S. H., CRAMER, D., HELMS, P., DENISON, D., BUSH, A. & WARNER, J. O. 1993. Lung function in white children aged 4 to 19 years: I-Spirometry. *Thorax,* 48**,** 794-802.

ROWBOTHAM, N. J. & DANIELS, T. E. 2022. Airway clearance and exercise for people with cystic fibrosis: Balancing longevity with life. *Pediatr Pulmonol,* 57 Suppl 1**,** S50-s59.

ROWBOTHAM, N. J., SMITH, S., LEIGHTON, P. A., RAYNER, O. C., GATHERCOLE, K., ELLIOTT, Z. C., NASH, E. F., DANIELS, T., DUFF, A. J. A., COLLINS, S., CHANDRAN, S., PEAPLE, U., HURLEY, M. N., BROWNLEE, K. & SMYTH, A. R. 2018. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax,* 73**,** 388-390.

ROWE, S. M., MILLER, S. & SORSCHER, E. J. 2005. Cystic fibrosis. *N Engl J Med,* 352**,** 1992-2001.

ROWLAND, T. W. 1993. Does peak VO2 reflect VO2max in children?: evidence from supramaximal testing. *Med Sci Sports Exerc,* 25**,** 689-93.

ROWLAND, T. W. 1996. *Developmental Exercise Physiology*, Champaign, Human Kinetics.

RUCKER, R. W. & HARRISON, G. M. 1974. Outpatient intravenous medications in the management of cystic fibrosis. *Pediatrics,* 54**,** 358-60.

RUF, K. & HEBESTREIT, H. 2009. Exercise-induced hypoxemia and cardiac arrhythmia in cystic fibrosis. *J Cyst Fibros,* 8**,** 83-90.

RUF, K., WINKLER, B., HEBESTREIT, A., GRUBER, W. & HEBESTREIT, H. 2010. Risks associated with exercise testing and sports participation in cystic fibrosis. *J Cyst Fibros,* 9**,** 339-45.

RYSGAARD, U. K., PEDERSEN, C. L., JENSEN, J. H., SORENSEN, L., PHILIPSEN, L. K. D., LEO-HANSEN, C. & OLESEN, H. V. 2022. Change in exercise capacity measured by Cardio-pulmonary Exercise Testing (CPET) in Danish people with cystic fibrosis after initiation of treatment with Lumacaftor/Ivacaftor and Tezacaftor/Ivacaftor. *J Cyst Fibros*.

SALH, W., BILTON, D., DODD, M. & WEBB, A. K. 1989. Effect of exercise and physiotherapy in aiding sputum expectoration in adults with cystic fibrosis. *Thorax,* 44**,** 1006-8.

SANDERS, D. B., BITTNER, R. C., ROSENFELD, M., REDDING, G. J. & GOSS, C. H. 2011. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. *Pediatr Pulmonol,* 46**,** 393-400.

SANDERS, D. B., HOFFMAN, L. R., EMERSON, J., GIBSON, R. L., ROSENFELD, M., REDDING, G. J. & GOSS, C. H. 2010. Return of FEV1 after pulmonary exacerbation in children with cystic fibrosis. *Pediatr Pulmonol,* 45**,** 127-34.

SANTANA-SOSA, E., GONZALEZ-SAIZ, L., GROENEVELD, I. F., VILLA-ASENSI, J. R., BARRIO GOMEZ DE AGUERO, M. I., FLECK, S. J., LOPEZ-MOJARES, L. M., PEREZ, M. & LUCIA, A. 2014. Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial. *Br J Sports Med,* 48**,** 1513-7.

SANTANA-SOSA, E., GROENEVELD, I. F., GONZALEZ-SAIZ, L., LOPEZ-MOJARES, L. M., VILLA-ASENSI, J. R., BARRIO GONZALEZ, M. I., FLECK, S. J., PEREZ, M. & LUCIA, A. 2012. Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial. *Med Sci Sports Exerc,* 44**,** 2-11.

SAWICKI, G. S., HELLER, K. S., DEMARS, N. & ROBINSON, W. M. 2015. Motivating adherence among adolescents with cystic fibrosis: youth and parent perspectives. *Pediatr Pulmonol,* 50**,** 127-36.

SAWICKI, G. S. & TIDDENS, H. 2012. Managing treatment complexity in cystic fibrosis: challenges and opportunities. *Pediatr Pulmonol,* 47**,** 523-33.

SAWYER, A., CAVALHERI, V. & HILL, K. 2020a. Effects of high intensity interval training on exercise capacity in people with chronic pulmonary conditions: a narrative review. *BMC Sports Science, Medicine and Rehabilitation,* 12**,** 22.

SAWYER, A., CAVALHERI, V., JENKINS, S., WOOD, J., CECINS, N., BEAR, N., SINGH, B., GUCCIARDI, D. & HILL, K. 2020b. High-Intensity Interval Training Is Effective at Increasing Exercise Endurance Capacity and Is Well Tolerated by Adults with Cystic Fibrosis. *J Clin Med,* 9.

SAYNOR, Z. L., BARKER, A. R., OADES, P. J. & WILLIAMS, C. A. 2013a. A protocol to determine valid VO_{2max} in young cystic fibrosis patients. *J Sci Med Sport,* 16**,** 539-44.

SAYNOR, Z. L., BARKER, A. R., OADES, P. J. & WILLIAMS, C. A. 2013b. Reproducibility of maximal cardiopulmonary exercise testing for young cystic fibrosis patients. *J Cyst Fibros,* 12**,** 644-50.

SAYNOR, Z. L., BARKER, A. R., OADES, P. J. & WILLIAMS, C. A. 2014. The effect of ivacaftor in adolescents with cystic fibrosis (G551D mutation): an exercise physiology perspective. *Pediatr Phys Ther,* 26**,** 454-61.

SAYNOR, Z. L., CUNNINGHAM, S., MORRISON, L., MAIN, E., VOGIATZIS, I., REID, S. & URQUHART, D. 2022. Exercise as airway clearance therapy (ExACT) in cystic fibrosis: a UK-based e-Delphi survey of patients, caregivers and health professionals. *Thorax***,** thoraxjnl-2022-219213.

SCHLUTER, D. K., OSTRENGA, J. S., CARR, S. B., FINK, A. K., FARO, A., SZCZESNIAK, R. D., KEOGH, R. H., CHARMAN, S. C., MARSHALL, B. C., GOSS, C. H. & TAYLOR-ROBINSON, D. 2022. Lung function in children with cystic fibrosis in the USA and UK: a comparative longitudinal analysis of national registry data. *Thorax,* 77**,** 136-142.

SCHMIDT, A. M., JACOBSEN, U., BREGNBALLE, V., OLESEN, H. V., INGEMANN-HANSEN, T., THASTUM, M. & OLUF SCHIOTZ, P. 2011. Exercise and quality of life in patients with cystic fibrosis: A 12-week intervention study. *Physiother Theory Pract,* 27**,** 548-56.

SCHNEIDERMAN, J. E., WILKES, D. L., ATENAFU, E. G., NGUYEN, T., WELLS, G. D., ALARIE, N., TULLIS, E., LANDS, L. C., COATES, A. L., COREY, M. & RATJEN, F. 2014. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *Eur Respir J,* 43**,** 817-23.

SCHNEIDERMAN-WALKER, J., POLLOCK, S. L., COREY, M., WILKES, D. D., CANNY, G. J., PEDDER, L. & REISMAN, J. J. 2000. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *J Pediatr,* 136**,** 304-10.

SCHNEIDERMAN-WALKER, J., WILKES, D. L., STRUG, L., LANDS, L. C., POLLOCK, S. L., SELVADURAI, H. C., HAY, J., COATES, A. L. & COREY, M. 2005. Sex differences in habitual physical activity and lung function decline in children with cystic fibrosis. *J Pediatr,* 147**,** 321-6.

SELVADURAI, H. C., BLIMKIE, C. J., COOPER, P. J., MELLIS, C. M. & VAN ASPEREN, P. P. 2004. Gender differences in habitual activity in children with cystic fibrosis. *Arch Dis Child,* 89**,** 928-33.

SELVADURAI, H. C., BLIMKIE, C. J., MEYERS, N., MELLIS, C. M., COOPER, P. J. & VAN ASPEREN, P. P. 2002a. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. *Pediatr Pulmonol,* 33**,** 194-200.

SELVADURAI, H. C., COOPER, P. J., MEYERS, N., BLIMKIE, C. J., SMITH, L., MELLIS, C. M. & VAN ASPEREN, P. P. 2003. Validation of shuttle tests in children with cystic fibrosis. *Pediatr Pulmonol,* 35**,** 133-8.

SELVADURAI, H. C., MCKAY, K. O., BLIMKIE, C. J., COOPER, P. J., MELLIS, C. M. & VAN ASPEREN, P. P. 2002b. The relationship between genotype and exercise tolerance in children with cystic fibrosis. *Am J Respir Crit Care Med,* 165**,** 762-5.

SHARMA, D., XING, S., HUNG, Y. T., CASKEY, R. N., DOWELL, M. L. & TOUCHETTE, D. R. 2018. Cost-effectiveness analysis of lumacaftor and ivacaftor combination for the treatment of patients with cystic fibrosis in the United States. *Orphanet J Rare Dis,* 13**,** 172.

SHAW, N., ERICKSON, C., BRYANT, S. J., FERGUSON, V. L., KREBS, M. D., HADLEY-MILLER, N. & PAYNE, K. A. 2018. Regenerative Medicine Approaches for the Treatment of Pediatric Physeal Injuries. *Tissue Eng Part B Rev,* 24**,** 85-97.

SHEEHAN, J. M., ROWLAND, T. W. & BURKE, E. J. 1987. A comparison of four treadmill protocols for determination of maximal oxygen uptake in 10-12-year-old boys. *Int J Sports Med,* 8**,** 31-34.

SHERRARD, L. J., TUNNEY, M. M. & ELBORN, J. S. 2014. Antimicrobial resistance in the respiratory microbiota of people with cystic fibrosis. *Lancet,* 384**,** 703-13.

SINAASAPPEL, M., STERN, M., LITTLEWOOD, J., WOLFE, S., STEINKAMP, G., HEIJERMAN, H. G., ROBBERECHT, E. & DORING, G. 2002. Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros,* 1**,** 51-75.

SINGH, S. J., MORGAN, M. D., SCOTT, S., WALTERS, D. & HARDMAN, A. E. 1992. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax,* 47**,** 1019-24.

STANOJEVIC, S., WADE, A., COLE, T. J., LUM, S., CUSTOVIC, A., SILVERMAN, M., HALL, G. L., WELSH, L., KIRKBY, J., NYSTAD, W., BADIER, M., DAVIS, S., TURNER, S., PICCIONI, P., VILOZNI, D., EIGEN, H., VLACHOS-MAYER, H., ZHENG, J., TOMALAK, W., JONES, M., HANKINSON, J. L., STOCKS, J. & ON BEHALF OF THE ASTHMA UK SPIROMETRY COLLABORATIVE GROUP 2009. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med,* 180**,** 547-52.

STANOJEVIC, S., WADE, A. & STOCKS, J. 2010. Reference values for lung function: past, present and future. *Eur Respir J,* 36**,** 12-9.

STEINKAMP, G. & WIEDEMANN, B. 2002. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax,* 57**,** 596-601.

STEVENS, D., OADES, P. J., ARMSTRONG, N. & WILLIAMS, C. A. 2009. Early oxygen uptake recovery following exercise testing in children with chronic chest diseases. *Pediatr Pulmonol,* 44**,** 480-8.

STEVENS, D., OADES, P. J., ARMSTRONG, N. & WILLIAMS, C. A. 2010. A survey of exercise testing and training in UK cystic fibrosis clinics. *J Cyst Fibros,* 9**,** 302-6.

STEVENS, D., OADES, P. J., ARMSTRONG, N. & WILLIAMS, C. A. 2011. Exercise metabolism during moderate-intensity exercise in children with cystic fibrosis following heavy-intensity exercise. *Appl Physiol Nutr Metab,* 36**,** 920-7.

STEVENS, D., STEPHENSON, A., FAUGHNAN, M. E., LEEK, E. & TULLIS, E. 2013. Prognostic relevance of dynamic hyperinflation during cardiopulmonary exercise testing in adult patients with cystic fibrosis. *J Cyst Fibros,* 12**,** 655-61.

STRATH, S. J., KAMINSKY, L. A., AINSWORTH, B. E., EKELUND, U., FREEDSON, P. S., GARY, R. A., RICHARDSON, C. R., SMITH, D. T. & SWARTZ, A. M. 2013. Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American Heart Association. *Circulation,* 128**,** 2259-79.

SUBBARAO, P., MILLA, C., AURORA, P., DAVIES, J. C., DAVIS, S. D., HALL, G. L., HELTSHE, S., LATZIN, P., LINDBLAD, A., PITTMAN, J. E., ROBINSON, P. D., ROSENFELD, M., SINGER, F., STARNER, T. D., RATJEN, F. & MORGAN, W. 2015. Multiple-Breath Washout as a Lung Function Test in Cystic Fibrosis. A Cystic Fibrosis Foundation Workshop Report. *Ann Am Thorac Soc,* 12**,** 932-9.

SULLIVAN, M. M., MOSS, R. B., HINDI, R. D. & LEWISTON, N. J. 1986. Supraventricular tachycardia in patients with cystic fibrosis. *Chest,* 90**,** 239-42.

TAKKEN, T., BONGERS, B. C., VAN BRUSSEL, M., HAAPALA, E. A. & HULZEBOS, E. H. J. 2017. Cardiopulmonary Exercise Testing in Pediatrics. *Ann Am Thorac Soc,* 14**,** S123-S128.

TAKKEN, T. & HULZEBOS, E. H. 2013. Exercise testing and training in chronic childhood conditions. *Hong Kong Physiotherapy Journal,* 31**,** 58-63.

TAYLOR-ROBINSON, D., WHITEHEAD, M., DIDERICHSEN, F., OLESEN, H. V., PRESSLER, T., SMYTH, R. L. & DIGGLE, P. 2012. Understanding the natural progression in %FEV_1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax,* 67**,** 860-6.

THIN, A. G., DODD, J. D., GALLAGHER, C. G., FITZGERALD, M. X. & MCLOUGHLIN, P. 2004. Effect of respiratory rate on airway deadspace ventilation during exercise in cystic fibrosis. *Respir Med,* 98**,** 1063-70.

THOMAS, C., MITCHELL, P., O'ROURKE, P. & WAINWRIGHT, C. 2006. Quality-of-life in children and adolescents with cystic fibrosis managed in both regional outreach and cystic fibrosis center settings in Queensland. *J Pediatr,* 148**,** 508-516.

THOMPSON, W. R. (ed.) 2010. *ACSM's Guidelines for exercise testing and prescription,* Philadelphia: Lippincott Williams & Wilkins.

TOMEZSKO, J. L., STALLINGS, V. A., KAWCHAK, D. A., GOIN, J. E., DIAMOND, G. & SCANLIN, T. F. 1994. Energy Expenditure and Genotype of Children with Cystic Fibrosis. *Pediatric Research,* 35**,** 451-460.

URQUHART, D., SELL, Z., DHOUIEB, E., BELL, G., OLIVER, S., BLACK, R. & TALLIS, M. 2012. Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis. *Pediatr Pulmonol,* 47**,** 1235-41.

URQUHART, D. S. 2011. Exercise testing in cystic fibrosis: why (and how)? *J R Soc Med,* 104 Suppl 1**,** S6-14.

UTTER, A. C., ROBERTSON, R. J., NIEMAN, D. C. & KANG, J. 2002. Children's OMNI Scale of Perceived Exertion: walking/running evaluation. *Med Sci Sports Exerc,* 34**,** 139-44.

VADAGAM, P. & KAMAL, K. M. 2018. Hospitalization costs of cystic fibrosis in the United States: a retrospective analysis. *Hosp Pract (1995),* 46**,** 203-213.

VAN DE WEERT-VAN LEEUWEN, P. B., ARETS, H. G., VAN DER ENT, C. K. & BEEKMAN, J. M. 2013. Infection, inflammation and exercise in cystic fibrosis. *Respir Res,* 14**,** 32.

VAN DE WEERT-VAN LEEUWEN, P. B., HULZEBOS, H. J., WERKMAN, M. S., MICHEL, S., VIJFTIGSCHILD, L. A., VAN MEEGEN, M. A., VAN DER ENT, C. K., BEEKMAN, J. M. & ARETS, H. G. 2014. Chronic inflammation and infection associate with a lower exercise training response in cystic fibrosis adolescents. *Respir Med,* 108**,** 445-52.

VAN DE WEERT-VAN LEEUWEN, P. B., SLIEKER, M. G., HULZEBOS, H. J., KRUITWAGEN, C. L., VAN DER ENT, C. K. & ARETS, H. G. 2012. Chronic infection and inflammation affect exercise capacity in cystic fibrosis. *Eur Respir J,* 39**,** 893-8.

VAN DER GIESSEN, L. J., GOSSELINK, R., HOP, W. C. & TIDDENS, H. A. 2007. Recombinant human DNase nebulisation in children with cystic fibrosis: before bedtime or after waking up? *Eur Respir J,* 30**,** 763-8.

VAN DER SCHANS, C., PRASAD, A. & MAIN, E. 2000. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev***,** CD001401.

VAN DOORN, N. 2010. Exercise programs for children with cystic fibrosis: a systematic review of randomized controlled trials. *Disabil Rehabil,* 32**,** 41-9.

VAN GOOL, K., NORMAN, R., DELATYCKI, M. B., HALL, J. & MASSIE, J. 2013. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. *Value Health,* 16**,** 345-55.

VANDENBRANDEN, S. L., MCMULLEN, A., SCHECHTER, M. S., PASTA, D. J., MICHAELIS, R. L., KONSTAN, M. W., WAGENER, J. S., MORGAN, W. J., MCCOLLEY, S. A., INVESTIGATORS & FOR THE INVESTIGATORS AND COORDINATORS OF THE EPIDEMIOLOGIC STUDY OF CYSTIC FIBROSIS 2012. Lung function decline from adolescence to young adulthood in cystic fibrosis. *Pediatr Pulmonol,* 47**,** 135-43.

VANDEVANTER, D. R., WAGENER, J. S., PASTA, D. J., ELKIN, E., JACOBS, J. R., MORGAN, W. J. & KONSTAN, M. W. 2010. Pulmonary outcome prediction (POP) tools for cystic fibrosis patients. *Pediatr Pulmonol,* 45**,** 1156-66.

VENDRUSCULO, F. M., JOHNSTONE, Z., DHOUIEB, E., DONADIO, M. V. F., CUNNINGHAM, S. & URQUHART, D. S. 2019. Airway clearance physiotherapy improves ventilatory dynamics during exercise in patients with cystic fibrosis: a pilot study. *Arch Dis Child,* 104**,** 37-42.

WADE, A., PAN, H., EATON, S., PIERRO, A. & ONG, E. 2006. An investigation of minimisation criteria. *BMC Med Res Methodol,* 6**,** 11.

WAGENER, J. S., RASOULIYAN, L., VANDEVANTER, D. R., PASTA, D. J., REGELMANN, W. E., MORGAN, W. J., KONSTAN, M. W. & FOR THE INVESTIGATORS AND COORDINATORS OF THE EPIDEMIOLOGIC STUDY OF CYSTIC FIBROSIS 2013. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol,* 48**,** 666-73.

WAINWRIGHT, C. E., ELBORN, J. S., RAMSEY, B. W., MARIGOWDA, G., HUANG, X., CIPOLLI, M., COLOMBO, C., DAVIES, J. C., DE BOECK, K., FLUME, P. A., KONSTAN, M. W., MCCOLLEY, S. A., MCCOY, K., MCKONE, E. F., MUNCK, A., RATJEN, F., ROWE, S. M., WALTZ, D., BOYLE, M. P. & FOR THE TRAFFIC AND TRANSPORT STUDY GROUPS 2015. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med,* 373**,** 220-31.

WANG, X., DOCKERY, D. W., WYPIJ, D., FAY, M. E. & FERRIS, B. G. J. 1993. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol,* 15**,** 75-88.

WARD, N., MORROW, S., STILLER, K. & HOLLAND, A. E. 2021. Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review. *Thorax,* 76**,** 763.

WARD, N., STILLER, K. & HOLLAND, A. E. 2019. Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey. *J Physiother,* 65**,** 43-50.

WARD, N., STILLER, K., ROWE, H., MORROW, S., MORTON, J., GREVILLE, H. & HOLLAND, A. E. 2018. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study. *Respir Med,* 142**,** 23-28.

WASFY, M. M. & BAGGISH, A. L. 2016. Exercise Dose in Clinical Practice. *Circulation,* 133**,** 2297-313.

WATERS, V., STANOJEVIC, S., ATENAFU, E. G., LU, A., YAU, Y., TULLIS, E. & RATJEN, F. 2012. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J,* 40**,** 61-6.

WENNINGER, K., AUSSAGE, P., WAHN, U. & STAAB, D. 2003. The revised German Cystic Fibrosis Questionnaire: Validation of a disease-specific health-related quality of life instrument. *Qual Life Res,* 12**,** 77-85.

WERKMAN, M., JENESON, J., HELDERS, P., ARETS, B., VAN DER ENT, K., VELTHUIS, B., NIEVELSTEIN, R., TAKKEN, T. & HULZEBOS, E. 2016. Exercise oxidative skeletal muscle metabolism in adolescents with cystic fibrosis. *Exp Physiol,* 101**,** 421-31.

WERKMAN, M. S., HULZEBOS, H. J., VAN DE WEERT-VAN LEEUWEN, P. B., ARETS, H. G., HELDERS, P. J. & TAKKEN, T. 2011. Supramaximal verification of peak oxygen uptake in adolescents with cystic fibrosis. *Pediatr Phys Ther,* 23**,** 15-21.

WHITING, P., AL, M., BURGERS, L., WESTWOOD, M., RYDER, S., HOOGENDOORN, M., ARMSTRONG, N., ALLEN, A., SEVERENS, H. & KLEIJNEN, J. 2014. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess,* 18**,** 1-106.

WILKES, D. L., SCHNEIDERMAN, J. E., NGUYEN, T., HEALE, L., MOOLA, F., RATJEN, F., COATES, A. L. & WELLS, G. D. 2009. Exercise and physical activity in children with cystic fibrosis. *Paediatr Respir Rev,* 10**,** 105-9.

WILLIAMS, C. A., BARKER, A. R., DENFORD, S., VAN BEURDEN, S. B., BIANCHIM, M. S., CATERINI, J. E., COX, N. S., MACKINTOSH, K. A., MCNARRY, M. A., RAND, S., SCHNEIDERMAN, J. E., WELLS, G. D., ANDERSON, P., BEEVER, D., BEVERLEY, Z., BUCKLEY, R., BUTTON, B., CAUSER, A. J., CURRAN, M., DWYER, T. J., GORDON, W., GRUET, M., HARRIS, R. A., HATZIAGOROU, E., ERIK HULZEBOS, H. J., KAMPOURAS, A., MORRISON, L., CÁMARA, M. N., REILLY, C. M., SAWYER, A., SAYNOR, Z. L., SHELLEY, J., SPENCER, G., STANFORD, G. E., URQUHART, D. S., YOUNG, R. & TOMLINSON, O. W. 2022. The Exeter Activity Unlimited statement on physical activity and exercise for cystic fibrosis: methodology and results of an international, multidisciplinary, evidence-driven expert consensus. *Chron Respir Dis,* 19**,** 14799731221121670.

WILLIAMS, C. A., BENDEN, C., STEVENS, D. & RADTKE, T. 2010. Exercise training in children and adolescents with cystic fibrosis: theory into practice. *Int J Pediatr,* 2010**,** 1-7.

WILLIAMS, C. A., SAYNOR, Z. L., TOMLINSON, O. W. & BARKER, A. R. 2014. Cystic fibrosis and physiological responses to exercise. *Expert Rev Respir Med,* 8**,** 751-62.

WILSCHANSKI, M. & DURIE, P. R. 1998. Pathology of pancreatic and intestinal disorders in cystic fibrosis. *J R Soc Med,* 91 Suppl 34**,** 40-9.

WILSON, J., YOU, X., ELLIS, M., URQUHART, D. S., JHA, L., DUNCAN, M., TIAN, S., HARRIS, R. A., KOTSIMBOS, T. & KEATING, D. 2021. VO2max as an exercise tolerance endpoint in people with cystic fibrosis: Lessons from a lumacaftor/ivacaftor trial. *J Cyst Fibros,* 20**,** 499-505.

XU, W., SUBBARAO, P. & COREY, M. 2004. Changing patterns of lung function decline in children with cystic fibrosis. *J Cyst Fibros,* 3.

YI, M. S., TSEVAT, J., WILMOTT, R. W., KOTAGAL, U. R. & BRITTO, M. T. 2004. The impact of treatment of pulmonary exacerbations on the health-related quality of life of patients with cystic fibrosis: does hospitalization make a difference? *J Pediatr,* 144**,** 711-8.

ZEMANICK, E. T., HARRIS, J. K., CONWAY, S., KONSTAN, M. W., MARSHALL, B., QUITTNER, A. L., RETSCH-BOGART, G., SAIMAN, L. & ACCURSO, F. J. 2010. Measuring and improving respiratory outcomes in cystic fibrosis lung disease: opportunities and challenges to therapy. *J Cyst Fibros,* 9**,** 1-16.

APPENDIX A: GRANT AWARD

Mr Sean Ledger
Senior Physiotherapist
Great Ormond Street Hospital NHS Foundation Trust
Cytstic Fibrosis Unit, Cardiothracic Department
Great Ormond Street
London WC1N 3JH

40 Bernard Street
London WC1N 1LE
T 020 7239 3000
F 020 7837 5062
www.gosh.org

Grant Holders:	**Mr Sean Ledger & Dr Eleanor Main**
Title of Research:	**A randomised controlled trial investigating the clinical and economic benefits of a new model of care for children with Cystic Fibrosis**
Value of Grant:	**£410,439.00**
Duration:	**36 months**
Start Date:	**1st May 2012**
Institution Ref:	**11AR13**
GOSHCC Grant Ref:	**V1252**

31st May 2012

Dear Sean and Eleanor,

I am pleased to inform you that Great Ormond Street Hospital Children's Charity (GOSHCC) has agreed to award funding of up to **£410,439** for the above project. As recently agreed, Dr Eleanor Maine will be a co-Principal Investigator on the study and will be copied in to all correspondence related to this application.

The funding is subject to GOSHCC Terms and Conditions of Funding and is approved on the condition that it is administered in accordance with the purposes for which it has been awarded. You will be advised of any changes to the Terms and Conditions and it is your responsibility to ensure that appropriate action is taken in order to comply with such changes.

To indicate your acceptance of this award, we request that you both please sign and return the Acceptance Form at the back of the Terms and Conditions by **30th June 2012**. The form needs to be signed by the grant holder(s), General Manager and the Head of Research & Innovation. Funded projects must commence within 12 months of the date of the offer letter unless otherwise agreed with the Charity, please indicate any changes to the start date within the Acceptance Form.

I would appreciate it if the following points and conditions could be noted:

In order that our award enables delivery of the stated research objectives, we require that all staff in receipt of salary funding are supported via their General Managers and Unit Chairs, to protect the percentage of time allocated within the proposal to do the research, for the duration of the award. Acceptance of this award will be taken as confirmation that

this condition will be met, and that individual job plans have been reviewed and revised accordingly.

It is also a condition of the award that the Charity receives an annual report on the progress of this project. This must be provided within three months of each anniversary of the commencement date of the project. A final report must be provided within three months of the end of the project. The Charity will write to notify the Grant Holder of the date by which the report is due and will set out the required format and content of the report. Failure to submit reports on time will jeopardise continuation of the Grant.

Please ensure we are notified if you intend on amending any of the details of this project, as approval for changes may not be sought retrospectively. Claims for reimbursement under the Grant should be made, in arrears, to the Charity's Finance Team. Please ensure that the above GOSHCC Grant Reference code is quoted on all correspondence, including recharge invoices.

I wish you every success with this project.

Yours sincerely,

Andrew Hibbert
Director of Finance

cc Lorna Gibson
Allan Goldman
Anne Layther
Tian Hao
Kathryn Caldwell
Eleanor Main

APPENDIX B: ETHICAL APPROVAL

NRES Committee South East Coast - Kent
Ground Floor
Skipton House
80 London Road
London
SE1 6LH

Telephone: 020 797 22551
Facsimile: 020 797 22592

10 August 2012

Mr Sean J Ledger
Cystic Fibrosis Unit, Level 8 Main Nurses Building
Great Ormond Street Hospital for Children
Great Ormond Street
WC1N 3JH

Dear Mr Ledger

Study title:	**INSPIRE-CF: a randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis**
REC reference:	**12/LO/1135**
Protocol number:	**11AR13**

The Research Ethics Committee reviewed the above application at the meeting held on 25 July 2012. Thank you for attending to discuss the study.

Ethical opinion

The following points were raised in discussion:

1. The Committee commented that this was a very interesting and well put together study which should produce some very meaningful results.

2. The Committee stated that in the child's assent form there was no opportunity for the participant to indicate dissent should they not wish to participate and would recommend that this is inserted as an option. The Committee strongly recommended that parents should not be able to overrule their child's decision if this option is taken.

   You indicated that you would be happy to insert this statement.

3. You and the Committee discussed and subsequently agreed that in the PIS for 11-15 year old participants a statement on pregnancy should be inserted. This statement should be consistent with the information in the parent PIS under section 5.

4. The Committee noted that A.38 of the application form mentions that data will be handled in 'agreement' with the Data Protection Act and emphasised that you must be 'compliant' with Act.

   You readily agreed that you would comply.

5. The Committee discussed the confounding variables to take into account which will be managed by minimisation by an independent third party. It was suggested that an

additional confounder of whether or not a child smokes cigarettes be included.

You commented that due to the participants medical condition this was not a possibility which had presented itself to date. However you would be happy to discuss this possibility with your clinical colleagues and adjust for this factor accordingly.

6. The Committee clarified the randomisation methodology which would take into account not only the age/gender of the participants but also take into account the percentage of lung function at the time of obtaining the data.

You commented that the statistical analysis was undertaken by statisticians within your organisation and you are reliant on their expertise to guide him.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

1. In the Participant information Sheet for 11-15 year old participants a statement on pregnancy should be inserted. This statement should be consistent with the information in the parent PIS under Section 5.

2. In the Children's assent form a statement should be inserted recognising that the child has a right to dissent if s/he wishes to.

3. Confirm that the researcher is 'compliant' with the Data Protection Act.

You must notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

<u>Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.</u>

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		25 June 2012
GP/Consultant Information Sheets	1.0	28 June 2012
Investigator CV	Sean James Ledger	
Other: CV: Eleanor Main		
Other: Letter from Funder		31 May 2012
Participant Consent Form: Children (6-10 Years)	1.0	26 June 2012
Participant Consent Form: Children (11-15 Years)	1.0	26 June 2012
Participant Consent Form: Parents	1.0	26 June 2012
Participant Information Sheet: Children (6-10 Years)	1.0	26 June 2012
Participant Information Sheet: Children (11-15 Years)	1.0	26 June 2012
Participant Information Sheet: Parents	1.0	26 June 2012
Protocol	1.0	28 June 2012
Questionnaire: CFQ-UK (Children Ages 6-11)		
Questionnaire: CFQ-UK (Children Ages 12-13)		
Questionnaire: CFQ-UK (Children Ages Adolescents and Adults)		
REC application	107522/338653/1/748	29 June 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/LO/1135	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Ray Godfrey
Chair

Email: NRESCommittee.SECoast-Kent@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" [SL-AR2]

Copy to: Mr Sean J Ledger - sean.ledger@gosh.nhs.uk
R&D Marice Lunny Marice.Lunny@gosh.nhs.uk

NRES Committee South East Coast - Kent

Attendance at Committee meeting on 25 July 2012

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Jim Appleyard	Retired Paediatrician	Yes	
Mrs Carole Brooks	Psychotherapist	Yes	
Mrs Helen Burn	Head of Pharmacy	Yes	
Mr Neal Clifton	Teacher	No	
Dr Beverly Donaldson	Midwife	No	
Dr Ray Godfrey	Statistician	Yes	
Mrs Sue Harrison	Managing Director of a Trade Association	No	
Mrs Liz Moorut	Chief Biomedical Scientist	Yes	
Dr Lynda Pearce	Membership Engagement Manager	Yes	
Dr Brijender Rana	Consultant in Public Health	Yes	
Mrs Amanda Richardson	Neonatal Sister	Yes	
Dr Amit Saha	Consultant Rheumatologist	Yes	
Mrs Heather Salzer	Ultrasound Clinical Specialist I	Yes	
Mr John Skilton	Senior Biomedical Scientist	Yes	
Mr Mike Tatlow	Health Informaticist	No	
Mrs Maureen Williams	Senior Lecturer Midwifery	No	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Halina Pounds	Co-Ordinator

APPENDIX C: CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov PRS DRAFT Receipt (Working Version)
Last Update: 04/23/2015 08:39

INSPIRE-CF: an Alternative Physiotherapy Model for Children With Cystic Fibrosis

This study is ongoing, but not recruiting participants.

Sponsor:	Great Ormond Street Hospital for Children NHS Foundation Trust
Collaborators:	
Information provided by (Responsible Party):	Great Ormond Street Hospital for Children NHS Foundation Trust
ClinicalTrials.gov Identifier:	NCT01889927

Purpose

The primary aim of the research is to evaluate whether an alternative model of cystic fibrosis (CF) physiotherapy care can produce statistically significant improvements in clinical and patient reported outcomes, and whether this alternative model is economically advantageous and/or sustainable.

Children randomised to the control group will receive 24-months of current model of CF care at Great Ormond Street Hospital (GOSH).

Children randomised to the intervention group will receive 24-months of current model of CF care at GOSH PLUS a weekly structured, individually prescribed and personally supervised exercise intervention at a local fitness facility or at school. The exercise prescription will include aerobic, anaerobic, strength, core conditioning and stretching components.

The main objectives of the study are:

1. Determine differences, if any, in lung function between the two groups;
2. Determine differences, if any, in exercise capacity between the two groups;
3. Evaluate cost of care of alternate model of care versus current model of care.

Condition	Intervention	Phase
Cystic Fibrosis	Exercise Intervention	N/A

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Efficacy Study
Official Title: INSPIRE-CF: A Randomised Controlled Trial Investigating the Clinical and Economic Benefits of an Alternative Model of Physiotherapy Care for Children With Cystic Fibrosis

Further study details as provided by Great Ormond Street Hospital for Children NHS Foundation Trust:

Primary Outcome Measure:

- Forced expiratory volume in one second (FEV1) [Time Frame: Baseline, 6, 12 and 24-month intervals.] [Designated as safety issue: No]

  Spirometry data will also to be collected at outpatient clinics, annual reviews and during hospital admissions.

Secondary Outcome Measures:

- Peak oxygen uptake (VO2Peak) [Time Frame: Baseline, 12 and 24-month intervals] [Designated as safety issue: No]
  Gold standard exercise test to determine peak oxygen uptake during exercise
- 10m-Modified Shuttle Walk Test [Time Frame: Baseline, 6, 12 and 24 months] [Designated as safety issue: No]
  Field test to assess functional exercise capacity. Distance covered and incremental level changes are evaluated over time.
- Lung Clearance Index [Time Frame: Baseline, 12 and 24 months] [Designated as safety issue: No]
  Multiple breath washout test to evaluate for changes in small airways
- Height, weight, body mass index measurements [Time Frame: Baseline, 6, 12 and 24 months] [Designated as safety issue: No]
  Height, weight and body mass index will be measured at regular intervals to evaluate for changes in growth parameters
- Cystic Fibrosis Questionnaire [Time Frame: Baseline, 12 and 24 months] [Designated as safety issue: No]
  Disease specific questionnaire to evaluate changes in quality of life in cystic fibrosis
- Cost of care [Time Frame: Baseline, 12 and 24 months] [Designated as safety issue: No]
  Evaluate differences in cost of care between the current model of CF care and the alternative model of care; and cost per patient.

Enrollment: 71
Study Start Date: May 2012
Estimated Primary Completion Date: June 2016
Estimated Study Completion Date: June 2016

Arms	Assigned Interventions
No Intervention: Group 1: Control Control Group (Arm 1): Children randomised to the control group will receive 24-months of current model of specialist CF care.	
Active Comparator: Group 2: Exercise Intervention Intervention group (Arm 2): Children randomised to the intervention group will receive 24-months of current model of specialist CF care PLUS a weekly structured, individually prescribed and personally supervised exercise intervention at a local fitness facility or at school.	Exercise Intervention The exercise intervention will include aerobic, anaerobic, strength, core conditioning and stretching components.

Eligibility

Ages Eligible for Study: 6 Years to 15 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Patients with a documented diagnosis of Cystic Fibrosis;
- Male or female aged 6 years or older at baseline and <17years old at the end of the 2-year study;
- Currently under the primary care of the GOSH CF Unit;

- Able to perform Spirometry with a baseline FEV1 percentage predicted of 40% or higher, as measured on at least 3 occasions in the previous year, during times of clinical stability (i.e. not during an exacerbation, and not during or within 2 weeks of intravenous antibiotics);
- The participant's parent or legal guardian must be able to give informed consent; assent will be sought from all children.

Exclusion Criteria:

- Patients who have had lung transplantation;
- Patients listed for lung transplantation;
- Clinically significant disease or medical condition other than CF or CF-related conditions that in the opinion of the multi-disciplinary clinical team, would compromise the safety of the patient;
- Orthopaedic impairment that compromises exercise performance;
- Mental impairment leading to inability to cooperate;
- Unable to understand both verbal and/or written instructions English. Children will need to be able to understand exactly what the physiotherapists are instructing them do, for safe and effective exercise training sessions. Information sheets and questionnaires are only available in English;
- Participants, parents or legal guardians who are unwilling to sign consent to participate in the study.

The following criteria will not exclude a child from participating in the study, but based on the hospital's exercise laboratory's infection control protocol, may preclude the participant from Cardiopulmonary Exercise Testing.

- Patients with Methicillin-Resistant Staphylococcus Aureus;
- Patients with Burkholderia Cepacia.

Contacts and Locations

Locations

United Kingdom

Great Ormond Street Hospital for Children NHS Foundation Trust

London, United Kingdom, WC1N 3JH

Investigators

Principal Investigator:	Sean J Ledger, BSc MSc	Cystic Fibrosis Unit, Great Ormond Street Hospital for Children NHS Foundation Trust
Principal Investigator:	Eleanor Main, BA MSc PhD	Institute of Child Health, University College London

More Information

Responsible Party:	Great Ormond Street Hospital for Children NHS Foundation Trust
Study ID Numbers:	11AR13
Health Authority:	United Kingdom: National Health Service

APPENDIX D: PATIENT INFORMATION SHEET (AGES 6-11 & 12-15 YEARS)

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF TRIAL

Participant Information Sheet for Children (6-10 years)

Version: 2.0 Date: 20/8/2012

REC Reference:	12/LO/1135	**NHS R&D Reference:**	11AR13
Funders Reference:	V1252		
Title of study:	**INSPIRE-CF:** a randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis		
Lead Investigators:	Sean Ledger and Dr Eleanor Main		

We thank your mum or dad or carer for helping you read this information

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What is research and why is this project being done?
Research is a way we try to find out the answers to questions. We think that doing exercise is good for children with cystic fibrosis (CF). The aim of this research is to see if adding a weekly personal exercise training session to your normal CF treatment plan, over the next 2 years, improves your lung function and fitness levels compared with normal treatment.

Why have I been asked to take part?
You have been asked to take part because you have CF and are being looked after at this hospital.

Did anyone else check the study is ok to do?
Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair. This project has been checked.

Do I have to take part?
No, you do not have to take part. You can take part if you want to but if you don't take part nothing will change and nobody will be cross with you. We will respect your wishes if you don't want to take part in the research, even if your parents want you to.

What will happen if I take part in the research?
This study is called a randomised trial. Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments.

There will be two groups in this research and each group will have a different treatment. We want to see if one is better than the other.

To try to make sure the groups are the same to start with, a computer will choose which group you will be in.

Group 1: One group will continue to receive normal CF care from the GOSH CF team.

Group 2: The second group will also receive this same CF care **PLUS** they will also do roughly an extra hour of fun exercise each week, near their home with a personal trainer.

If you say yes that you would like to take part we will fill in a form with your parent or guardian to show us that you have said yes to take part.

↓

You will come to the hospital for a few hours on the day you join the research

↓

First, you will be asked to do some lung function tests just like the ones you normally do

↓

We will then show you the equipment and the laboratory where you will do a bicycle test

↓

We will stick some sticky pads on your chest so that we can measure what your heart does when you exercise

↓

We will also check how much oxygen is in your blood with an oxygen monitor and we will ask you how hard you feel you are exercising during the test. This test takes 10-minutes.

↓

After the test is completed you will then have a 1-hour lunch break.

↓

The next exercise test is a walking test – called a 'bleep test'. You will walk and then run to the sound of bleeps that get faster and faster. You may have done this type of test at your school already!. This test takes 10-15 minutes.

↓

Finally, after the bleep test you will answer some questions about your CF

Exercises for Group 2 children:
If you are in the group where you will do exercise with a personal trainer. We will make a time each week to meet at a gym near you for some exercise. We will make sure this happens at a time that suits you and your family and your school. These sessions will be fun and we hope will make you fitter. The exercise will consist of fitness and muscle strengthening exercise, and also exercises to make your tummy stronger. At the end of the sessions you will do some stretching.

What are the possible disadvantages and risks of taking part? And what are the side effects of the treatment?
There are no real disadvantages to taking part that we can think of. When you do the exercise tests you will feel a bit tired in your muscles, you might feel a bit short of breath and it might make you cough and clear secretions during the test. You will have plenty of time to rest after exercise test so your muscles can recover. You might feel some mild leg muscle ache which is normal after doing exercise. We will make sure that you have enough rest after the exercise tests and that you can eat and drink normally.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study will help treat young people like you with CF in the future.

What happens when the research projects stops?
When the study stops you will continue with the same physiotherapy and exercise treatment that you were doing before the study.

What if there is a problem or something goes wrong?
If something goes wrong you should let your parents/guardians know first and then speak to one of the members of our team.

Will anyone else know that I am doing this?
We will keep your information in confidence. This means we will only tell those who have a need or a right to know.

What will happen to the results of the study?
The results of this study will be published in a cystic fibrosis or physiotherapy journal when the research is finished. Your name will be kept private and no one will be able to tell you took part in the study. If you want to know the results we will tell you them at the end.

Who has reviewed the study?
Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. This research has been checked.

Who can I contact for further information?
Please feel free to ask your doctors any questions about the study or about any of the treatments.

Contact for Further Information
Sean Ledger
Research Physiotherapist | INSPIRE-CF Trial
Cystic Fibrosis Unit
Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London
WC1N 3JH

Mobile No: [redacted]
e-mail: sean.ledger@gosh.nhs.uk

THANK YOU FOR READING THIS INFORMATION SHEET.
WE HOPE YOU HAVE FOUND THIS HELPFUL.

NHS Number:
|__|__|__|__|__|__|__|__|__|__|

GOSH Number:
|__|__|__|__|__|__|__|

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

INSPIRE- CF TRIAL

Assent Form for Children (6-10 years)
(To be completed by the child and their parent/guardian)

Version: 2.0 Date: 20/8/2012

REC Reference:	12/LO/1135	**NHS R&D Reference:**	11AR13
Funders Reference:	V1252		
Title of study:	**INSPIRE-CF:** a randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis		
Lead Investigators:	Sean Ledger and Dr Eleanor Main		

Child (or if unable, parent on their behalf) / young person to please circle all they agree to. Every child has the right to refuse if he/she wishes to, and it is strongly recommended that parents should not overrule their child's decision if this option is taken.

	Please circle
Have you read (or had read to you) information about this project.	YES / NO
Has somebody else explained this project to you?	YES / NO
Do you understand what this project is about?	YES / NO
Have you asked all the questions you want?	YES / NO
Have you had all your questions answered in a way you understand?	YES / NO
Do you understand its ok to stop taking part at any time?	YES / NO
Are you happy to take part?	YES / NO

If any answers are 'no' or you don't want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your Name: _____ Date: _____

Your **parent or guardian** must write their name here too if they are happy for you to take part!

_____	_____	___/___/___
Name of Parent/Guardian	Signature	Date
_____	_____	___/___/___
Name of Person taking consent	Signature	Date

When completed, 3 copies need to be made, 1 for the participant, 1 for the investigator site file and the original must be kept in the medical notes.

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF TRIAL

Participant Information Sheet for Children (11-15 years)

Version: 2.0 Date: 20/8/2012

REC Reference:	12/LO/1135	**NHS R&D Reference:**	11AR13
Funders Reference:	V1252		
Title of study:	**INSPIRE-CF:** a randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis		
Lead Investigators:	Sean Ledger and Dr Eleanor Main		

We are asking you if you would like to join our research study. Before you decide, we would like you to understand what is being done and what it would involve for you. Please read this information leaflet carefully. Talk to your family and friends, doctor or nurse about it, if you want to.

Why are we doing this research?

The aim of this study is to see if adding a weekly personal exercise training session to the current CF treatment plan, over 2 years, improves lung function and fitness levels compared with normal treatment.

Why have I been invited to take part?

You have been invited to take part in this study because you have CF and are being looked after at this hospital. Children with CF usually try to do physiotherapy and exercise to keep fit and to help keep their lungs clear. This research is to find out whether doing an extra supervised exercise session in a local gym every week is a better way of looking after children with CF.

Do I have to take part?

No. It is up to you. If you agree to take part we will then ask you and your parent/guardian to sign a form that says that you agree to take part. We will give you a copy of this information sheet and your signed forms to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop this will not affect the care you receive.

What will happen to me if I take part?

This study is called a randomised trial. Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. There will be two groups in this research and each group will have a different treatment. The results are compared to see if one is better than the other. To try to make sure the groups are the same to start with, each participant is put into a group randomly (a computer chooses which group you will be in and you will have a 50/50 chance of being in either group).

At the beginning, and in the middle and at the end of the 2 year study, children in both groups will do some lung function tests and a bicycle exercise test. We will also ask you to do a shuttle walking test (you may know this as the 'bleep' test) and answer some questions about your CF.

Before the first exercise test, called a Cardiopulmonary Exercise Test or CPET for short, a member of our research team will meet with you and your parent/legal guardian to show you the testing equipment, the laboratory and the testing procedures.

Group 1: One group will continue to receive CF care as you know it from the GOSH CF team.

Group 2: The second group will also receive this same CF care **PLUS** they will also do an extra hour of exercise each week, near their home with a personal trainer.

If you agree to participate in the study we will discuss with you, your usual medical team and your parent/legal guardian child to arrange suitable testing times and time for a weekly exercise session.

Measurements for all participants

The first part of the study will be done on the first day that you join the research. All of the study testing will be carried out Great Ormond Street Hospital.

First, you will be asked to do some lung function tests in the lung function laboratory (just like the ones you normally do).

Second, you will go to the exercise laboratory. We will sit you to a stationary bike so that you can pedal safely and comfortably. You will wear a facemask or mouthpiece which will measure the air you breathe in and out during the exercise test. You will also have your heart activity measured using standard electrodes (small sticky pads that attach to your skin) and oxygen levels measured during the tests. We set aside about an hour to set up equipment, but the bike test only takes 10-15minutes to complete.

After the test is completed you will then have a 1-hour lunch break.

After lunch we will ask you to do a 'bleep test', which will give us different information about how fit you are (you may have already done one of these at school before!). You will walk between two cones that are 10 meters apart. You will try to match the sound of the bleeps to your walk. The bleeps start off slowly at first then and then get quicker. You will have to walk or run faster to keep in time with the bleeps. This test will also take approximately 15 minutes.

After you have finished the exercise test we will ask you to answer some questions about your CF.

Exercises for Group 2 children

If you are in the group where you will do exercise with a personal trainer, we will arrange a time each week to meet at a gym near you for some exercise. We will work with you, your family and your school if necessary so that it fits into your weekly schedule. These sessions will be fun and we hope will make you fitter.

The exercise will consist of fitness and muscle strengthening exercise, and also exercises to make your tummy stronger. At the end of the sessions you will do some stretching.

What are the possible disadvantages and risks of taking part? And what are the side effects of the treatment?

There are no real disadvantages to taking part that we can think of. When you do the exercise tests you will feel a bit tired in your muscles, you might feel a bit short of breath and it might make you cough and clear secretions during the test. You will have plenty of time to rest after exercise test so your muscle can recover. You might feel some mild leg muscle ache which is normal after doing exercise. We will make sure that you have enough rest after the exercise tests and that you can eat and drink normally.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study will help treat young people like you with CF in the future.

What happens when the research projects stops?

When the study stops you will continue with the same physiotherapy and exercise treatment that you were doing before the study.

What if there is a problem or something goes wrong?

If something goes wrong you should let your parents/guardians know first and then speak to one of the members of our team.

What happens if I am pregnant or plan on becoming pregnant?

You should not take part in this study if you are pregnant, or if you plan on getting pregnant during the study.

Will anyone else know that I am doing this?

We will keep your information in confidence. This means we will only tell those who have a need or a right to know.

What will happen to the results of the study?

The results of this study will be published in a cystic fibrosis or physiotherapy related journal when the study is finished. Your name will be kept out of any publication and no one will be able to tell you took part in the study. If you want to know the results we will give you a summary sheet at the end.

Who has reviewed the study?

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. This research has been checked.

Who can I contact for further information?

Please feel free to ask your doctors any questions about the study or about any of the treatments.

Contact for Further Information

Sean Ledger
Research Physiotherapist | INSPIRE-CF Trial
Cystic Fibrosis Unit
Great Ormond Street Hospital for Children NHS
Foundation Trust
Great Ormond Street
London WC1N 3JH

Mobile No: [redacted]
e-mail: sean.ledger@gosh.nhs.uk

THANK YOU FOR READING THIS INFORMATION SHEET.

WE HOPE YOU HAVE FOUND THIS HELPFUL.

NHS Number:
|__|__|__|__|__|__|__|__|__|__|

GOSH Number:
|__|__|__|__|__|__|__|

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

INSPIRE- CF TRIAL

Assent Form for Children (11-15 years)
(To be completed by the child and their parent/guardian)

Version: 2.0 Date: 20/8/2012

REC Reference:	12/LO/1135	**NHS R&D Reference:**	11AR13
Funders Reference:	V1252		
Title of study:	**INSPIRE-CF:** a randomised controlled trial investigating the clinical and economic benefits of an alternative model of physiotherapy care for children with Cystic Fibrosis		
Lead Investigators:	Sean Ledger and Dr Eleanor Main		

Child (or if unable, parent on their behalf) / young person to please circle all they agree to.
Every child has the right to refuse if he/she wishes to, and it is strongly recommended that parents should not overrule their child's decision if this option is taken.

	Please circle
Have you read (or had read to you) information about this project.	YES / NO
Has somebody else explained this project to you?	YES / NO
Do you understand what this project is about?	YES / NO
Have you asked all the questions you want?	YES / NO
Have you had all your questions answered in a way you understand?	YES / NO
Do you understand its ok to stop taking part at any time?	YES / NO
Are you happy to take part?	YES / NO

If any answers are 'no' or you don't want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your Name: _____ Date: _____

Your **parent or guardian** must write their name here too if they are happy for you to take part!

_____	_____	___/___/___
Name of Parent/Guardian	Signature	Date
_____	_____	___/___/___
Name of Person taking consent	Signature	Date

APPENDIX E: PARENT INFORMATION SHEETS (6-11 & 12-15 YEARS)

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF PROGRAMME

Participant Information Sheet for Children (6-10 years)

Version: 1.0 Date: 1/9/2012

Lead Investigators: Sean Ledger and Dr Eleanor Main

We thank your mum or dad or carer for helping you read this information

---

What is research and why is this project being done?
We think that doing exercise is good for children with cystic fibrosis (CF). The aim of this programme is to see if adding a weekly personal exercise training session to your normal CF treatment plan, over the next 2 years, improves your lung function and fitness levels.

Why have I been asked to take part?
You have been asked to take part because you have CF and were part of the Frequent Flyer Programme.

Do I have to take part?
No, you do not have to take part. You can take part if you want to but if you don't take part nothing will change and nobody will be cross with you. We will respect your wishes if you don't want to take part in the programme, even if your parents want you to.

What will happen if I take part in the programme?
You will receive normal CF care from the GOSH CF team **PLUS** they will also do roughly an extra hour of fun exercise each week, near your home with a personal trainer.

If you say yes that you would like to take part we will fill in a form with your parent or guardian to show us that you have said yes to take part.

↓

You will come to the hospital for a few hours on the day you join the programme

↓

First, you will be asked to do some lung function tests just like the ones you normally do

↓

We will then show you the equipment and the laboratory where you will do a bicycle test

↓

We will stick some sticky pads on your chest so that we can measure what your heart does when you exercise

↓

We will also check how much oxygen is in your blood with an oxygen monitor and we will ask you how hard you feel you are exercising during the test. This test takes 10-minutes.

↓

After the test is completed you will then have a 1-hour lunch break.

↓

The next exercise test is a walking test – called a 'bleep test'. You will walk and then run to the sound of bleeps that get faster and faster. You may have done this type of test at your school already!. This test takes 10-15 minutes.

↓

Finally, after the bleep test you will answer some questions about your CF

You will do exercise with a personal trainer like you did in the Frequent Flyer programme. There are **4 trainers** this time so you won't always have the same person.

We will make a time each week to meet at a gym near you for some exercise. We will make sure this happens at a time that suits you and your family and your school. These sessions will be fun and we hope will make you fitter. The exercise will consist of fitness and muscle strengthening exercise, and also exercises to make your tummy stronger. At the end of the sessions you will do some stretching.

What are the possible disadvantages and risks of taking part? And what are the side effects of the treatment?
There are no real disadvantages to taking part that we can think of. When you do the exercise tests you will feel a bit tired in your muscles, you might feel a bit short of breath and it might make you cough and clear secretions during the test. You will have plenty of time to rest after exercise test so your muscles can recover. You might feel some mild leg muscle ache which is normal after doing exercise. We will make sure that you have enough rest after the exercise tests and that you can eat and drink normally.

What are the possible benefits of taking part?
We cannot promise the programme will help you but the information we get from this programme will help treat young people like you with CF in the future.

What happens when the programme projects stops?
When the programme stops you will continue with the same physiotherapy and exercise treatment that you were doing before the programme.

What if there is a problem or something goes wrong?
If something goes wrong you should let your parents/guardians know first and then speak to one of the members of our team.

Will anyone else know that I am doing this?
We will keep your information in confidence. This means we will only tell those who have a need or a right to know.

What will happen to the results of the programme?
The results of this programme will be published in a cystic fibrosis or physiotherapy journal when the research is finished.

NHS Number:
|__|__|__|__|__|__|__|__|__|__|

GOSH Number:
|__|__|__|__|__|__|__|

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF PROGRAMME

Assent Form for Children (6-10 years)
(To be completed by the child and their parent/guardian)

Version: 1.0 Date: 1/09/2012

Lead Investigators: Sean Ledger and Dr Eleanor Main

Child (or if unable, parent on their behalf) / young person to please circle all they agree to. Every child has the right to refuse if he/she wishes to, and it is strongly recommended that parents should not overrule their child's decision if this option is taken.

	Please circle
Have you read (or had read to you) information about this project.	YES / NO
Has somebody else explained this project to you?	YES / NO
Do you understand what this project is about?	YES / NO
Have you asked all the questions you want?	YES / NO
Have you had all your questions answered in a way you understand?	YES / NO
Do you understand its ok to stop taking part at any time?	YES / NO
Are you happy to take part?	YES / NO

If any answers are 'no' or you don't want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your Name: _____ Date: _____

Your **parent or guardian** must write their name here too if they are happy for you to take part!

_____	_____	___/___/___
Name of Parent/Guardian	Signature	Date
_____	_____	___/___/___
Name of Person taking consent	Signature	Date

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF PROGRAMME

Participant Information Sheet for Children (11-15 years)

Version: 1.0 Date: 1/09/2012

Lead Investigators: Sean Ledger and Dr Eleanor Main

We are asking you if you would like to join our INSPIRE-CF programme. Before you decide, we would like you to understand what is being done and what it would involve for you. Please read this information leaflet carefully. Talk to your family and friends, doctor or nurse about it, if you want to.

Why are we doing this programme?

The aim of this programme is to see if adding a weekly personal exercise training session to the current CF treatment plan, over 2 years, improves lung function and fitness levels.

Why have I been invited to take part?

You have been invited to take part in this programme because you have CF and were in the Frequent Flyer Programme. Children with CF usually try to do physiotherapy and exercise to keep fit and to help keep their lungs clear. This programme is to find out whether doing an extra supervised exercise session in a local gym every week is a better way of looking after children with CF.

Do I have to take part?

No. It is up to you. If you agree to take part we will then ask you and your parent/guardian to sign a form that says that you agree to take part. We will give you a copy of this information sheet and your signed forms to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop this will not affect the care you receive.

What will happen to me if I take part?

At the beginning, and in the middle and at the end of the 2 year programme, you will do some lung function tests and a bicycle exercise test. We will also ask you to do a shuttle walking test (you may know this as the 'bleep' test) and answer some questions about your CF.

Before the first exercise test, called a Cardiopulmonary Exercise Test or CPET for short, a member of our research team will meet with you and your parent/legal guardian to show you the testing equipment, the laboratory and the testing procedures.

You will continue to receive CF care as you know it from the GOSH CF team **PLUS** also do an extra hour of exercise each week, near your home or school with a personal trainer.

If you agree to participate in the programme we will discuss with you, your usual medical team and your parent/legal guardian child to arrange suitable testing times and time for a weekly exercise session.

Measurements for all participants

The first part of the programme will be done on the first day that you join the research. All of the programme testing will be carried out Great Ormond Street Hospital.

First, you will be asked to do some lung function tests in the lung function laboratory (just like the ones you normally do).

Second, you will go to the exercise laboratory. We will sit you to a stationary bike so that you can pedal safely and comfortably. You will wear a facemask or mouthpiece which will measure the air you breathe in and out during the exercise test. You will also have your heart activity measured using standard electrodes (small sticky pads that attach to your skin) and oxygen levels measured during the tests. We set aside about an hour to set up equipment, but the bike test only takes 10-15minutes to complete.

After the test is completed you will then have a 1-hour lunch break.

After lunch we will ask you to do a 'bleep test', which will give us different information about how fit you are (you may have already done one of these at school before!). You will walk between two cones that are 10 meters apart. You will try to match the sound of the bleeps to your walk. The bleeps start off slowly at first then and then get quicker. You will have to walk or run faster to keep in time with the bleeps. This test will also take approximately 15 minutes.

After you have finished the exercise test we will ask you to answer some questions about your CF.

Exercises Sessions

If you are in the group where you will do exercise with a personal trainer. There are 4 trainers involved with this programme so you won't always have the same trainer. We will arrange a time each week to meet at a gym near you for some exercise. We will work with you, your family and your school if necessary so that it fits into your weekly schedule. These sessions will be fun and we hope will make you fitter.

The exercise will consist of fitness and muscle strengthening exercise, and also exercises to make your tummy stronger. At the end of the sessions you will do some stretching.

What are the possible disadvantages and risks of taking part? And what are the side effects of the treatment?

There are no real disadvantages to taking part that we can think of. When you do the exercise tests you will feel a bit tired in your muscles, you might feel a bit short of breath and it might make you cough and clear secretions during the test. You will have plenty of time to rest after exercise test so your muscle can recover. You might feel some mild leg muscle ache which is normal after doing exercise. We will make sure that you have enough rest after the exercise tests and that you can eat and drink normally.

What are the possible benefits of taking part?

We cannot promise the programme will help you but the information we get from this programme will help treat young people like you with CF in the future.

What happens when the research projects stops?

When the programme stops you will continue with the same physiotherapy and exercise treatment that you were doing before the programme.

What if there is a problem or something goes wrong?

If something goes wrong you should let your parents/guardians know first and then speak to one of the members of our team.

What will happen to the results of the programme?

The results of this programme will be published in a cystic fibrosis or physiotherapy related journal when the programme is finished.

NHS Number:
|__|__|__|__|__|__|__|__|__|__|

GOSH Number:
|__|__|__|__|__|__|__|

Great Ormond Street Hospital for Children NHS Foundation Trust

INSPIRE- CF PROGRAMME

Assent Form for Children (11-15 years)
(To be completed by the child and their parent/guardian)

Version: 1.0 Date: 1/09/2012

Lead Investigators: Sean Ledger and Dr Eleanor Main

Child (or if unable, parent on their behalf) / young person to please circle all they agree to.
Every child has the right to refuse if he/she wishes to, and it is strongly recommended that parents should not overrule their child's decision if this option is taken.

	Please circle
Have you read (or had read to you) information about this project.	YES / NO
Has somebody else explained this project to you?	YES / NO
Do you understand what this project is about?	YES / NO
Have you asked all the questions you want?	YES / NO
Have you had all your questions answered in a way you understand?	YES / NO
Do you understand its ok to stop taking part at any time?	YES / NO
Are you happy to take part?	YES / NO

If any answers are 'no' or you don't want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your Name: _____ Date: _____

Your **parent or guardian** must write their name here too if they are happy for you to take part!

_____	_____	___/___/___
Name of Parent/Guardian	Signature	Date
_____	_____	___/___/___
Name of Person taking consent	Signature	Date

APPENDIX F: 10 METER MODIFIED SHUTTLE WALK TEST SHEET

Participant Name: …….. **Hospital Number:** ……..

LEVEL	SHUTTLE TIME	SHUTTLE NUMBER	DISTANCE
1	20.00	1 2 3	30
2	15.00	1 2 3 4	70
3	12.00	1 2 3 4 5	120
4	10.00	1 2 3 4 5 6	180
5	8.57	1 2 3 4 5 6 7	250
6	7.50	1 2 3 4 5 6 7 8	330
7	6.67	1 2 3 4 5 6 7 8 9	420
8	6.00	1 2 3 4 5 6 7 8 9 10	520
9	5.46	1 2 3 4 5 6 7 8 9 10 11	630
10	5.00	1 2 3 4 5 6 7 8 9 10 11 12	750
11	4.62	1 2 3 4 5 6 7 8 9 10 11 12 13	880
12	4.29	1 2 3 4 5 6 7 8 9 10 11 12 13 14	1020
13	4.00	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	1170
14	3.75	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	1330
15	3.53	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	1500
16	3.33	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	1680
17	3.16	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	1870
18	3.00	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	2070
19	2.86	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	2280
20	2.73	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	2500
21	2.61	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	2730
22	2.5	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	2970
23	2.4	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	3200
24	2.31	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26	3480
25	2.22	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27	3750

OUTCOME	RESTING	POST-TEST	MINIMUM	MAXIMUM	3-MIN POST TEST
SpO_2					
Heart Rate					
OMNI Scale (0-10)					

Number of completed levels		**Total completed levels + shuttles**	
Number of shuttles after last completed level		**Total Distance**	m

Reason for stopping test Breathless ☐ Low S_pO_2 ☐ Not matching pace ☐ Tired legs ☐ Other ☐

Researcher Name: _____ **Signature:** _____**Date:** ____/____/____

APPENDIX G: CYSTIC FIBROSIS QUESTIONNAIRE (CHILD)

This questionnaire is formatted for use by an interviewer. Please use this format for younger children. For older children who seem able to read and answer the questions on their own, such as 12 and 13 year olds, use this questionnaire in its self-report format.

There are directions for the interviewer for each section of the questionnaire. Directions that you should *read* to the child are indicated by quotation marks. Directions that you are to *follow* are underlined and set in italics.

Interviewer: *Please ask the following questions*

A. What is your date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

B. Are you?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school for reasons **NOT** related to your health?

☐ Yes ☐ No

D. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

E. What year are you in now at school?

(If summer, year you just finished)

- ☐ Reception
- ☐ Year 1
- ☐ Year 2
- ☐ Year 3
- ☐ Year 4
- ☐ Year 5
- ☐ Year 6
- ☐ Year 7
- ☐ Not in school

Interviewer: *Please read the following to the child:*

"These questions are for children like you who have cystic fibrosis. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future."

"For each question that I ask, choose one of the answers on the cards I'm about to show you."

Present the light green card to the child.

"Look at this card and read with me what it says:

very true, mostly true, somewhat true, not at all true."

"Here's an example: If I asked you if it is **very true, mostly true, somewhat true, not at all true** that elephants can fly, which one of the four answers on the card would you choose?"

Present the light green card to the child.

"Now, look at this card and read with me what it says:

always / often / sometimes / never."

"Here's another example: If I asked you if you go to the moon **always, often, sometimes, or never**, which answer on the card would you choose?"

Present the light green card to the child.

"Now, I will ask you some questions about your everyday life."

"Tell me if you find the statements I read to you to be** very true, mostly true, somewhat true, or not at all true**."

Please tick the box indicating the child's response.

"During the past **two weeks**":	**Very True**	**Mostly True**	**Somewhat True**	**Not at all True**
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted.....	☐	☐	☐	☐
4. You were able to run as quickly and for as long as others	☐	☐	☐	☐
5. You were able to participate in sports that you enjoy (e.g., swimming, football, dancing or others)	☐	☐	☐	☐
6. You had difficulty carrying or lifting heavy things such as books, your school bag, or a rucksack.....	☐	☐	☐	☐

Interviewer: *Present the light green card to the child.*

Please tick the box indicating the child's response.

"And during these past **two weeks**, tell me how often":	**Always**	**Often**	**Sometimes**	**Never**
7. You felt tired	☐	☐	☐	☐
8. You felt mad	☐	☐	☐	☐
9. You felt grouchy	☐	☐	☐	☐
10. You felt worried	☐	☐	☐	☐
11. You felt sad	☐	☐	☐	☐
12. You had trouble falling asleep	☐	☐	☐	☐
13. You had bad dreams or nightmares	☐	☐	☐	☐
14. You felt good about yourself	☐	☐	☐	☐
15. You had trouble eating	☐	☐	☐	☐
16. You had to stop fun activities to do your treatments	☐	☐	☐	☐
17. You were forced to eat	☐	☐	☐	☐

Interviewer: *Present the light green card to the child.*

*"**Now tell me if you find the statements I read to you to be** very true, mostly true, somewhat true, **or** not at all true**."***

Please tick the box indicating the child's response.

"During the past **two weeks**":	**Very True**	**Mostly True**	**Somewhat True**	**Not at all True**
18. You were able to do all of your treatments	☐	☐	☐	☐
19. You enjoyed eating	☐	☐	☐	☐
20. You got together with friends a lot	☐	☐	☐	☐
21. You stayed at home more than you wanted to	☐	☐	☐	☐
22. You felt comfortable sleeping away from home (at a friend or family member's house or elsewhere)	☐	☐	☐	☐
23. You felt left out	☐	☐	☐	☐
24. You often invited friends to your house	☐	☐	☐	☐
25. You were teased by other children	☐	☐	☐	☐
26. You felt comfortable discussing your illness with others (friends, teachers)	☐	☐	☐	☐
27. You thought you were too short	☐	☐	☐	☐
28. You thought you were too thin	☐	☐	☐	☐
29. You thought you were physically different from others your age	☐	☐	☐	☐
30. Doing your treatments bothered you	☐	☐	☐	☐

Interviewer: ***Present the light green card to the child again***

Please tick the box indicating the child's response.

"Tell me how often in the past **two weeks**":	**Always**	**Often**	**Sometimes**	**Never**
31. You coughed during the day	☐	☐	☐	☐
32. You woke up during the night because you were coughing	☐	☐	☐	☐
33. You had to cough up mucus.....	☐	☐	☐	☐
34. You had trouble breathing	☐	☐	☐	☐
35. Your stomach hurt.....	☐	☐	☐	☐

*Please make sure **all** the questions have been answered.*

Thank you for your cooperation

These questions are for children like you who have cystic fibrosis. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Please fill in the answer or tick the box that matches your response to these questions.

A. What is your date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

B. Are you?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school for reasons **NOT** related to your health?

☐ Yes ☐ No

D. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

E. What year are you in now at school?

(If summer, year you just finished)

- ☐ Year 6
- ☐ Year 7
- ☐ Year 8
- ☐ Year 9
- ☐ Year 10
- ☐ Year 11
- ☐ Not in school

Please tick the box matching your response.

In the past **two weeks**:	**Very True**	**Mostly True**	**Somewhat True**	**Not at all True**
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted	☐	☐	☐	☐
4. You were able to run as quickly and for as long as others	☐	☐	☐	☐
5. You were able to participate in sports that you enjoy (e.g., swimming, football, dancing or others)	☐	☐	☐	☐
6. You had difficulty carrying or lifting heavy things such as books, your school bag, or a rucksack	☐	☐	☐	☐

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:	**Always**	**Often**	**Sometimes**	**Never**
7. You felt tired.....	☐	☐	☐	☐
8. You felt mad.....	☐	☐	☐	☐
9. You felt grouchy.....	☐	☐	☐	☐
10. You felt worried	☐	☐	☐	☐
11. You felt sad	☐	☐	☐	☐
12. You had trouble falling asleep.....	☐	☐	☐	☐
13. You had bad dreams or nightmares.....	☐	☐	☐	☐
14. You felt good about yourself.....	☐	☐	☐	☐
15. You had trouble eating	☐	☐	☐	☐

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:

	Always	Often	Sometimes	Never
16. You had to stop fun activities to do your treatments	☐	☐	☐	☐
17. You were forced to eat	☐	☐	☐	☐

Please tick the box matching your response.

During the past **two weeks**:

	Very True	Mostly True	Somewhat True	Not at all True
18. You were able to do all of your treatments	☐	☐	☐	☐
19. You enjoyed eating	☐	☐	☐	☐
20. You got together with friends a lot	☐	☐	☐	☐
21. You stayed at home more than you wanted to	☐	☐	☐	☐
22. You felt comfortable sleeping away from home (at a friend or family member's house or elsewhere)	☐	☐	☐	☐
23. You felt left out	☐	☐	☐	☐
24. You often invited friends to your house	☐	☐	☐	☐
25. You were teased by other children	☐	☐	☐	☐
26. You felt comfortable discussing your illness with others (friends, teachers)	☐	☐	☐	☐
27. You thought you were too short	☐	☐	☐	☐
28. You thought you were too thin	☐	☐	☐	☐
29. You thought you were physically different from others your age	☐	☐	☐	☐

During the past **two weeks**:	**Very True**	**Mostly True**	**Somewhat True**	**Not at all True**
30. Doing your treatments bothered you	☐	☐	☐	☐

Please tick the box matching your response.

Let us know how often in the past **two weeks**:	**Always**	**Often**	**Sometimes**	**Never**
31. You coughed during the day	☐	☐	☐	☐
32. You woke up during the night because you were coughing	☐	☐	☐	☐
33. You had to cough up mucus	☐	☐	☐	☐
34. You had trouble breathing	☐	☐	☐	☐
35. Your stomach hurt	☐	☐	☐	☐

Please make sure all the questions have been answered.

Thank you for your cooperation

APPENDIX H: CYSTIC FIBROSIS QUESTIONNAIRE (ADOLESCENTS & ADULTS)

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Demographics

Please fill-in the information or tick the box indicating your answer.

A. What is your date of birth?

Date | | | | | | | | |
Day Month Year

B. What is your gender?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school or work for reasons **NOT** related to your health?

☐ Yes ☐ No

D. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]

F. What is the highest level of education you have completed?

- ☐ Some secondary school or less
- ☐ GCSEs/ O-levels
- ☐ A/AS-levels
- ☐ Other higher education
- ☐ University degree
- ☐ Professional qualification or post-graduate study

G. Which of the following best describes your current work or school status?

- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not attending school or working due to my health
- ☐ Not working for other reasons

Section II. Quality of Life

Please tick the box indicating your answer.

	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
*During the past **two weeks**, to what extent have you had difficulty:*				
1. Performing vigorous activities such as running or playing sports.....	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, shopping, or school bags.....	☐	☐	☐	☐
4. Climbing one flight of stairs.....	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

	Always	Often	Sometimes	Never
***During the past two weeks**, indicate how often:*				
6. You felt well	☐	☐	☐	☐
7. You felt worried.....	☐	☐	☐	☐
8. You felt useless.....	☐	☐	☐	☐
9. You felt tired.....	☐	☐	☐	☐
10. You felt full of energy	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad.....	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	**Very true**	**Somewhat true**	**Somewhat false**	**Very false**
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐

29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, getting promoted at work, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Section III. School, Work, or Daily Activities

Questions 35 to 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals?

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ **Go to Question 44**

43. Has your mucus been mostly:

☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks:***	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with wind?	☐	☐	☐	☐
48. Have you had diarrhoea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please make sure you have answered all the questions.

Thank you for your cooperation

APPENDIX I: CYSTIC FIBROSIS QUESTIONNAIRE (PARENT/CARER)

Understanding the impact of your child's illness and treatments on his or her everyday life can help your healthcare team keep track of your child's health and adjust his or her treatments. For this reason, we have developed a quality of life questionnaire specifically for parents of children with cystic fibrosis.

We thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your child's health, as he or she perceives it. This information will allow us to better understand how he or she feels in everyday life. Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your child's situation.

Section I. Demographics

Please fill-in the information or tick the box indicating your answer.

A. What is your child's date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

B. What is your relationship to the child?

- ☐ Mother
- ☐ Father
- ☐ Grandmother
- ☐ Grandfather
- ☐ Other relative
- ☐ Foster mother
- ☐ Foster father
- ☐ Other (please describe)

C. Which of the following best describes your child's racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

D. During the **past two weeks,** has your child been on holiday or out of school for reasons **NOT** related to his or her health?

☐ Yes ☐ No

E. What is **your** date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

F. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

G. What is the highest level of education **you** have completed?

- ☐ Some secondary school or less
- ☐ GCSEs/O-levels
- ☐ A/AS-levels
- ☐ Other higher education
- ☐ University degree
- ☐ Professional qualification or post-graduate study

H. Which of the following best describes your current work status?

- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business
- ☐ Full time homemaker
- ☐ Not working due to my health
- ☐ Not working for other reason

Section II. Quality of Life

Please indicate how your child has been feeling during the past two weeks by ticking the box matching your response.

To what extent has your child had difficulty:	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities such as running or playing sports.....	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Climbing stairs as fast as others	☐	☐	☐	☐
4. Carrying or lifting heavy objects such as books, a school bag, or rucksack	☐	☐	☐	☐
5. Climbing several flights of stairs.....	☐	☐	☐	☐

Please tick the box matching your response.

*During the past **two weeks**, indicate how often your child:*	**Always**	**Often**	**Sometimes**	**Never**
6. Seemed happy.....	☐	☐	☐	☐
7. Seemed worried.....	☐	☐	☐	☐
8. Seemed tired.....	☐	☐	☐	☐
9. Seemed short-tempered	☐	☐	☐	☐
10. Seemed well	☐	☐	☐	☐
11. Seemed grouchy	☐	☐	☐	☐
12. Seemed full of energy.....	☐	☐	☐	☐
13. Was absent or late for school or other activities because of his/her illness or treatments ……..	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your child's health over the past **two weeks,** indicate:*

14. The extent to which your child participated in sports and other physical activities, such as P.E. (physical education)
1. Has not participated in physical activities
2. Has participated less than usual in sports
3. Has participated as much as usual but with some difficulty
4. Has been able to participate in physical activities without any difficulty

15. The extent to which your child has difficulty walking
1. He or she can walk a long time without getting tired
2. He or she can walk a long time but gets tired
3. He or she cannot walk a long time, because he or she gets tired quickly
4. He or she avoids walking whenever possible, because it's too tiring for him or her

Please tick the box that matches your response to these questions.

*Thinking about your child's state of health during the past **two weeks**, indicate the extent to which each sentence is true or false for your child:*

	Very true	Somewhat true	Somewhat false	Very false
16. My child has trouble recovering after physical effort	☐	☐	☐	☐
17. Mealtimes are a struggle	☐	☐	☐	☐
18. My child's treatments get in the way of his/her activities	☐	☐	☐	☐
19. My child feels small compared to other kids the same age	☐	☐	☐	☐
20. My child feels physically different from other kids the same age	☐	☐	☐	☐
21. My child thinks that he/she is too thin	☐	☐	☐	☐
22. My child feels healthy	☐	☐	☐	☐
23. My child tends to be withdrawn	☐	☐	☐	☐
24. My child leads a normal life	☐	☐	☐	☐

25. My child has less fun than usual.....	☐	☐	☐	☐
26. My child has trouble getting along with others	☐	☐	☐	☐
27. My child has trouble concentrating	☐	☐	☐	☐
28. My child is able to keep up with his/her school work or holiday activities	☐	☐	☐	☐
29. My child is not doing as well as usual in school or holiday activities.....	☐	☐	☐	☐
30. My child spends a lot of time on his/her treatments everyday.....	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

31. How difficult is it for your child to do his/her treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

32. How do you think your child's health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Section III. Symptom Difficulties

The next set of questions is designed to determine the frequency with which your child has certain respiratory difficulties, such as coughing or shortness of breath.

*Please indicate how your child has been feeling during the past **two weeks.***	**A great deal**	**Somewhat**	**A little**	**Not at all**
33. My child had trouble gaining weight	☐	☐	☐	☐
34. My child was congested	☐	☐	☐	☐
35. My child coughed during the day	☐	☐	☐	☐
36. My child had to cough up mucus	☐	☐	☐	☐ ↓ **Go to Question 38**

37. My child's mucus has been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*During the past **two weeks:***	**Always**	**Often**	**Sometimes**	**Never**
38. My child wheezed	☐	☐	☐	☐
39. My child had trouble breathing	☐	☐	☐	☐
40. My child woke up during the night because he/she was coughing	☐	☐	☐	☐
41. My child had wind	☐	☐	☐	☐
42. My child had diarrhoea	☐	☐	☐	☐
43. My child had abdominal pain	☐	☐	☐	☐
44. My child has had eating problems	☐	☐	☐	☐

Please make sure you have answered all the questions.

Thank you for your cooperation

APPENDIX J: INSPIRE-CF EXERCISE PROGRAMME