School of Physiotherapy and Exercise Science

Telehealth in Cystic Fibrosis: Does the Integration of Modern Technology with Traditional Care Improve Health Related Outcomes?

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AUTHOR'S DECLARATION

I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary education institution.

Jamie Wood

30th April 2020

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy (Physiotherapy) at Curtin University, Western Australia. This degree was completed on a part-time basis. Studies were undertaken between May 2013 and March 2018, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Physiotherapy Department and Department of Respiratory Medicine at Sir Charles Gairdner Hospital, and the Institute for Respiratory Health, Western Australia.

This research project was developed in association with my supervisors, who have been involved in editing both the thesis and all associated publications.

All material presented in this thesis is original.

ABSTRACT

This chapter presents the four studies that form this research programme in extended abstract form. This research programme was designed to:

i) evaluate and compare the magnitude of decline in spirometry between adults with cystic fibrosis (CF) living in the Perth metropolitan area and in rural and remote Western Australia (WA) (Study 1, presented in Chapter 3);

ii) examine the uptake and participant satisfaction with telehealth clinics provided via videoconferencing for adults with CF living in rural and remote WA (Study 2; Part A, presented in Chapter 4);

iii) explore the working profile of adults with CF living in rural and remote WA (Study 2; Part B, presented in Chapter 4);

iv) investigate the usability of a smartphone application (app) developed for adults with CF to report their symptoms suggestive of a respiratory exacerbation to the CF team (Study 3; Part A; presented in Chapter 5); and observer agreement between clinicians interpreting the app data (Study 3, Part B; presented in Chapter 5); and,

v) examine the impact of the app on health outcomes in adults with CF in a randomised controlled trial (RCT) (Study 4, presented in Chapter 6).

A comparison of the magnitude of decline in spirometry between adults with cystic fibrosis living in the Perth metropolitan area and in rural and remote Western Australia (Study 1)

Background and aims

The Australian CF Standards of Care recommend that all adults with CF attend a minimum of four outpatient clinics with a specialist CF team per year. In the year preceding this study, this recommendation was not met for those living in rural and remote WA. This may negatively impact on long-term health outcomes, as it is known that those with CF who receive care in a specialist centre have improved forced expiratory volume in 1 second (FEV_1) and weight. This study evaluated and compared the magnitude of decline in spirometry between adults with CF living in metropolitan Perth and in rural and remote WA.

Methods

Adults with CF were included if they i) attended the Sir Charles Gairdner (SCGH) CF Centre for the entire period from January 2010 to December 2012; and ii) performed spirometry on at least two occasions during this time period. An analysis was conducted to determine the magnitude of decline in spirometry (FEV_1 and percentage predicted FEV_1 [$ppFEV_1$], forced vital capacity [FVC] and percentage predicted FVC [ppFVC]) of all adults with CF attending the adult CF clinic at SCGH during this time period. The decline in spirometry over this 3-year period was compared between adults with CF living in metropolitan Perth vs. those living in rural and remote WA (defined as living greater than 100km from the geographical centre of Perth). Analysis of the primary outcome was conducted using mixed effects models.

Results

A total of 156 participants met the inclusion criteria and were included in the audit and analyses. In total, 2,748 ((mean [range] 219 (8 [2 to 24]) and (21 [3 to 58])) data points (episodes of spirometry) were available for participants living in metropolitan (n = 130) and in rural and remote (n = 26) areas respectively.

There was no clear effect on the magnitude of decline in FEV_1 (mean difference [95% confidence interval, CI] 0.00 [-0.01 to 0.01], p = 0.16), $ppFEV_1$ (0.07 [-0.07 to 0.21], p = 0.31), FVC (0.00 [-0.01 to 0.01], p = 0.31) or ppFVC (0.05 [-0.10 to 0.20], p = 0.53) between participants living in metropolitan and in rural and remote areas. Results remained unchanged when stratified for age (18 to 29 years or ≥ 30 years).

Discussion and conclusion

No clear effect on the magnitude of decline of spirometry was demonstrated when comparing adults with CF living in the metropolitan area and in rural and remote WA. This was unexpected, however may have been due to several limitations. The sample size was limited to the available participants and therefore the analyses may have been underpowered to detect small differences. Further, the 26 participants living in rural and remote WA averaged a total of only eight spirometry recordings over the 3-year study period, rendering it difficult to formulate any precision around the estimated magnitude of decline. This would draw attention to the lack of appropriate disease surveillance in this group. The results of this audit highlight the need for improved access to care and disease monitoring in adults with CF living in rural and remote WA.

Telehealth clinics for adults with cystic fibrosis living in rural and remote Western Australia (Study 2, Part A)

Background and aims

At the commencement of this study, 15% (n = 28) of adults with CF in WA lived in rural and remote areas. Those living in these areas have difficulty accessing specialist care at the SCGH CF Centre due to geographical, time and financial barriers. This study sought to improve access to care by offering telehealth clinics via videoconferencing, and evaluate its uptake and impact on satisfaction and health-related outcomes such as healthcare utilisation (HCU), spirometry, weight and health-related quality of life (HRQoL).

Methods

Adults with CF aged 18 years or more and living a minimum of 100km from the SCGH CF Centre were eligible to participate in this study. Telehealth clinics were offered via videoconferencing over a 12-month period (approximately every 3 months or sooner if clinically indicated). Participants were still able attend clinics 'in-person' at the CF centre if they preferred. On the day of the telehealth clinic, participants attended their nearest regional hospital. The participant's height, weight and spirometry were measured (according to American Thoracic Society spirometry guidelines) by a designated health professional. Uptake, satisfaction and measures of HCU were collected at the end of the study. The HCU data obtained during the study were compared with the 12-month period preceding the study. Participants completed other measurements at baseline, at each clinic (telehealth or in-person) and at the completion of the study period. These measures comprised spirometry, weight, HRQoL and absenteeism and presenteeism. Analysis of the primary outcome was conducted using descriptive statistics.

Results

For the 21 participants, total CF clinics attended increased from 46 (median [range] per participant 2 [0 to 6]) in the 12-month period preceding the study to 100 (5 [2 to 8]) during the intervention (incidence rate ratio [IRR] 3.7, $p < 0.01$). Of the 100 clinics attended in total, 66

were delivered via telehealth. Satisfaction with telehealth was high and most (94%) participants agreed that telehealth was a good way to deliver CF care. There was an improvement in the vitality domain of the Cystic Fibrosis Questionnaire – Revised (mean difference [95% CI] 11 [1 to 22], p = 0.04). No clear differences were observed in other outcomes.

Discussion and conclusion

Telehealth had good uptake and increased clinic attendance in adults with CF living in rural and remote WA, and had high satisfaction amongst participants. The increase in HCU, resulting from increased detection and treatment of exacerbations, may improve long-term outcomes in this population. These findings highlight the inadequate clinical surveillance amongst participants in the 12-months preceding the study.

The impact of cystic fibrosis on work attendance and performance in adults living in rural and remote Western Australia: a sub-analysis (Study 2, Part B)

Background and aims

As the expected age of survival for people with CF increases to above 40 years, there is a need for adults with CF to stay in the work force for longer. However, there are few data available regarding the impact that CF has on work attendance and performance. Telehealth clinics for adults with CF were implemented and evaluated, and, as part of this study work absenteeism and presenteeism was quantified.

Methods

During CF clinics (telehealth and in-person) throughout a 12-month period, participants completed the absenteeism and presenteeism questions of the World Health Organisation's Health and Work Performance Questionnaire (HPQ). Responses were used to calculate relative absenteeism and relative presenteeism. Relative absenteeism is the time absent from work. A maximum score of 1 indicates 100% absenteeism; a score of 0 indicates no absenteeism. Negative scores indicate the hours worked exceeded the employer's expectations. Relative presenteeism is self-rated work performance compared to others in similar employment. A score of 1 represents equal performance, 0 represents worst performance, and a maximum score of 2 represents performance at least twice as good as colleagues. Analyses were conducted using descriptive statistics.

Results

Data from 23 adults with CF (14 female, mean [standard deviation, SD] age 31 [10] years) were available. Data were collected during a total of 91 CF clinic attendances. Participants were engaged in paid work on 61 (67%) of these occasions. Twenty-two (96%) participants were employed on at least one occasion and 11 (48%) were employed throughout the entire 12 months. For those employed, the median (range) number of hours worked per week was 38 (10

to 80). Relative absenteeism (mean [range]) in those employed was 0.1 (-1.2 to 0.9). Relative presenteeism in those employed was 1.0 (0.0 to 1.8).

Discussion and conclusion

Despite having a chronic disease that is associated with a substantial treatment burden, most adults with CF living in rural and remote WA were engaged in paid work during the 12-month study period. Absenteeism scores were variable, and demonstrated that CF affected the work attendance of many, but not all participants. Presenteeism scores, while also variable, demonstrated that on average participants felt they performed as well as their colleagues at work. The use of the HPQ is novel in this population, and warrants further consideration as a tool for quantifying absenteeism and presenteeism in adults with CF.

The usability of a smartphone application for reporting respiratory symptoms in adults with cystic fibrosis, and observer agreement between clinicians (Study 3, Part A/Part B)

Background and aims

In CF, respiratory exacerbations increase HCU and costs, impair lung function and HRQoL, and reduce survival. Delayed identification and treatment can lead to more severe respiratory exacerbations and worse clinical outcomes. Delayed reporting of worsening respiratory symptoms by people with CF is one of the key factors in the late identification of respiratory exacerbations by the CF team. Therefore, there is a need for a novel approach to facilitate the early identification and treatment of respiratory exacerbations in this population. This study investigated the usability of a smartphone application (app), designed by the research team, for adults with CF to report respiratory symptoms to the CF team (Part A). Further, it examined the observer agreement in clinical decision making between experienced clinicians interpreting the app responses (Part B).

Methods

Part A: Adults with CF used the app weekly for 4 weeks. The app comprised 10 yes/no questions regarding respiratory symptoms and two questions regarding emotional well-being. Usability was measured with the System Usability Scale (SUS). Participants were also asked to provide feedback on the wording of the app questions. Part B: Observer agreement was examined by providing a physician and a nurse practitioner who were experienced in providing CF care with 45 symptom responses from the app embedded across three separate clinical scenarios. For each scenario the clinicians, who were blinded to each other's responses, were asked to indicate whether or not they would: (i) initiate telephone contact, and/or (ii) request the person with CF attend a CF clinic. Analyses were conducted using descriptive statistics and Cohen's kappa statistic

Results

Part A: Ten participants (5 females, mean [SD] age 33 [11] years, ppFEV$_1$ 49 [27]) completed the study. The mean (SD) SUS score was 94 (6). Participants provided feedback regarding the wording of certain app questions. Part B: For the clinical scenarios, there was perfect agreement between clinicians deciding it was appropriate to initiate contact ($\kappa = 1.0$, $p < 0.001$), and near-perfect agreement for requesting the person to attend a CF clinic ($\kappa = 0.86$, $p < 0.001$).

Discussion and conclusion

The results of this study demonstrated that amongst adults with CF, an app used to report respiratory symptoms suggestive of a respiratory exacerbation has excellent usability. Further, the symptom responses provided can be interpreted consistently between clinicians who are experienced in the management of this clinical population. The app was revised based on participant feedback, and the difference in responses from clinicians relating to one specific question, before investigating its impact on health outcomes in an RCT.

A smartphone application for reporting respiratory symptoms in adults with cystic fibrosis improves the detection of respiratory exacerbations: a randomised controlled trial (Study 4)

Background and aims

In CF, respiratory exacerbations have a profound and long-lasting detrimental impact. An app has previously been developed for adults with CF to report respiratory symptoms to the CF team. In a previous study, it was demonstrated that the app had excellent usability, and the data could be interpreted consistently between clinicians. In this RCT, the impact of the weekly use of this app was examined on the number of courses of IV antibiotics and other health-related outcomes.

Methods

A 12-month RCT was undertaken. Adults were eligible for inclusion if they had a diagnosis of CF and had required IV antibiotics in the preceding 12 months for a respiratory exacerbation. Participants were randomised to an intervention group or a control group. Participants in both groups received usual care, which comprised routine outpatient clinic appointments and the ability to contact the nurse practitioner via phone or email. Those in the intervention group were provided with the app and asked to use it weekly or sooner if they felt their respiratory symptoms had worsened. The app comprised 12 yes/no questions relating to symptoms suggestive of a respiratory exacerbation, and two questions relating to emotional wellbeing. Participants were contacted by the nurse practitioner if they answered yes to any questions, and their care was triaged accordingly (e.g. advised to attend the CF clinic, commence oral and/or inhaled antibiotics, or no intervention). The primary outcome measure was the number of courses of IV antibiotics. Other outcomes included the number of courses of oral and inhaled antibiotics, number and days of hospital admissions, time to detection of exacerbation requiring oral and/or IV antibiotics by the CF team, antibiotic and hospital admission costs, spirometry, body mass index (BMI), HRQoL, feelings of anxiety and depression, treatment adherence and adherence to the weekly use of the app. The physicians prescribing the antibiotics were blinded

to group allocation. Analysis of the primary outcome was conducted using negative binomial regression.

Results

Sixty participants (31 male, mean [SD] age 31 [9] years, ppFEV$_1$ 60 [18] %) were recruited, with 29 (48%) allocated to the intervention group. Over the 12-month follow-up, there was no clear effect of the app on the number of courses of IV antibiotics (IRR [95% CI] 1 [0.6 to 1.7]), however the number of courses of oral antibiotics increased in the intervention group (1.5 [1.0 to 2.2]). The median (interquartile range [IQR]) time to detection of a respiratory exacerbation requiring oral or IV antibiotics was shorter in the intervention group compared with the control group (70 [123] vs.141 [140] days; p = 0.02). There was a good level of adherence to the weekly use of the app amongst participants in the intervention group (mean [range] 77 [25 to 100]%). Subgroup analyses demonstrated a meaningful increase in oral antibiotic prescription, and reduction in IV antibiotic prescription, compared with the 12 months preceding the study in participants in the intervention group with adherence to the weekly use of the app ≥ 80% (n = 15). No between-group differences were observed in other outcomes.

Discussion and conclusion

This was the first app used by adults with CF to report changes in their respiratory symptoms directly to the CF team. The high level of adherence to the weekly use of the app was attributed to the low reporting burden and use of technology already owned by participants, and was somewhat better than earlier work that has investigated home monitoring interventions in a CF population. Provision of the app facilitated the earlier detection of respiratory exacerbations and treatment in the form of oral antibiotics. While these data do not demonstrate a clear effect on the number of courses of IV antibiotics for the participants over a 12-month period, this study supports the continued development and investigation of similar apps and technologies used to identify respiratory exacerbations, with the aim of improving long-term health outcomes.

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Wood, J, Mulrennan, S, Hill, K, Cecins, N, Morey, S, Jenkins, S. Telehealth clinics increase access to care for adults with cystic fibrosis living in rural and remote Western Australia. J Telemed Telecare. 2017;23(7):673–679.

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Wood J, Mulrennan S, Morey S, Cecins N, Hill K, Jenkins S. Telehealth clinics for adults with cystic fibrosis living in rural and remote Western Australia. Proceedings of the 11th Australasian Cystic Fibrosis Conference. 2015:P22.

INVITED PRESENTATIONS

Thoracic Society of Australia and New Zealand Annual Scientific Meeting 2018: “Using modern technology to optimise clinical care in cystic fibrosis” (March 23rd to 27th, Adelaide, Australia).

Australasian Cystic Fibrosis Conference 2017: “Opportunities for telemedicine and technology in cystic fibrosis” (August 5th to 8th, Melbourne, Australia).

AWARDS AND GRANTS

Thoracic Society of Australia & New Zealand and the Australian Annual Scientific Meeting 2019, Gold Coast, Queensland – Physiotherapy Special Interest Group Prize: best oral presentation.

European Cystic Fibrosis Conference 2018, Belgrade, Serbia – Best Physiotherapy Abstract Award.

Western Australian Health Excellence Awards 2016 Winner – Overcoming inequities: telehealth improves access to care for adults with cystic fibrosis living in rural and remote Western Australia.

Curtin University Faculty of Health Sciences Mark Liveris Seminar 2016 – best oral presentation.

Thoracic Society of Australia & New Zealand and the Australian Annual Scientific Meeting 2016, Perth, Western Australia – Physiotherapy Special Interest Group Prize: best oral presentation.

Principal Investigator: Sir Charles Gairdner Hospital Research Advisory Committee Grant 2015: "A pilot study and randomised controlled trial investigating the usability of a smartphone application, and its impact on the number of exacerbations requiring intravenous antibiotics in adults with cystic fibrosis – $45,000.

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LIST OF ABBREVIATIONS

3MST	3-minute step test
AAD	Adaptive aerosol delivery
ACT	Airway clearance technique
App	Application
ATS	American Thoracic Society
AUD	Australian dollars
BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRD	Cystic fibrosis-related diabetes
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CFTR	Cystic fibrosis transmembrane regulator
CHQ	Child Health Questionnaire
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRDQ	Chronic Respiratory Disease Questionnaire
CT	Computed tomography
eICE	Early Intervention in Cystic Fibrosis Exacerbation
EQ-5D	EuroQol-5D
FEV_1	Forced expiratory volume in 1 second
FFM	Fat free mass
FVC	Forced vital capacity
HADS	Hospital Anxiety and Depression Scale
HCU	Healthcare utilisation
HPQ	Health and Work Performance Questionnaire
HR	Hazard ratio
HRQOL	Health-related quality of life
IQR	Interquartile range
IRR	Incidence rate ratio
IV	Intravenous
LCI	Lung clearance index
MET	Metabolic equivalent of task
MVPA	Moderate-vigorous physical activity
OR	Odds ratio
$ppFEV_1$	Percent predicted forced expiratory volume in 1 second
ppFVC	Percent predicted forced vital capacity
RCT	Randomised controlled trial
rhDNase	Recombinant human deoxyribonuclease

SCGH	Sir Charles Gairdner Hospital
SD	Standard deviation
SF-36	Short Form 36
SpO2	Oxygen saturation
SUS	System Usability Scale
TAQ-CF	Treatment Adherence Questionnaire – Cystic Fibrosis
TeSS	Telehealth Satisfaction Scale
TIDES	International Depression/Anxiety Epidemiological Study
UK	United Kingdom
US	United States
USD	United States dollars
WA	Western Australia
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

This chapter outlines the background, aims and significance of this programme of research. The research undertaken is presented in this chapter in three sections. The first section relates to access to care for adults with cystic fibrosis (CF) living in rural and remote Western Australia (WA). Specifically, the role of telehealth, via videoconferencing, was explored as a way to improve access to care and other health outcomes. The research aims contained within this section correspond with the methods, results and discussion presented in Study 1 (Chapter 3) and Part A of Study 2 (Chapter 4). The second section relates to the working profile, in particular absenteeism and presenteeism, of adults with CF living in rural and remote WA. The research aims contained within this section correspond with the methods, results and discussion presented in Part B of Study 2 (Chapter 4). The third section relates to the identification of respiratory exacerbations in adults with CF. Specifically, the first two studies aimed to examine the usability of a smartphone application (app) for reporting symptoms and the observer agreement between clinicians interpreting the app data. Finally, the impact of the app on health outcomes was investigated in a randomised controlled trial (RCT). The research aims contained within this section correspond with the methods, results and discussion presented in Part A and Part B of Study 3 (Chapter 5), and Study 4 (Chapter 6).

1.1 Telehealth for adults with cystic fibrosis living in rural and remote Western Australia

This section provides the rationale for the research undertaken in Study 1 (Chapter 3) and Part A of Study 2 (Chapter 4).

1.1.1 Background

In the general population, people living in areas of low population density, such as rural and remote areas of Australia, have poorer health outcomes when compared with those living in metropolitan areas (1). A key contributor to this is reduced access to care, that is, the inability of a person to utilise health services that are necessary to improve or maintain their health. This is due in part to the lower numbers of health professionals with recently updated skills (in specialist clinical areas) working in rural and remote areas, and the large distances needed to travel to specialist healthcare facilities (2). Of note, earlier work has demonstrated that people with CF, who have complex healthcare needs (3, 4), have poorer health outcomes when not managed in specialist CF centres (5, 6).

In WA, the state adult specialist CF centre is at Sir Charles Gairdner Hospital (SCGH), in Perth. Of the 190 adults with CF who attended this centre at the time of commencing this study, 28 (15%) lived outside Perth, with distances to the centre ranging between 100 and 2,567 km. Due to limited specialist CF resources in these rural and remote areas, these adults with CF travel long distances to attend their scheduled routine clinics at SCGH. The geographical, time and financial barriers associated with travelling long distances is a major contributor to low rates of attendance at CF clinics.

The Australian CF Standards of Care recommend that people with CF attend CF clinics with a specialist multidisciplinary CF team a minimum of four times per year (4). In the years preceding this study, an internal audit revealed that this recommendation was not met for adults with CF living in rural and remote WA. This may negatively impact on long-term health outcomes, as it is known that those with CF receiving care in a CF centre have better forced expiratory volume in 1 second (FEV_1) and weight compared to those that do not (5, 6).

Therefore, Study 1explored the differences in magnitude of decline in spirometry between adults with CF living in the Perth metropolitan area and in rural and remote areas, and Study 2 (Part A) examined the use of telehealth (via videoconferencing) in the provision of CF clinics for adults with CF living in rural and remote WA.

1.1.2 Research questions

Do adults with CF living in rural and remote areas of WA have a different magnitude of decline in spirometry over a 3-year period compared with those living in the Perth metropolitan area?

In adults with CF living in rural and remote WA:

i. What is the uptake of and satisfaction with telehealth clinics?

ii. What is the impact of telehealth clinics on healthcare utilisation (HCU) outcomes including CF clinic attendance, hospital admissions and antibiotic use?

iii. What is the impact of telehealth clinics on other health outcomes including spirometry, nutritional status and health-related quality of life (HRQoL)?

1.1.3 Significance

Adults with CF living in rural and remote WA are at a geographical, time and financial disadvantage in regard to attending the SCGH CF Centre. Further, people living in areas of low population density often have limited access to healthcare professionals with recently updated skills in specialist areas, such as CF. Describing differences in the magnitude of decline in spirometry over a 3-year period may provide a catalyst to improve services to people with CF living in these areas. The provision of CF clinics via telehealth, in the form of videoconferencing, is a novel intervention that has not been investigated in an Australian CF cohort. Telehealth may improve access to care, and have a subsequent positive impact on longer-term health outcomes, by slowing the magnitude of decline in spirometry over time, and optimising HRQoL.

1.2 The working profile of adults with cystic fibrosis living in rural and remote Western Australia

This section provides the rationale for the research undertaken in Part B of Study 2 (Chapter 4).

1.2.1 Background

As the expected age of survival increases, adults with CF will likely stay in the work force for longer. Previous studies have reported that, in adults with CF, employment status is related to age and time spent in hospital (7), lung function and HRQoL (8). While it is known that many (80%) have engaged in paid employment at some point in their adult life (9), there are minimal data available regarding the impact that CF has on work attendance (absenteeism) (9) and work performance (presenteeism) (10).

1.2.2 Research question

i. In adults with CF living in rural and remote WA, what are the levels of absenteeism and presenteeism?

1.2.3 Significance

Many adults with CF will need to maintain employment throughout their life. There are few data available regarding the impact of CF on absenteeism and presenteeism in the workplace. For the first time, this study will quantify absenteeism and presenteeism using the World Health Organisation's Health and Work Performance Questionnaire in a CF population. The results of this study will describe the work attendance and performance of adults with CF, providing an insight that may be used by other people with CF to inform future employment decisions.

1.3 A smartphone application for reporting respiratory symptoms in adults with cystic fibrosis

This section provides the rationale for the research undertaken in Part A and B of Study 3 (Chapter 5) and Study 4 (Chapter 6).

1.3.1 Background

Respiratory exacerbations can have a severe and long-lasting impact on people with CF, by accelerating the magnitude of decline in FEV_1 (11), increasing the time spent in hospital (12), reducing HRQoL (13, 14) and physical activity (15), increasing feelings of depression (16), and ultimately increasing the risk of mortality (17). A respiratory exacerbation has been defined as having a change in four or more disease-specific criteria comprising cough, sputum, haemoptysis, dyspnoea, fatigue, sinus pain and discharge, fever, reduced FEV_1, anorexia or weight loss, and changes in physical examination of the chest or chest radiography (18).

The early detection of respiratory exacerbations is an integral component of CF care. Up to 25% of people with CF who have a respiratory exacerbation fail to have their lung function completely recover following treatment (19). Delayed initiation of treatment (i.e. antibiotics) has been associated with this failure of lung function to recover to pre-exacerbation levels (19). Therefore, strategies that are targeted at the early identification of respiratory exacerbations may be a vital step in optimising long-term outcomes in people with CF.

In people with CF who develop a respiratory exacerbation, delayed identification of the exacerbation is often due to delayed presentation to a CF clinic. The reasons for this delay are multifactorial, and include commitments such as work, study and family, as well as the barriers to attending a CF clinic such as travel and financial burden, a lack of education and understanding around the need to report respiratory symptoms sooner, and feelings of anxiety and depression associated with attending a CF clinic (20). The use of telehealth is becoming an increasingly popular way of reducing the barriers associated with accessing CF care.

The impact of telehealth technology in CF has been evaluated in interventions aimed at identifying respiratory exacerbations (21-25), providing increased support for people awaiting lung transplantation (26), providing exercise assessment and training (27, 28) and promoting physical activity (29). Although adults with CF are likely to be comfortable with the use of mobile technologies, the effectiveness of telehealth at detecting respiratory exacerbations has previously been compromised by suboptimal adherence (i.e. 10% to 67%) (21-25). This is likely due to the high reporting burden experienced by participants, such as daily reporting of respiratory symptoms and/or regular spirometry. Minimising this burden in order to optimise adherence is an important consideration when designing telehealth technology.

There is a need for a novel approach to facilitate the early identification and treatment of respiratory exacerbations in this population. For this reason, a smartphone application (app) was developed that can be used by adults with CF to report symptoms suggestive of a respiratory exacerbation to the CF team. To optimise adherence, the app was designed to exclusively utilise smartphone technology that was mobile and already owned by the majority of young adults in today's society. It was hypothesised that more frequent surveillance of symptoms would shorten the time to detect respiratory exacerbations, reducing the risk of more severe exacerbations requiring treatment with intravenous (IV) antibiotics.

1.3.2 Research questions

i. In adults with CF, what is the usability and satisfaction of an app used to report symptoms suggestive of a respiratory exacerbation?

ii. Amongst clinicians experienced in providing CF care, what is the observer agreement in clinical decision making based on the symptom responses obtained using this app?

iii. In adults with CF, what is the impact of an app used to report symptoms suggestive of a respiratory exacerbation over a 12-month period on:

a) The number of respiratory exacerbations requiring IV antibiotics and IV antibiotic days.

b) Measures of HCU (time to detection of first respiratory exacerbation requiring IV, oral and inhaled antibiotics, antibiotics costs, number and cost of hospital admissions, and number and cost of CF clinics attended).

c) Spirometry, nutritional status, HRQoL, feelings of anxiety and depression, absenteeism and presenteeism, and treatment adherence.

iv. In adults with CF, what is the adherence to and usability of this app over a 12-month period?

1.3.3 Significance

This app was a novel technology that aimed to overcome the barriers leading to delayed treatment, by enabling the participant to identify and report symptoms suggestive of a respiratory exacerbation without attending a CF clinic. The app was downloaded on the participant's own smartphone, allowing for integration into their lifestyle more seamlessly. The majority of home monitoring interventions investigated in past studies have noted somewhat poor adherence amongst users, likely due to the high reporting burden using monitoring equipment that was large and not portable outside of the home.

Parts A and B of Study 3 were designed to ensure the usability of the app was high, and that there was agreement in clinical decision making by those interpreting the app data (i.e. demonstrating feasibility). Study 4 was designed to investigate the impact of the app on health outcomes, as well as to further examine its usability and the level of adherence to its use. It was contended that the use of the app would result in faster detection of respiratory exacerbations and initiation of treatment in adults with CF. This in turn would lead to less severe exacerbations and decrease the need for treatment with IV antibiotics. Further, improved surveillance and detection of respiratory exacerbations would possibly lead to improved longer-term outcomes such as spirometry and HRQoL.

1.4 Summary

This programme of research investigated novel solutions utilising modern technology. The global aim was to use telehealth to improve access to care and facilitate the detection of respiratory exacerbations amongst adults with CF, with the intention of meeting recommended standards of care and ultimately improving health outcomes The telehealth interventions investigated, and subsequent results, provide a substantial, original and significant contribution to the knowledge and understanding of this field, being the integration of modern technology with traditional care for adults with CF.

CHAPTER 2

LITERATURE REVIEW

This literature review comprises five parts, which each part containing several sections.

Part 1 describes the incidence, pathophysiology, morbidity and mortality of cystic fibrosis (CF); Part 2 discusses CF care in detail, including the evidence for centre-based care, the treatment burden experienced by people with CF and the levels of adherence to treatment regimens, and adult CF care in Western Australia (WA); Part 3 explores the definition, impact, identification and treatment of respiratory exacerbations in CF; and, Part 4 describes the role of telehealth in CF care to date; and Part 5 provides a conclusion relating to the literature covered in this review.

2.1 Cystic fibrosis: incidence, pathophysiology, morbidity and mortality

This part contains two sections. Specifically, i) the incidence, prevalence and cost of CF; and, ii) the pathophysiology, morbidity and mortality associated with this condition, and the monitoring of disease trajectory.

2.1.1 Incidence, prevalence and cost

Cystic fibrosis is one of the most common genetic diseases affecting the Caucasian population (30). In Australia, the incidence of CF is 1 in 3,000 live births (31). Currently, there are approximately 3,150 people with CF living in Australia (31) (out of a national population of 25,647,003) (32) and approximately 90,000 people with CF worldwide (33). Previously considered to be largely a paediatric disease, advancements in treatment options and models of care have seen the median life expectancy of those with CF in Australia increase in recent decades to 44 years currently (31). The median age of survival shows geographical disparities, with differences seen between the United States (US) (43 years), United Kingdom (UK) and Germany (47 years), and Canada (53 years) (33). While it is difficult to determine, it has been suggested that differences in survival age between countries may be due differences in healthcare systems and access to care (34). This increase in survival has resulted in a greater proportion of people with CF living into adulthood, with adults now comprising 54% of the total CF population in Australia (31).

With the recent development and availability of cystic fibrosis transmembrane regulator (CFTR) modulator therapies (medications that improve the production, processing and/or function of the defective CFTR) (35), the life expectancy of people with CF is expected to continue to increase. Trials investigating these new therapies have demonstrated reductions in mucus plugging and peribronchial thickening as seen on computed tomography (36), as well as clinically important improvements in lung function and quality of life (37-39). This poses an interesting future dilemma for healthcare; people with CF will have, on average, milder disease severity but the number of people with CF will

grow rapidly as a result of fewer premature deaths, potentially placing increased strain on CF centres and the healthcare system.

An analysis of Australian CF Registry data from 2003 to 2005 (of 2,255 cases, published in 2013) estimated that the mean annual cost per person for providing CF care ranged between $14,700 (Australian dollars; AUD) and $48,800 AUD, with the cost increasing with more severe disease (40). The lifetime cost per person was estimated to be $443,400 AUD in this same sample (40). These estimates reflect the cost of medications and hospital resources (staffing, equipment, clinic rooms, and bed days) utilised in both outpatient and inpatient settings. The high cost of care for adults with CF in WA reflects these data; calculations extrapolated from unpublished data obtained from the Department of Activity Based Costing at Sir Charles Gairdner Hospital (SCGH) for the financial year 2016/17, demonstrated that the approximate total cost to the hospital for inpatient and outpatient care was $4,771,465 AUD and $635,807 AUD, respectively. With 185 adults attending the CF centre at SCGH during that financial year, the mean cost per person equated to $29,228 AUD.

More recently in 2018, a retrospective analysis of 1,196 people with CF (mean [standard deviation, SD] age 16 [9] years) in the US found that 90% had at least one respiratory exacerbation in the 12-month study period, at an estimated cost of $44,589 (United States dollars; USD) to $116,169 USD per exacerbation (41). Of note, US costing estimates are likely to be greater than those in Australia due to the differences in healthcare funding (i.e. insurance vs. government).

Similar economic evaluations undertaken in 2020 would look vastly different given the cost of CFTR modular therapies. Each of the widely used modulator therapies costs the Australian government approximately $270,000 AUD per person annually (42), which will increase the estimated lifetime cost of care for a person with CF by 30 to 40 times. However, these are simplistic estimates that do not factor in the expected reduction in healthcare utilisation resulting from the expected improved outcomes relating to CFTR modulator therapies. Further, the true cost of CF to society is likely to be more accurate when additional factors are considered such as absenteeism and presenteeism relating to school, university and work, as well as the time and cost associated with disease-related travel to

and from healthcare facilities. These factors contribute to a secondary financial impact on families and carers.

2.1.2 Pathophysiology, morbidity, mortality and monitoring disease trajectory

Cystic fibrosis is a multi-system disease, predominantly affecting the lungs, pancreas, intestinal tract and liver (43). It results from a defective gene on the seventh chromosome which is responsible for encoding human CFTR protein (43). The CFTR protein contained in epithelial cells functions as a channel for the movement of chloride ions across the cell membrane, regulating the movement of water and the production of protective layers of mucus within organs (43). Defective CFTR inhibits the ability of the cells to move chloride ions and thus water to the cell surface, leading to a dehydrated and thick cell mucus layer, negatively impacting the function of the cilia. In the lungs, this leads to a cycle of inflammation and infection, and permanent airway damage known as bronchiectasis (43). Secondary to the progression of bronchiectasis, respiratory complications experienced can include haemoptysis and pneumothorax (44). Throughout the lifespan, the progression of bronchiectasis eventually leads to respiratory failure, with this being the most common cause of death (45).

The extrapulmonary manifestations of CF include pancreatic destruction and an inability to produce digestive enzymes (known as pancreatic insufficiency) and insulin, meconium ileus in infancy, distal intestinal obstructive syndrome and liver disease (46). Many people with CF will also develop osteoporosis, CF-related diabetes (CFRD) and renal insufficiency (46). The psychological impact of CF also needs to be considered, with levels of anxiety and depression reported as being at least similar (47, 48) or higher (49, 50) than that observed in the general population.

Disease trajectory is most commonly assessed using spirometry, in particular forced expiratory volume in 1 second (FEV_1) (51, 52). Regular use of spirometry is well established in CF clinics and healthcare centres across both metropolitan and rural and remote areas. Based on measures of FEV_1 expressed as a percentage of that estimated in a healthy population (percentage predicted FEV_1 [$ppFEV_1$]), people with CF can be classified as having mild (FEV_1 > 80% predicted), moderate (40 to

80% predicted) or severe (< 40% predicted) lung disease. Analysis of 14,372 people with CF in the European Cystic Fibrosis Society Patient Registry demonstrated that factors which increased the odds of an FEV_1 decline, after adjustment for age, were low body mass index (BMI) (odds ratio [OR], 95% confidence interval [CI] 6.0, 5.0 to 7.3), chronic infection with *Pseudomonas aeruginosa* (2.4, 2.0 to 2.7), pancreatic insufficiency (2.0, 1.6 to 2.5) and presence of CFRD (1.8, 1.6 to 2.2) (53). Other epidemiological studies suggest that frequent exacerbations (11, 17, 54), female sex (55), genotype, poor childhood growth, infection with mucoid *Pseudomonas aeruginosa* and meconium ileus (56) also influence the progression of lung disease. Two smaller but often cited studies also draw attention to the role of centre-based CF care in optimising disease outcomes including FEV_1 (5, 6), which will be explored more thoroughly in Section 1.2.1.

Notwithstanding the widespread use of spirometry to monitor disease trajectory and quantify disease severity, measures of FEV_1 have several limitations. These relate predominantly to the effort required during the repeated forced expiratory manoeuvres to perform spirometry (52), which makes collection of these measures challenging during respiratory exacerbations and impossible in young children (e.g. under the age of 5 or 6 years). Further, FEV_1 can be highly variable and lack the sensitivity to detect small changes in lung function, especially in those with mild disease (51, 57, 58).

In light of these limitations, other outcomes are increasingly being utilised to provide guidance to clinicians regarding disease trajectory. Computed tomography (CT) is the gold standard for detecting structural lung disease in CF and CT scores have been correlated with several important measures in this population such as FEV_1 (59), lung clearance index (LCI) (60), respiratory exacerbation rates (61), health-related quality of life (HRQoL) (62) and, survival in those awaiting lung transplantation (63). The LCI requires less effort to measure, and appears to be more sensitive to changes in lung mechanics than spirometry, with data from 67 adults with CF demonstrating that the sensitivity to changes in lung function of LCI was 81%, compared with 63% for $ppFEV_1$ (64). Peak rate of oxygen uptake measured during cardiopulmonary exercise testing (CPET) has been shown to be an independent predictor of lung transplantation or death at 10-year follow-up (65).

Despite these findings, access to CT, CPET and LCI is more limited compared to spirometry, especially in rural and remote areas. Further, CT and CPET are far more expensive to undertake, and CT results in substantial radiation exposure (66). Thus, while being increasingly utilised for research purposes, the uptake of CT, CPET and LCI still remains limited in clinical practice, and therefore FEV_1 is likely to remain part of the routine assessment of people with CF for the foreseeable future.

2.2 Cystic fibrosis care

This part contains four sections. Specifically, i) centre-based care in the management of CF; ii) barriers to care for people with CF; and, iii) treatment burden and adherence; and, 4) adult CF care in WA.

2.2.1 Centre-based care

International standards of care recommend that people with CF attend specialist CF centres (4, 67), which are most often located within a tertiary healthcare setting. Each centre is recommended to have a specialist multidisciplinary team, consisting of medical, physiotherapy, pharmacy, nursing, dietetic, social work and psychology professionals (4, 67). Centralised care in tertiary centres also provides the opportunity for the CF team to collaborate with on-site specialist secondary services (e.g. intravascular access, endocrinology, immunology and hepatology). While the recommendations regarding centre-based care are generally accepted and agreed with by clinicians, it is often not practical to offer this care to all people with CF for geographical reasons, especially in countries with areas of low population density such as Australia.

Even in the absence of evidence from randomised controlled trials (RCTs), centre-based care is generally viewed as superior to decentralised care (i.e. managed in local healthcare facilities by general practitioners). There are however, two well-known retrospective studies that provide evidence to support a specialist model of care. Data from 97 adults with CF, published in 1998, demonstrated that those who were managed in a paediatric and then adult CF centre throughout their lifespan in the UK had a higher BMI which correlated with greater FEV_1 ($r = 0.52$, $p < 0.001$) (6). Data published in 2009 in Belgium on 217 children with CF showed that those who were referred late to a specialist CF centre following diagnosis had a lower FEV_1 at age 13 years (mean [SD] 77 [22]% vs. 87 [19]%, $p = 0.01$) (5). While these were retrospective observational studies with relatively small samples in differing geographical locations, the results lend support to the need to provide a centralised and collaborative approach to the management of this complex disease.

Outreach services, whereby the clinical team from the CF centre visits the person with CF in their local community and/or collaborates with local healthcare professionals, have been implemented in Australia for some time. Children and adolescents (n =116) with CF living in Queensland and northern New South Wales receiving outreach services from the CF team at the Royal Children's Hospital in Brisbane reported their HRQoL (using the PedsQL™ and Cystic Fibrosis Questionnaire) to be similar as those managed at the CF centre (68). Children (n = 79) in rural and remote Victoria, and Tasmania, who received outreach services from the Royal Children's Hospital in Melbourne had similar FEV_1 and BMI to those attending the CF centre (69). While outreach services may not always be the most practical solution given the travel and time burden on the clinicians, these two studies support the continued role of the CF centre in providing care to people with CF living in rural and remote areas. The use of technology such as videoconferencing, which can be used to provide outpatient clinics, may help to reduce this burden on both the people with CF and the CF centre clinicians.

The Australian CF Standards of Care recommend that people with CF attend a minimum of four CF clinic per year for disease monitoring and evaluation of their treatment regimen (4). Further, guidelines are provided regarding the specific provision of outpatient and inpatient care at tertiary centres, as well as outreach clinics for people with CF living in rural and remote areas. As the most recent edition of the Australian CF Standards of Care was published in 2008, telehealth was not included as a potential way of providing care to people with CF. Also, several of the recommended standards are based on clinician consensus rather than robust published data. The delivery of adult CF care in WA prior to the commencement of the research undertaken as part of this thesis will be described in more detail in Section 2.2.4.

More recently, it has been acknowledged that future models of care need to consider different management approaches that incorporate newer, innovative technologies for improving disease monitoring, reducing the disease burden and improving access to care (3, 33). The emerging role of telehealth in CF will be further described in Section 2.4.2.

2.2.2 Barriers to care

As life expectancy and the proportion of people with CF living into adulthood increases (31, 33), so does the burden facing people with CF in regard to accessing health care and completing treatment regimens. The main barriers to accessing care are complex and include distance, time, financial and psychological factors (20, 70, 71).

The strong clinical recommendation to offer care through specialist CF centres creates a barrier to care for many people with CF, due to the distance required to travel to the centre. This challenge is further amplified in Australia and is reflected in the general population; that is, it is known that people living in areas of low population density, such as rural and remote areas of Australia, have poorer health outcomes when compared with those living in metropolitan areas (1). A key contributor to poorer health outcomes is the inability of people to utilise health services that are necessary to improve or maintain their health. This is due in part to the lower numbers of health professionals with recent clinical experience in these specialist areas, and as mentioned, the large distances needed to travel to specialist healthcare facilities (2). This is discussed in regard to WA in Section 2.2.4.

Several factors lead to time being perceived as a barrier, encompassing competing adult commitments such as family, study and work, combined with the expectation of attendance at regular outpatient clinics (4) and disease-related treatment burden (71) (described further in Section 2.2.3). It is also now a realistic expectation for most people with CF that enrolment in higher levels of education and ongoing employment are attainable (72). In reality, this expectation is somewhat more of a necessity (i.e. to support oneself financially) as more people with CF live into adulthood. While many people with CF report that CF adversely impacts on their ability to work (7, 8, 73), UK data from 2014 in 254 adults with CF demonstrated that 65% were engaged in higher education or employment (including being self-employed), with the median (interquartile range [IQR]) hours worked per week being 37 (22 to 40) (9). Similarly, French data from 2012 in 207 adults with CF reported that 76% were engaged in study or employment (74). While the ability for adults with CF to study and work is

undoubtedly positive, it does compete with the time available for completing treatments vital for maintaining clinical stability.

As mentioned, the necessity of attending four or more CF clinics per year at a CF centre is in itself a major lifestyle disruption. As each clinic is multidisciplinary in nature, attendance can take several hours, not including the time waiting for new prescriptions to be filled at the pharmacy. Further, the costs of attending include private or public transport, parking at the centre, paying for prescriptions for several medications, and taking unpaid time off work or using annual or sick leave. Often CF centres will not provide expensive equipment such as nebulisers and airway clearance devices free of charge, further adding to the financial strain on people with CF. Finally, psychological barriers to care can include denial of one's own disease status, not wanting to have poor health status confirmed by clinicians or objective measures such as spirometry, or an inability to engage with the CF centre due to overwhelming feelings of anxiety and depression (20).

While the barriers to receiving care for people with CF are prolific, technology-based solutions tailored to the demographic of this population are very appealing as a tool to attempt to overcome the barriers described. In particular, solutions that can minimise the geographical and time barriers are highly desirable in order to improve access to care and potentially improve health outcomes.

2.2.3 Treatment burden and adherence

As described in Section 2.2.2, people with CF have many competing commitments in daily life (work, study, family), constantly threatening their ability to adhere to a complex prescribed treatment regimen. For adults with CF, the daily treatment undertaken to maintain clinical stability involves airway clearance, inhaled therapy, supplemental nutritional intake, exercise, and oral medications including antibiotics and digestive enzymes (33, 75, 76). This is in addition to the regular (at least 3-monthly) CF clinics attended at the CF centre as described in Section 2.2.1.

Sawicki and colleagues investigated the treatment burden amongst 204 adults with CF (71), and observed that participants were completing a median (range) of 7 (0 to 20) treatments per day, for a

mean (SD) total of 108 (58) minutes. The majority of treatment was related to physiotherapy, specifically inhaled therapy (41 [31] minutes), airway clearance (29 [27] minutes) and exercise (29 [23]) minutes.

Given the amount of time consumed by the daily treatment regimen of people with CF, it is not surprising to see at least some level of non-adherence with treatment regimens. Sawicki and colleagues reported that 139 (68%) of participants completed an airway clearance technique (ACT) as part of their prescribed treatment regimen, however only 49% reported completing their ACT on the day of data collection. This is consistent with a literature review of treatment adherence in CF, finding adherence to ACT and exercise being 40 to 55%, with varying levels reported for other treatments (inhaled medications and pancreatic enzymes = 65 to 80%, antibiotics = 80 to 95%) (77).

Common reasons reported by adults with CF for not completing treatment include feeling healthier than usual (i.e. don't need to do the treatment), too busy/no time, forgetting, being too tired, the medications are too expensive, not wanting to complete treatment in public, and having other commitments (70, 78-80). While it is understandable that adherence to such a time-consuming treatment regimen will not be perfect, the consequences of not completing regular treatment are severe for people with CF and include increased rates of respiratory exacerbations, longer hospitalisation and poorer lung function (81).

This large treatment burden, combined with a busy lifestyle and the need to attend the CF centre regularly, can negatively impact adherence to essential treatment amongst people with CF. Therefore, strategies must be considered that aim to reduce some of this burden in order to facilitate improved adherence to treatment. This may come in the form of newer technologies that allow for care to be delivered with less impact on factors such as time, travel and finances.

2.2.4 Adult cystic fibrosis care in Western Australia

In WA, the adult CF centre is at SCGH in Perth. Approximately 190 adults with CF attend SCGH, with approximately 25 to 30 (13% to 16%) living outside of the Perth metropolitan area at any time.

The distance this cohort lives from the SCGH CF centre ranges between 100 and 2,567km, with as few as one adult with CF living in many of the rural and remote areas, in towns that can have populations as low as 1,200 people. With limited specialist CF resources in these areas, and the difficulty in providing outreach clinics across such a vast geographical area (approximately 2,500,000 km^2) due to limited CF centre staffing and travel costs, adults with CF have travelled long distances (via car or plane) to attend their scheduled CF clinics at SCGH. The travel and financial burden for people with CF is suspected to be a major contributor to their previously observed low rates of attendance at clinics.

In 2012 (prior to the commencement of this PhD research), an internal audit revealed that only 22% of the adults living in rural and remote WA met the recommendation of attending four or more CF clinics per year, in contrast to 79% of adults living in the metropolitan area. This lack of routine clinical assessment is likely to have impacted on the CF team's ability to identify respiratory exacerbations and provide necessary treatment, potentially worsening health outcomes such as lung function, nutritional status and HRQoL in this group over time. Telehealth, in the form of providing outpatient clinics via videoconferencing, is a potential solution to this problem.

2.3 Respiratory exacerbations in cystic fibrosis

This part contains three sections. Specifically, i) the definition of a respiratory exacerbation in CF;

ii) the impact of respiratory exacerbations on the healthcare system and people with CF; and, iii) the identification and treatment of respiratory exacerbations.

2.3.1 Definition of a respiratory exacerbation in cystic fibrosis

Defining a respiratory exacerbation in CF is a point of contention (82-87), and thus a universally agreed definition is still lacking. Despite this lack of consensus, the rate of respiratory exacerbations is one of the key outcome measures used in clinical trials (88). This is because these events have a negative impact on health outcomes (13, 17, 54, 89, 90) and healthcare utilisation (HCU) (40, 41, 91) (discussed in Section 2.3.2), and an apparent ease of being measured (as a rate or frequency) when comparing the efficacy of a new intervention (92). In clinical practice, physicians often adopt a pragmatic approach to define respiratory exacerbations (rather than using a specific set of criteria), resulting in differing approaches being used between physicians, CF centres and in clinical trials (84-86). The lack of an agreed definition, and use of a wide-ranging list of potential outcomes to define a respiratory exacerbation, also makes it difficult to measure the severity of a respiratory exacerbation. The provision of treatment is often relied upon as surrogate marker for a respiratory exacerbation, with exacerbation severity being judged on the level of treatment required (i.e. oral and inhaled vs. intravenous [IV] antibiotics). This provides further challenges to accurately defining respiratory exacerbations in people with CF.

One of the first clinical trials to define a respiratory exacerbation for research purposes investigated the effect of inhaled recombinant human deoxyribonuclease (rhDNase), also known as Pulmozyme ®. In this double blind, placebo RCT involving 968 adults and children with CF, a respiratory exacerbation was defined as a change in four or more disease-specific criteria comprising cough, sputum, haemoptysis, dyspnoea, fatigue, sinus pain and discharge, fever, worsening FEV_1, anorexia or weight loss, and changes in physical examination of the chest or

chest radiography (18). The intervention demonstrated a reduction in the number of respiratory exacerbations in this group by 22% (relative risk [95% CI] 0.78 [0.57 to 1.06]) with once daily administration of rhDNase, and by 34% (0.66 [0.48 to 0.91]) with twice daily administration (18). Following publication, this particular definition of a respiratory exacerbation, known as Fuchs criteria, was more widely adopted.

In 2001, Dakin and colleagues sought to further define respiratory exacerbations by surveying physicians experienced in providing CF care throughout Australia (83). They also raised concern with the use of 'therapeutic intervention as a surrogate measure of exacerbations' due to the requirement that all physicians would need to be utilising the same therapeutic approach in clinical practice; and therefore aimed to evaluate the level of consensus via their survey. Participants were provided with a list of signs, symptoms and investigations (based on previous literature) and asked to rate their helpfulness (not helpful; slightly helpful; helpful; or very helpful) in detecting respiratory exacerbations according to clinical scenarios specific to paediatric and adult care of people with CF. Analysis of responses (n = 62) highlighted the variability between physicians, with consensus (defined as > 74% or < 26% of respondents rating the criteria as helpful or very helpful) achieved on only eight (50%) of the 16 criteria. While this study did little to further define a respiratory exacerbation in CF, it did draw attention to the need for wider consensus in both clinical practice and research.

Other studies have attempted to provide clarity on defining a respiratory exacerbation of CF over subsequent years. Analysis of data from 11,692 children and adults with CF from the Epidemiologic Study of CF (US and Canadian observational study) determined that the signs or symptoms with the strongest association with the initiation of treatment for respiratory exacerbations in people ≥ 18 years of age (complete data available on n = 999) were a relative reduction in ppFEV$_1$ (OR [95% CI], 3.8 [2.7 to 5.3]), newly detected *Pseudomonas aeruginosa* (3.2 [1.0 to 10.1]), increased cough frequency (2.8 [1.4 to 5.8]), sinusitis (2.7 [1.6 to 4.9]), new crackles on auscultation (2.5 [1.7 to 3.7)] and haemoptysis (2.4 [1.8 to 3.4]) (87). In those ≥ 6 years of age, there was a large increase in being prescribed treatment with antibiotics (oral or IV) when comparing those with any two criteria (48% increase in prescribed treatment) and

those with any three criteria (75% increase in prescribed treatment) of the 10 disease-specific criteria investigated. This indicated that the presence of three or more of the defined exacerbation criteria was a strong indicator for the need for treatment. The authors of the Epidemiologic Study of CF made recommendations regarding the definition of a respiratory exacerbation that were not too dissimilar to Fuchs criteria, being four out of a possible 12 signs and symptoms.

A report from the EuroCareCF Working Group, published in 2011, drew attention to the ability of the Fuchs criteria in discriminating differences in rates of respiratory exacerbations in a large multicentre RCT investigating the efficacy of hypertonic saline (93). This working group proceeded to recommended that the Fuchs criteria be used in future European clinical trials to identify respiratory exacerbations (82). They also provided a modified version of the Fuchs criteria that they intended to validate in the future, defining a respiratory exacerbation as the need for antibiotic treatment based on the presence of two out of six of the original signs and respiratory symptoms (change in sputum, increased cough, increased fatigue or lethargy, anorexia or weight loss, decreased relative pp$FEV_1 \geq 10\%$, increased dyspnoea).

The earlier work that attempted to define a respiratory exacerbation in people with CF is overtly clinician-centric. In 2009, two groups of researchers sought to incorporate feedback from people with CF into the definition of a respiratory exacerbation. Abbot and colleagues interviewed 47 adults with CF (age $\geq$ 16 years) regarding the symptoms they experienced at the commencement of a respiratory exacerbation, as well as perceived changes in respiratory symptoms during recovery from the exacerbation (94). The participants reported a range of symptoms that they associated with the onset of a respiratory exacerbation, which appeared to be influenced by their underlying disease severity. Common themes across all disease severities (reported in $\geq$ 80% of the sample) were the presence of tiredness and fatigue, disturbed sleep and increased cough and sputum. The main differences observed were that participants with mild underlying lung disease reported that they often felt unwell with general aches, cold symptoms, runny nose and sore throat; while those with more severe disease described a decrease in their ability to undertake activities and increased dyspnoea at rest or with light activities. There was greater consensus

across disease severities regarding the respiratory symptoms that participants associated with recovery; these were increased energy, less fatigue, better sleep, decreased cough and sputum, and improved mood.

Goss and colleagues also explored this theme, by undertaking 25 qualitative interviews with parents of young children with CF (n = 4), adolescents (age 12 to 17, n = 9) and adults (n = 12) with CF who (or their children) were currently being treated with oral or IV antibiotics for a respiratory exacerbation (95). The authors aimed to obtain commonalities in reported respiratory symptoms and then use these to create a new symptom diary for use in clinical practice and research. The respiratory symptoms reported as most 'bothersome' during a respiratory exacerbation were (percentage [%] of times cited) cough (70%), fatigue (43%), chest congestion (39%), difficulty breathing/shortness of breath (39%) and wheezing (39%). The three most commonly cited triggers for seeking treatment for a respiratory exacerbation were constant cough (36%), thick dark sputum (32%) and shortness of breath (28%). Eight respiratory symptoms (cough, chest tightness, difficulty breathing, wheeze, coughing up mucus, fevers and chills, fatigue) were selected for the new symptom diary known as the CF Respiratory Symptom Diary (CFRSD), which also assesses symptom severity. This diary has been used as an outcome in CF studies (95, 96).

Bringing together the themes explored in this section, a study published in 2014 explored the views of both CF multidisciplinary team members (n = 38) and adults with CF (n = 31) in regard to signs and symptoms suggestive of a respiratory exacerbation (97). McCourt and colleagues conducted parallel Delphi surveys across 13 centres in the UK and Ireland. The five highest ranked responses from the clinicians (increased sputum, decrease in relative $ppFEV_1 \geq$ 10%, increased shortness of breath, increased inflammatory markers, fever or increased temperature) and adults with CF (decrease in relative $ppFEV_1 \geq 10\%$, increased shortness of breath, trouble breathing, feeling the need to do more airway clearance, increased night symptoms) varied somewhat, highlighting the need for consideration of the views of both clinicians and people with CF when defining a respiratory exacerbation.

It is clear that the definition of a respiratory exacerbation in CF is a point of contention. This is in contrast to other respiratory diseases such as chronic obstructive pulmonary disease (COPD) (98) and asthma (99), where more delineated criteria are accepted. For future studies seeking to define respiratory exacerbations in CF cohorts, it would be reasonable to use signs and symptoms acknowledged by both clinicians and people with CF, combined with a level of pragmatism to ensure it is relevant in a real-world setting.

2.3.2 Impact of exacerbations

In CF, respiratory exacerbations have profound and long-lasting negative consequences which will be detailed in this section. Specifically, themes will be explored relating to i) HCU; ii) lung function, further respiratory exacerbations and survival; and, iii) HRQoL and mood; and iv) other impacts.

2.3.2.1 Healthcare utilisation and cost

According to the Australian CF Data Registry 2017 Annual Report (31), 734 (23%) of the 3,151 people with CF required treatment with IV antibiotics at least once for a respiratory exacerbation during that 12-month period. The data reported pertaining to oral and inhaled antibiotic use specifically for respiratory exacerbations were less clear, as they were captured as either ‘continuous’ or ‘as needed’, whereas IV antibiotics would likely have only been prescribed for an acute respiratory exacerbation. Taking this into account, over a 12-month period ‘as needed’ oral and inhaled antibiotics in isolation were prescribed to 1,090 (35%) and 406 (13%) people at least once.

Also using data from the Australian CF Data Registry, approximately one quarter (24%) of people with CF in Australia in 2017 had at least one hospital admission for respiratory causes (n = 753) (31). However, further interpretation of the registry data needs to be approached with caution, as there is no way to determine whether those listed as having no antibiotics or having no respiratory exacerbations, reflects an absence of data recorded and submitted to the registry. In regard to CF clinic attendances, the mean number of clinics was 5.9 for children and adolescents, and 5.4 for adults, yet there is no way to establish whether each CF clinic

attendance was routine only, or an additional attendance for monitoring of an acute respiratory exacerbation.

In comparison, the US CF Foundation Patient Registry reports that of 30,775 people with CF in the US in 2018, 10,439 (34%) experienced a respiratory exacerbation requiring treatment with IV antibiotics, and received a mean of 27.5 days of IV antibiotics per year per person, with an average of 17.9 days in hospital per person (100). The mean number of CF clinics attended per person was 4.3. In the UK, there were data from 10,509 people with CF in the UK Cystic Fibrosis Registry in 2017 (101). During this year, 4,400 (45%) people required IV antibiotics for a respiratory exacerbation, and 3,715 (38%) had at least one hospital admission, with the median (IQR) admission days per person throughout the year being 27 (14 to 45). No UK data were available in 2017 regarding the average number of CF clinic attendances per person.

While it is hard to estimate the exact cost of respiratory exacerbations in CF due to the complexity of the economics and burden involved, the use of 2018/19 Australian activity based funding (ABF) data provided by the Independent Hospital Pricing Authority (102) can provide a lower bound estimate of the costs associated with inpatient hospital care. Sir Charles Gairdner Hospital receives funding of between $12,846 and $19,294 AUD for each inpatient admission for a respiratory exacerbation (based on a 14-day admission). The use of ABF data as a surrogate marker of true hospital costs does have limitations. Specifically, ABF (which is a federal source of funding in Australia) potentially underestimates the true cost associated with hospital admissions as it does not include the other sources of hospital funding (e.g. state government, philanthropic or grant funding for clinical trials) that contribute to its ability to provide ongoing care. A different method of estimating the cost of an inpatient admission utilises figures provided by the SCGH Department of Activity Based Costing. Each inpatient day is calculated to cost the hospital $1,309 AUD providing an estimate of $18,326 AUD for a 14-day admission. This estimate also likely underestimates true costs, at it excludes the cost of medications and allied health services.

As discussed in Part 2.2, US data from 2018 estimated that the cost of care per respiratory exacerbation (receiving oral or IV antibiotics, with or without hospitalisation) was $44,589 USD to $116,169 USD (41). This study used Medicaid insurance information to provide estimates, which potentially inflated the costs when compared to healthcare systems that are not insurance driven. In contrast, another US group published data in 2017 and estimated the mean cost of providing treatment for respiratory exacerbations for people with CF to be $12,784 USD for an exacerbation of any type (receiving oral or IV antibiotics, with or without hospitalisation), or $36,319 USD for those treated with IV antibiotics (with or without hospitalisation) (91). This study, which was led by a pharmaceutical company, again estimated costs based on the data obtained from medical records and the database of a national healthcare insurer.

Overall, it is clear that respiratory exacerbations lead to variable, but generally high costs to the healthcare system through hospital admissions, cost of antibiotics and CF clinic attendances. With the advancement of pharmacological options for treatment, specifically CFTR modulators, the future projected costs of providing care for respiratory exacerbations may change, for example, if they are less frequent and/or less severe, and require fewer hospital admissions. However, this reduction in cost for the treatment of respiratory exacerbations will likely be overshadowed by the costs of the CFTR modulator treatments (approximately $270,000 per person per year), and therefore efforts still need to be directed toward detecting respiratory exacerbations sooner to allow for the faster provision of antibiotic treatment.

2.3.2.2 Lung function, risk of further exacerbations and survival

As previously described (Section 2.1.2), FEV_1 has historically been the most common marker of disease trajectory in CF, with the immediate impact on FEV_1 widely accepted as an indicator of a respiratory exacerbation (18, 82, 83, 87). However, it is the medium to long-term impact of respiratory exacerbations on FEV_1 and survival that is more concerning.

In 2010, Sanders and colleagues reported on data that had been collected by the US Cystic Fibrosis Foundation Registry between 2003 and 2006 on 8,479 respiratory exacerbations in

people with CF treated with IV antibiotics (19). Specifically, they analysed the proportion of participants (age ≥ 6 years) in whom FEV_1 returned to baseline levels (defined as the best FEV_1 in the 6 months prior to initiation of treatment) within 3 months following treatment. In 25% of respiratory exacerbations, the participants' FEV_1 did not recover to baseline levels, which would likely lead to an accelerated loss of lung function over time. In 2017, the same authors used US Cystic Fibrosis Foundation Registry data from 2004 to 2011 (13,954 respiratory exacerbations) to report that the participants in whom FEV_1 had failed to return to baseline levels, described as non-responders (n = 2,762 [19.8%]), had a shorter median (95% CI) time to the next respiratory exacerbation, being 235 (218 to 252) days, vs. > 365 days in responders (hazard ratio [HR] [95% CI] 1.1 [1.1 to 1.2]) (103). Further, non-responders had a greater number of respiratory exacerbations over the following 3 years than responders, being mean (95% CI) 5.0 (4.8 to 5.1) vs. 3.5 (3.4 to 3.5), respectively.

Several other studies have explored the relationship between respiratory exacerbations and FEV_1. In a small Italian sample (n = 51), the number of respiratory exacerbations per year, quantified retrospectively, was strongly related to FEV_1 decline per year, with each exacerbation resulting in an additional mean (95% CI) loss of 30 (9 to 52) ml (89). In Canada, two studies reported similar findings; the first, a 3-year prospective cohort study (n = 446), demonstrated an increased risk of a 5% decline in FEV_1 from baseline in those with more than two respiratory exacerbations per year (HR [95% CI] 1.5 [1.1 to 2.0]) (17); the second, a retrospective study (n = 851), found that the mean (95% CI) rate of annual FEV_1 decline was double in those who had a respiratory exacerbation (2.5 [2.1 to 2.8]%) vs. those who had not had an exacerbation (1.2 [1.0 to 1.5]%) (54). The former Canadian study also demonstrated that participants who had experienced > 2 respiratory exacerbations requiring IV antibiotics per year were at increased risk of lung transplantation or death during the 3-year study period (HR [95% CI] 4.05 [1.15 to 14.28]) (17).

People with CF who experience multiple respiratory exacerbations requiring treatment with IV antibiotics in a year are at increased risk of having a respiratory exacerbation in the future, as follows. A prospective study which followed 249 people (97% adults) with CF for 4.5 years

found that having a several (≥ 4) respiratory exacerbations requiring treatment with IV antibiotics in the previous two years increased the odds of future respiratory exacerbations (OR [95% CI] 3.16 [1.93 to 5.17) (104). Similarly, data from 13,579 children and adults in the US demonstrated that the risk of having a respiratory exacerbation requiring treatment with IV antibiotics increased with the number of respiratory exacerbations experienced in the previous year (i.e. in those with 1, 2, 3 or ≥ 4 exacerbations) (105).

Finally, one of the earliest epidemiological studies exploring survivorship models based on longitudinal data in 11,630 people with CF from the US demonstrated that a higher number of annual respiratory exacerbations predicted decreased 5-year survivorship (106). The results of this work, along with those presented earlier, highlight the impact that respiratory exacerbations have on FEV_1, the risk of future respiratory exacerbations and, ultimately, survival.

2.3.2.3 Health-related quality of life and mood

Measurements of HRQoL and feelings of anxiety and depression are often collected in CF research and are increasingly used in the clinical setting. Several different instruments have been used to measure HRQoL and mood in CF previously, with the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (107) and Hospital Anxiety and Depression Scale (HADS) (108) seen most commonly in the published literature to date.

In 2013, Bradley and colleagues investigated the impact of changes in respiratory exacerbation status (categorised as no, mild [no hospitalisation] or severe [hospitalisation] respiratory exacerbation) on HRQoL using the CFQ-R and EuroQol (EQ-5D) in people with CF age ≥ 16 years (109). Participants from five CF centres in the UK were asked to complete measures during two CF clinic attendances, between 8 and 12 weeks apart. Of the 94 participants, 60 (64%) had no respiratory exacerbations, 15 (16%) had a mild respiratory exacerbation, and 19 (20%) had a severe respiratory exacerbation. Worse HRQoL scores on the CFQ-R and EQ-5D were observed for participants with a mild exacerbation compared to those with no exacerbation, and worse again scores were seen for participants with a severe exacerbation when compared with those with a mild or no exacerbation (HRQoL data not available).

In a cross-sectional observational study of 162 children and adults with CF from the US published in 2002, those with a recent respiratory exacerbation (defined as within the previous 6 months) had reduced physical and psychosocial summary scores on the Child Health Questionnaire (CHQ) and Short Form 36 (SF-36) (scores were combined from both measures) (13). Specifically, physical summary scores were worse when compared to a baseline score of mean (SD) 50 (7) out of 100 for participants with no exacerbations, if one (42 [12]), two (40 [10]) or three or more (32 [11]) respiratory exacerbations were experienced (all $p < 0.01$). Psychosocial summary scores fell from a baseline of 53 (7) for those with no exacerbations if one (50 [12]), two (47 [11]) or three or more (42 [11]) exacerbations were experienced (all $p < 0.01$). A difference in score of ≥ 5 is considered clinically important for the combined CHQ and SF-36 scores (13).

Bradley and colleagues explored the relationship between respiratory exacerbations requiring treatment with IV antibiotics in hospital and HRQoL (as measured by the Chronic Respiratory Disease Questionnaire [CRDQ]) in Northern Ireland as early as 2001 (110). In an adult sample ($n = 18$), mean (95% CI) CRDQ scores (also measured at the commencement of treatment) had improved by 20 (12 to 28) out of 100 at the cessation of treatment. Of note, this study also found that the relationship between FEV_1 and HRQoL was weak (although the correlation coefficient was not reported). The improvement in HRQoL result following IV antibiotic treatment is also supported by US data from 2010, in which mean (95% CI) scores on the Respiratory Scale of the CFQ-R (also measured at the commencement of treatment) improved by 12 (6 to 17) out of 100 in 52 children and adolescents with CF (111). A change in score of four is considered clinically important on this scale of the CFQ-R (112).

The International Depression/Anxiety Epidemiological Study (TIDES) included 154 centres across nine countries. Data from the UK centres extracted from this study sought to quantify feelings of anxiety and depression in people with CF using the HADS (47). In total, 2,065 adolescents (age ≥ 12 years) and adults completed the HADS during CF clinics, including those who were currently experiencing a respiratory exacerbation, with data compared to a normative sample (1,788 healthy adults from the UK). In general, feelings of anxiety and depression in the

participants with CF were similar to those in the general population, however adults with CF had slightly greater feelings of anxiety and depression than adolescents with CF. This was observed for both males (mean [SD] anxiety 5.7 [3.9] vs. 4.9 [3.2], $p < 0.01$, depression 3.4 [3.3] vs. 1.9 [2.0], $p < 0.01$) and females (anxiety 6.6 [4.3] vs. 5.7 [3.8], $p = 0.01$, depression 3.4 [3.4] vs. 2.4 [2.0], $p < 0.01$). Clinically, the combined mean anxiety and depression scores for adult males (9.1) and females (10.0) fell within the 'mild' range (8 to10) on the HADS. The combined scores for adolescent females (8.1) were just within the 'mild' range, while adolescent males (6.8) were in the normal range. In this study, for all adults, older age, unemployment for health reasons and poor lung function were associated with greater feelings of anxiety and depression.

While 130 (6%) of the TIDES sample were on IV antibiotics at the time the survey was administered, a regression analysis demonstrated that current IV antibiotic use was not associated with greater feelings of anxiety or depression (47). It was however, beyond the scope of that study to determine whether feelings of anxiety and depression had worsened from baseline in these participants specifically. Of note, the presence of recent haemoptysis, which is one of the widely accepted criteria used to define a respiratory exacerbation, was associated with greater feelings of anxiety and depression in women.

The findings of these studies, demonstrating the impact of respiratory exacerbations on HRQoL, confirms the importance of using the number or rate of respiratory exacerbations as an outcome in trials investigating interventions that aim to detect and/or prevent the occurrence of respiratory exacerbations. Telehealth studies with this aim will be discussed in detail in Section 2.4.2.2.

2.3.2.4 Other impacts (on physical activity, body mass index and complications of intravenous antibiotic use)

Other notable impacts of respiratory exacerbations are reduced physical activity (15), loss of weight and bone density (113, 114), and increased resistance to antibiotics through their repeated use (33).

In Australian adults with CF admitted to hospital with a respiratory exacerbation (n = 24), Ward and colleagues demonstrated that less time was spent in daily physical activity over a 24 hour measurement period in hospital compared to one month post discharge (mean [SD] time ≥ 3 metabolic equivalent of task [METs] 95 [58] min/day vs. 209 [111] min/day) (15). As the exacerbation component of this study took place during an inpatient stay, the necessity of spending large amounts of time within the hospital room (to meet clinician review/treatment requirements) may have contributed to the decreased participation in physical activity.

Two studies have further explored the relationship between physical activity and respiratory exacerbations. In 2015, Savi and colleagues measured physical activity in 60 adults with CF from Italy and the UK with a SenseWear Pro3 Armband (115). Data were averaged over 5 days and reported with the participants grouped according to how many respiratory exacerbations they had experienced in the year preceding the study. The group of adults who had > 2 exacerbations in the previous year spent less time in daily physical activity (> 3 METs) than their counterparts with fewer exacerbations; however, this group had a lower FEV_1 at baseline and the association between respiratory exacerbations and physical activity was no longer present when other baseline variables were controlled for in the analysis. Cox and colleagues examined whether levels of daily moderate-vigorous physical activity (MVPA) was a predictor of respiratory exacerbations requiring hospitalisation, and magnitude of change in lung function, over a prospective 3-year period in 53 adults with CF (116). Following a regression analysis, they found no association between levels of physical activity and respiratory exacerbations requiring hospitalisation. This was despite the study demonstrating that 30 mins of MVPA in bouts of at least 10 mins throughout the day was a predictor of slower magnitude of decline in FEV_1 over the 3-year period.

Data collected on 85 Italian adults with CF who underwent bone densitometry demonstrated that males with > two respiratory exacerbations in the 12 months prior to the scan had lower whole-body fat free mass (FFM) (divided by height squared and reported as FFM indices) when compared to those with fewer exacerbations (mean [SD] 18.0 [1.9] kg/m^2 vs. 19.3 [1.4] kg/m^2, p = 0.02) (113). Further, the same male participants also had lower total bone mineral density

measures as a Z-score (-1.4 [1.2] vs. -0.67 [0.9], p = 0.03). These results were not replicated in the female participants. Possible reasons for this include that the total sample of females was relatively small (n = 85) and that, on average, females (n = 41) had a poorer nutritional status compared to males at baseline when measured as BMI (mean [SD] 20 [3] kg/m^2 vs. 22 [2] kg/m^2) and a greater proportion were underweight as defined by a BMI < $18.5kg/m^2$ (number [%] 10 [24%] vs. 2 [5%]).

As previously discussed (Section 2.1.2), low BMI is a predictor of future FEV_1 decline (53). This relationship is likely to be due, at least in part, to the effect acute respiratory exacerbations have on both outcomes. During respiratory exacerbations, the higher metabolic demand (117) is often accompanied by a temporary loss of appetite (118). The temporal relationship between respiratory exacerbations and BMI is however somewhat unclear; that is, is lower BMI influenced by frequent respiratory exacerbations, or are frequent respiratory exacerbations influenced by lower BMI? The association is likely complex and synergistic.

While there are several potential risks associated with the regular use of oral, inhaled and IV antibiotics (including but not limited to allergy, bronchospasm, kidney and liver failure, IV access related complications), concerns regarding antibiotic resistance are prominent (33). The main reasons for increased antibiotic resistance are thought to be prolonged use as well as inappropriate choices of antibiotics by clinicians (33).

In CF, respiratory exacerbations clearly have a substantial negative impact on the person with CF and the healthcare system, adversely impacting on clinical trajectory, HRQoL and other outcomes. It is therefore essential to focus strategies on the early and accurate identification, and effective treatment of respiratory exacerbations.

2.3.3 Identification and treatment of respiratory exacerbations

The controversy surrounding the agreed definition of a respiratory exacerbation (discussed in Section 2.3.1) only increases the difficulty faced by clinicians regarding identifying and treating such exacerbations. Traditional CF care involves the identification of changes in respiratory symptoms during routine outpatient clinics (recommended at least 4 times per year), where

spirometry and assessment by the multidisciplinary CF team is completed (4). It is also not uncommon for people with CF, or their families or carers, to contact the CF team sooner than their next clinic appointment if they feel that they have worsening respiratory symptoms. It is considered important to identify and treat respiratory exacerbations promptly once worsening symptoms appear, with data supporting that delayed identification of respiratory exacerbations and initiation of treatment has been associated with failure of FEV_1 to return to pre-exacerbation levels (19). Although, these data were not collected prospectively, and further investigation of the relationship between symptom onset, presentation to a CF clinic and health outcomes is warranted.

The delayed identification of a respiratory exacerbation in people with CF is often due to delayed presentation to a CF clinic. The reasons for this delay are multifactorial, and include competing life commitments such as work, study and family. There are also barriers to attending a CF clinic, such as travel and financial burden, a lack of education and understanding around the need to report respiratory symptoms sooner, and feelings of anxiety and depression associated with attendance (20).

As discussed in Section 2.2.3, people with CF are expected to complete a daily treatment regimen designed to reduce airway obstruction via ACT and inhaled mucolytic therapy, maintain/increase physical activity and exercise capacity, optimise nutritional status, and prevent respiratory exacerbations with maintenance oral and inhaled antibiotics and vaccinations (33, 75, 76). The treatment of a respiratory exacerbation often involves increasing the frequency or time of some of these daily treatments, and commencing additional oral, inhaled or IV antibiotics, with or without hospitalisation. Complications associated with respiratory exacerbations (haemoptysis, pneumothorax, sinusitis, fungal disease, and distal intestinal obstructive syndrome) may also need concurrent treatment and/or result in modifications to the treatment plan (33, 75, 76, 119).

Similar to their definition, the optimal provision of treatment for respiratory exacerbations is not universally agreed (87, 93, 120-122). This is likely to be due to several factors. First, the

decision regarding whether to treat a respiratory exacerbation and what treatment to provide can vary between clinicians (84, 86). Second, people with CF may choose to delay or not accept particular treatments based on their current lifestyle, treatment burden and beliefs about treatments. Third, it is widely felt that in vitro antibiotic susceptibility testing of bacteria does not accurately represent the observed clinical response (123), and therefore best practice guidelines for the use of antibiotic therapy, based on observed clinical responses, are instead followed (75). Finally, the optimal duration of antibiotic treatment, in particular for IV administration, is not evidence based and therefore remains clinician and CF centre dependent (generally given for 10 to 14 days) (121, 122, 124, 125). The use of two IV antibiotics that work synergistically has been demonstrated to provide better outcomes than one antibiotic alone (75), however the best combination of IV antibiotics is still unclear (126).

Mild respiratory exacerbations are generally managed in the outpatient setting with oral and inhaled antibiotics (92, 127, 128). The addition or change of mucolytic therapy and ACTs may also be appropriate (92). If the exacerbation is deemed more severe, if the person is considered high risk (e.g. low baseline FEV_1, severe complication such as haemoptysis or pneumothorax), or if response to oral and inhaled antibiotic therapy has been suboptimal, treatment with IV antibiotics with or without hospitalisation will be considered. The cessation of treatment for a respiratory exacerbation is guided by an improvement in FEV_1 to or near baseline levels, and improvement in symptoms (75, 121, 122, 125). These goals may differ depending on the clinical scenario, and may also be guided by the preference or lifestyle factors of the person with CF.

Identifying respiratory exacerbations in people with CF is challenging due a number of factors which have been described in this chapter. This includes the controversy around defining an exacerbation, and the reliance on traditional methods of care for detecting changes in symptoms. Given the relatively younger demographic of adults with CF, it makes sense to consider the use of newer technologies such as smartphone applications to assist in the identification of respiratory exacerbations. This may facilitate the provision of necessary treatment sooner, potentially leading to improved longer-term health outcomes.

2.4 Telehealth

This part contains two sections. Specifically, i) the definition of telehealth; and, ii) the use of telehealth in CF, including for outpatient care, for home monitoring, to improve adherence to treatment, and to promote exercise, exercise testing, and physical activity.

2.4.1 Definition

There are well over 100 peer reviewed definitions of the term that is defined in this thesis as 'telehealth' (129), with telemedicine and eHealth also being commonly used. The World Health Organisation (WHO) supports the use of the terms telehealth and telemedicine interchangeably, and has adopted the broad description of telehealth as "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities" (130).

The WHO also goes on to define the key elements of telehealth as those which: i) provide clinical support; ii) overcome geographical barriers to connect users in different locations; iii) utilise various types of information and communication technologies; and aim to improve health outcomes (130). Specific types of modern technology that are already available for use in the delivery of telehealth include videoconferencing, text messaging and other forms of digital messaging and apps.

In countries with similar areas of low population density to Australia, such as the US and Canada, telehealth has been utilised for some time in an attempt to improve access to healthcare and patient outcomes by overcoming geographical barriers, and reducing the burden on the healthcare system in people with chronic respiratory diseases such as asthma (131, 132) and COPD (133-137). The use of telehealth is also increasing in chronic conditions such as heart failure and diabetes, with the aim of improving patient self-management and to deliver forms of home monitoring and rehabilitation (138-141).

With the increasing utilisation of newer information and communication technologies throughout society, it seems inevitable that many of these innovations will be integrated within the healthcare setting in the future. It is important however, that this is approached with some caution to ensure that a sufficient evidence base is established supporting the role of telehealth in improving access to care and health outcomes. Consideration also needs to be given to data protection and the privacy of participants when using telehealth technologies, and the need for access and connectivity to the relevant systems. These potential barriers need to be overcome to ensure the integration of modern technology with traditional care is a success.

2.4.2 Telehealth in CF

The demographic profile of adults with CF makes them an obvious case for the use of newer technologies in the provision of healthcare. While earlier work has corroborated that telehealth technology is, in general, acceptable to people with CF, consistent improvements in health outcomes have yet to be demonstrated, likely due to the variability in study designs and outcomes used (142). To date, health outcomes most commonly used to evaluate telehealth in CF pertain to respiratory exacerbations and the number of hospitalisations, magnitude of decline of FEV_1, HRQoL, feelings of anxiety and depression, and disease-related burden.

The use of telehealth in different aspects of CF care will be discussed in themes of outpatient care, home monitoring, adherence to recommended treatment, and the promotion of exercise, exercise testing and physical activity.

2.4.2.1 Improving access to outpatient care

The first work in CF to explore the use of videoconferencing for supportive care was conducted by Wilkinson and colleagues in the UK (26). The participants in this study were age > 16 years and listed for lung transplantation. A 6-month prospective pilot RCT was undertaken examining the use of videoconferencing to provide weekly physiotherapy support in between monthly routine face to face outpatient clinics. The impact on HRQoL, feelings of anxiety and depression, HCU, carer burden and satisfaction was measured. Sixteen participants (median [range] age 27 [21 to 41] years) were enrolled, of whom only seven completed the study with

the high attrition explained by death (n = 4) and lung transplantation (n = 3). The intervention group was provided with internet access and videoconferencing equipment, as well as a spirometer, oximeter and thermometer. These participants undertook weekly sessions with a physiotherapist (discussing aspects of care and reviewing the available clinical outcomes), with other members of the CF team available if necessary.

While no between-group differences were seen in feelings of anxiety and depression and HCU, both groups had increased feelings of anxiety and depression when compared to baseline (26). This finding may due to the fact that the participants were 6 months further into the time they had been listed for lung transplantation and potentially closer to death at the time of the follow-up assessments, rather than an effect from the interventions provided as part of the study. Satisfaction with the videoconferencing was high; with 100% of participants in the intervention group feeling that it was a 'good service' and expressing a desire for it to be continued. Participants in the intervention group also preferred videoconferencing to telephone calls or extra face to face follow-up. Despite the study being small with high levels of attrition (56%), it showed that videoconferencing could be used with high levels of satisfaction amongst participants, and was preferred over other modes of contact. This provides encouragement for the multidisciplinary CF team to explore the use of videoconferencing in the provision of care to people with CF, particularly those with high travel and time burden and living in rural and remote areas.

One other small, short-term study conducted in Israel explored the use of message and videoconferencing communication to provide additional multidisciplinary input in the outpatient setting over a 3-month period, on this occasion using WhatsApp and Skype (143). Eighteen children and adults with CF were allocated to intervention (n = 9, mean [SD] age 21 [6] years) or control (n = 9, age 25 [11] years) groups, with the intervention group receiving motivational and treatment related messages and videoconferencing calls from the multidisciplinary CF team. Despite the intervention group receiving a median (range) of 5 (4 to 6) Skype videoconferencing calls and between 22 and 45 WhatsApp messages per participant throughout the 3-month

period, no clear effect was demonstrated on HRQoL, adherence and satisfaction. This study was however unlikely to be powered to detect changes in these outcomes.

Of note, three (17%) of the participants in this study who had been assigned to the intervention group during randomisation changed to the control group as they did not want to, or were unable to, undertake the intervention due to busy schedules (n = 2) and lack of internet connection (n = 1) (143). The authors also described difficulties experienced with the scheduling of videoconferencing calls as the participants were required to be in their own home, and two or three attempts were often required to successfully undertake each session. Poor internet connection was also experienced at times for those participants living in remote areas. These issues highlight some of the concerns with the integration of new technology and subsequent services into clinical practice; in this instance incompatibility with the person's lifestyle/schedule as they were required to be home, and the need for users to have sufficient connectivity to participate. Future telehealth technologies should consider utilising mobile technologies that provide the user with the option of being in a location that preferentially suits their lifestyle.

2.4.2.2 Facilitating home monitoring

Home monitoring consists of the person with CF performing clinical assessments in their own home, potentially facilitating the earlier detection of respiratory exacerbations by the CF team. As early as 2005, the feasibility of home monitoring solutions for use in people with CF were being investigated, such as the performance of home spirometry by the participant and the recording of respiratory symptoms using an online portal (144).

In 2009, Bella and colleagues published data relating to the implementation of a home monitoring programme for the detection of respiratory exacerbations involving the use of the OXYTEL M32 system (Vivisol, Monza, Italy), which has the ability to record spirometry, percutaneous oxygen saturation (SpO_2) and pulse rate (21). This was a non-randomised, matched control study conducted over a 4-year period. The control participants were recruited each time a participant was allocated to the intervention group and received usual care, and were

matched for age, sex, FEV_1, bacterial colonisation, oxygen dependency and other co-morbidities. Participants in the intervention group were asked to provide twice weekly data on continuous overnight SpO_2 and pulse rate, and morning spirometry. If changes in clinical status were observed by the CF medical team, the participant was contacted for assessment of the need for antibiotic treatment. Only 17 (57%) (mean [SD] age 16 [6] years, $ppFEV_1$ 68 [22] %) of the 30 participants recruited to the intervention group had > 6 months of transmitted data and included in the analysis. The length of follow-up for the intervention and matched controls were 29 [13] and 30 [20] months, respectively.

Adherence to the intervention was suboptimal, being measured as 'average compliance' to overnight oximetry, which was 52.4% (21). This, alongside the 43% attrition from the intervention group (compared to 7% in control), is likely explained by the requirement for twice weekly reporting over a relatively long study duration (mean 29 months). The intervention group had higher rates (per 100 person months) of CF clinic attendance (incidence rate ratio [95% CI] 1.25 [1.03 to 1.52]) and treatment cycles (treatment completed at home) (1.46 [1.09 to 1.96]) when compared to the control group, however there was no clear effect on hospitalisation rates and FEV_1. This draws attention to the cost-benefit of telehealth interventions; in this case overall HCU increased in the intervention group (via the telehealth intervention and CF clinic attendance) yet no improvements in number of hospitalisations or FEV_1 were observed. A cost analysis relating to HCU was explored by this group in a subsequent publication, discussed later in this section.

Grzincich and colleagues went on to conduct a multicentre pilot RCT, examining the feasibility of, and participant satisfaction with, home monitoring over a 4-week period (145). Sixty adults with CF (mean [range] age 29 [19 to 44] years) from four Italian CF centres were enrolled in the study. A total of 30 were allocated to the intervention group which consisted of using a digital recording device to record measurements of spirometry, SpO_2 and respiratory symptoms. The frequency of measurement was adjusted according to disease severity; participants with mild disease ($ppFEV_1$ > 77%, n = 22) were asked to complete only spirometry every day for the first week and then twice per week for the remaining weeks. Participants with moderate disease (n =

32) were asked to complete the same spirometry regimen with the addition of measuring daytime SpO_2 bi-daily every day, and overnight once per week during the first week, reducing to bi-daily twice per week and overnight once per week for the remaining weeks. Those with severe disease (n = 6), completed the same regimen as the moderate group except with overnight SpO_2 twice per week instead of once. The control group received usual care, consisting of attending regular CF clinics including assessment of spirometry and oximetry.

Fifteen (50%) of the participants allocated to the intervention group did not complete the study due to protocol 'failures' (145). A failure was defined as either refusing to continue monitoring, completing < four spirometry measurements in the first week, not sending acceptable SpO_2 data in the first week, or sending no acceptable data in any of the second to fourth weeks. The most common participant feedback regarding how to improve the system included reducing the frequency of data transfer (n = 7, 23%) and improving certain aspects of the equipment (n = 8, 27%). Despite the high rate of attrition, 80% of participants in the intervention group expressed a desire to continue using the system in some form in future. Given the high rate of attrition, future studies would need to consider minimising the monitoring burden to improve adherence, by reducing the frequency of reporting and/or utilising more mobile technologies to gather data.

Bella and colleagues continued to explore the role of telehealth in CF, publishing data in the subsequent years relating to their ongoing telehealth program, including FEV_1 outcomes and basic cost analysis relating to HCU. They reported data on the change in FEV_1 over time between participants utilising telehealth (twice weekly spirometry and overnight oximetry) over a 4.5 year period (n = 16) and a group of controls (n = 16) (matched for age, sex, FEV_1, bacterial colonisation, oxygen dependency and other co-morbidities) (24). Over the study period, they found a mean (SD) improvement in relative FEV_1 in the telehealth group of 4.0 (13.0)% compared with a reduction in the control group of -14.3 (14.8)% ($p < 0.01$). On face value these results are impressive, however the sample size was small, and the use of retrospectively matched controls potentially introduced selection bias. Further, a t-test was used rather than a regression analysis, which may be less accurate as baseline covariates could not be

included in the model. In this study, the yearly average adherence to twice weekly reporting ranged from 23% to 42% throughout the 4.5 year study period.

The authors also examined the cost benefit of telehealth over a retrospective 2-year period in 19 participants using the same telehealth system (146). While they reported a total cost saving of €132,144,91, or €3,303.62 per participant, these figures were based on the presumed prevented HCU as a result of the early detection of respiratory exacerbations (i.e. estimating the resultant HCU should the exacerbation not have been detected). These results need to be interpreted with caution, as this method is far less rigorous than obtaining cost benefit data using a prospective, RCT research design.

Similar to the work undertaken in Italy, Sarfaraz and colleagues examined the feasibility of once daily spirometry and symptom reporting for the detection of respiratory exacerbations in 51 children and adults with CF age ≥ 12 years, at two centres in the UK (25). All participants were asked to perform spirometry and grade their respiratory symptoms (i.e. cough, sputum, breathlessness, fatigue) from 1 to 4 depending on severity, every evening on a personal digital assistant for the 6-month study period. Using a somewhat pragmatic approach for defining a respiratory exacerbation (i.e. three consecutive days of a 1-point increase in 3 symptoms and/or a decline in FEV_1 > 10%), the CF team would contact the participant by phone if their reported data met these criteria, and invite them to attend a CF clinic for further assessment. If a participant failed to report data for two consecutive days, they were contacted by the CF team to remind them to continue. Respiratory exacerbation data were compared with the same participants' data from the same 6-month period (in regard to months of the year) in the year preceding the study, as well as the 6 months directly following the study.

This study experienced high attrition (n = 32 [63%]); 14 participants (27%) withdrew (lack of data in run-in period = 8 [16%], respiratory exacerbation during run-in period on two attempts = 3 [6%], lung transplantation = 1 [2%], liver transplantation = 1, relocated = 1) and 18 (35%) did not record sufficient data to be deemed eligible (defined as > 50% completion) for inclusion in the analyses (25). Nineteen participants (mean [standard error] age 26 [1] years) completed the

study, with 53 respiratory exacerbations (mean [range] 3 [0 to 7] per participant) detected, of which 27 (51%) were treated with oral antibiotics and 26 (49%) were treated with IV antibiotics. The only clear difference in prescription of antibiotics in either of the comparison periods was for oral antibiotics, where fewer oral antibiotics were administered in the 6 months following the study (14 total courses vs. 27 total courses in the study period, $p = 0.02$). Further examination of the raw data reveals that the prescription of 27 courses of oral antibiotics in the study period was also higher than that observed in the 6-month period in the previous year (total courses = 19). Therefore, this result likely reflects an increased rate of detection of respiratory exacerbations and subsequent provision of oral antibiotics as a result of the intervention.

While the authors stated that the poor adherence to the intervention was contrary to their expectations, this does not seem completely surprising given the daily reporting burden experienced by the participants (25). Similar to other work discussed earlier in this section, participants were also required to be at home to use the telehealth system, and therefore it did not appear compatible with their lifestyle/schedule. While not reported by the authors, it may have been beneficial to compare the adherence with reporting for the 19 participants who completed the study in the first and last 3 months of the study period, to ascertain potential reporting fatigue as the intervention progressed.

The most recent and methodologically robust study aiming to improve the detection of respiratory exacerbations through home monitoring was the Early Intervention in Cystic Fibrosis Exacerbation (eICE) study conducted by Lechtzin and colleagues in the US (96). This multicentre RCT in 267 adolescents (age ≥ 14) and adults with CF (mean [SD] age 27 [12] years) examined the impact of home spirometry and symptom reporting via the CFRSD using a Viasys AM2 device (CareFusion, Yorba Linda, California, US) on outcomes measured over 12 months. Outcomes included change in FEV_1, time to and rates of respiratory exacerbation, other measures of HCU, HRQoL, change in respiratory symptoms, and adherence to the study protocol. The intervention group were asked to complete the home monitoring twice weekly, with the system alerting the CF team if a respiratory exacerbation was detected, defined as either a relative decrease in FEV_1 by > 10% or worsened CFRSD symptoms from baseline in

two or more categories. The control group were able to contact the CF clinic triage telephone line at any time to report acute changes in clinical status, and both groups were asked to attend 3-monthly CF clinics (total of 5 clinics, including at baseline, in the 12-month study period).

In this study, there was no clear effect of the intervention on the magnitude of decline of FEV_1 over the 12-month study period (mean difference [95% CI] 0.0 [– 0.1 to 0.1]L) (96). The intervention facilitated the detection of respiratory exacerbations sooner when compared to control (HR [95 % CI] 1.45 [1.1 to 1.9]). Participants in the intervention group also had a higher number of acute CF clinic attendances (153 vs. 64, defined as resulting from home monitoring or calls to the triage line) and a higher proportion of oral antibiotics were prescribed at acute CF clinic attendances for protocol defined respiratory exacerbations (72/108 [67%] vs. 19/44 [43%], p = 0.01.). To reduce the confounding effect of the increased contact with the CF team via the home monitoring system, the authors chose to measure the proportion of events for each HCU outcome during acute CF clinics, and only when the protocol defined exacerbation criteria were met. The increased prescription of oral antibiotics in the intervention group may have reduced the need for IV antibiotics and hospitalisation, as the proportions of participants in the intervention group requiring these were fewer than that seen in the control group (IV antibiotics, 35 [32%] vs. 23 [52%], p = 0.03; hospitalisation, 31 [29%] vs. 22 [50%], p = 0.01).

Although this study demonstrated that home monitoring resulted in the earlier detection of respiratory exacerbations and increased provision of oral antibiotic treatment amongst participants in the intervention group, this did not translate to a reduced magnitude of decline of FEV_1 (96). Participants in the intervention group did report less symptoms (measured by the CFRSD) over the study period (mean difference [95% CI] -4.1 [-7.8 to -0.5], p = 0.03) compared to those in the control group, which in this instance may have been due to receiving an increased number of courses of oral antibiotics. Consistent with earlier work, the level of attrition in this study was greater in the intervention group when compared to the control group (n = 33 [24%] vs. n = 21 [16%]). Of these, 20 (15%) participants in the intervention group withdrew due to ‘participant decision’, as opposed to 11 (8%) in the control group. This is not surprising given the high reporting burden associated with twice weekly spirometry and

symptom reporting which needed to be completed at home. Participants in the intervention group corroborated this with higher scores on self-reported protocol burden measured on a scale of 0 to 10 compared to the control group (mean 2.9 vs. 0.6, $p < 0.001$). Strengthening the argument that the reporting burden was too great, adherence to the home monitoring protocol was low, with 19% of participants reporting data twice weekly ≥ 80% of the time, and 50% reporting data once weekly ≥ 80% of the time (96).

Thus, previous research investigating home monitoring interventions aimed at detecting respiratory exacerbations more rapidly and facilitating the earlier provision of treatment share a common theme of high reporting burden when using devices that are not mobile (i.e. desktop computers or large, bulky medical devices). This subsequently required the participants to be present at home in order to complete the reporting, which is not conducive to the active and busy lifestyles lived by many adults with CF. On occasion, monitoring was also required continuously overnight (e.g. with oximetry) or required a large amount of physical effort (e.g. spirometry). Therefore, the low level of adherence to the interventions described reflects the inability of the reporting system to be integrated into the user's lifestyle/schedule, and this should be the focus of future interventions in this area. It would be advisable for home monitoring studies to incorporate small, mobile technology already owned by the participants. Smartphones are an example of a technology that meets this description with the capabilities of reporting medical information to the CF team.

2.4.2.3 Promotion of exercise, exercise testing, and physical activity

The role of telehealth in improving engagement with physical activity and exercise amongst people with CF has been explored in a small number of studies. In 2013, Cox and colleagues published data examining the feasibility of assessing exercise capacity (using the 3-minute step test [3MST]) via telehealth in the form of videoconferencing (27). Ten adults with CF (mean [SD] age 32 [7] years) completed the 3MST twice within a 24-hour period, once via telehealth and once in-person with a clinician. Both sessions were conducted in a controlled environment at the hospital (i.e. telehealth was conducted with the participant and clinician in separate rooms). There were no differences in physiological responses (pulse rate and SpO_2) between the

two tests, and participant satisfaction was high with similar ratings on a 5-point Likert scale for 'ease of clinician interaction' (mean [SD] 4.8 [0.4] vs. 5.0 [0.0]), p = 0.34) and 'participant comfort' (4.7 [0.9] vs. 4.8 [0.4], p = 0.68) observed with telehealth and in-person, respectively. Only one (10%) participant preferred in-person supervision of the assessment (as opposed to 'no preference') and the mean (95% CI) usability of the telehealth system, using the System Usability Scale (SUS), was rated high at 86 (80 to 91)%. The only negative observation relating to the use of the videoconferencing was the 'ease of hearing the metronome', which was reduced during the telehealth assessment compared to the in-person session (3.3 [0.4] vs. 4.8 [0.1], p < 0.01). This study, the first to use telehealth for the assessment of exercise capacity in this population, provided encouragement to researchers and clinicians in regard to repeating this model of assessment with participants' in their own homes.

Two studies have since evaluated the feasibility of using telehealth to promote exercise in people with CF within their own home. Chen and colleagues in the US implemented a 6-week program for 10 children with CF consisting of three 30-min interactive group sessions per week of aerobic, resistance, and flexibility exercises (148). A telehealth platform was used to provide videoconferencing and monitoring of heart rate via a Polar monitor, and sessions were supervised by a clinician. The participants completed 85% of the sessions and usability measured via the SUS was high at 91%. In nine adults (mean [SD] age 31 [9] years), Tomlinson and colleagues investigated the feasibility of offering an 8-week supervised, personalised exercise training intervention conducted via videoconferencing (Skype) for adults with CF (28). Participants completed 68% of the sessions, with two participants (22%) withdrawing due to time pressures. Satisfaction with telehealth was high (90%), despite technical issues (video or audio delay) being reported during 25% of the videoconferencing calls. These two studies, alongside the work undertaken by Cox and colleagues, demonstrate high usability and satisfaction with the use of telehealth in the assessment and performance of exercise, as well as highlighting the need for technology that provides a certain level of video and audio quality within the system.

Finally, Cox and colleagues designed an internet-based program for monitoring and promoting physical activity participation for adults with CF and examined its feasibility and acceptability amongst users (29). Ten adults (mean [SD] age 30 [8]) years used the program (ActivOnline) for an 8-week period, with fortnightly phone support from a physiotherapist designed to facilitate goal setting and improve motivation. There was a good level of feasibility reported, with participants logging in mean [SD] 13 (11) times during the study period and recording a mean (range) of 35 (15 to 57) sessions of physical activity (approximately 4 per week per participant). Acceptability was high, with a median (IQR) SUS score of 89 (84 to 95). When measured on a 5-point Likert scale, 'perceived benefit' (median [IQR] 4.0 [3.0 to 4.8]) and 'desire to use the program' (3.5 [3.0 to 4.8]) were also good. This intervention was well designed to target the demographic features of the participants, and the authors acknowledged that a more mobile-friendly version of the program (i.e. an app) may improve acceptability further.

2.4.2.4 Promotion of adherence to recommended treatment

A 6-week, multicentre study conducted in the UK investigated the acceptability of an adaptive aerosol delivery (AAD) nebuliser device used to monitor adherence and facilitate the re-ordering of nebulised medications from the pharmacy (148). The AAD device contained a 'disc' which stored information regarding the required medication dose, details of the completed treatment sessions (medication, date, time, duration, delivered dose), medication expiry date and the number of doses remaining, allowing for the timely dispensing of more medication. Nineteen participants (6 children, 13 adults) with CF completed the study, with 1,180 (80%) of 1,473 expected treatment sessions completed in full. Regarding the telehealth aspect of the study (i.e. remote ordering of more medication from the pharmacy and delivery to home), participants were divided on its benefit, with 44% viewing it as 'great', and 44% viewing it as 'inconvenient', most likely explained by the requirement to be at home at specific times in order to receive the medication at the time of scheduled delivery.

One further study investigated the use of text messaging to improve adherence to nebulised medication in 17 children and adolescents with CF (mean [range] age 12 [5 to 16] years) (149).

The authors developed an automated system that sent text message reminders up to twice daily to the participant and/or their parent(s)/carer for a period of 6 months. Adherence to the nebulised medications, measured with an AAD nebuliser device as in the previous study, was compared between the 6-month study period and the 6-month period preceding the study. Mean (SD) adherence during the study period was 80 (29) %, which was similar to the preceding 6-month period (81 [25] %). The lack of improvement in adherence was possibly due to the already high level of adherence amongst the participants in the preceding 6-month period (i.e. a ceiling effect), and this intervention may have more impact in a group with lower levels of baseline nebuliser medication adherence.

2.5 Conclusion

Cystic fibrosis is a common genetic, multi-system disease affecting the Caucasian population, with an incidence of 1 in 3,000 live births in Australia (31). Advancements in treatment options and models of care have seen the median life expectancy increase in recent decades to 44 years in Australia (31), with respiratory failure secondary to bronchiectasis remaining the most common cause of death (45). The estimated cost of providing care for a person with CF is variable, and it is now expected to increase dramatically with new CFTR modular therapies that cost approximately $270,000 AUD per person annually (42).

It is recommended that people with CF have their care managed in centralised CF centres, by an experienced multidisciplinary team (3, 4), due to known improvements in health outcomes such as FEV_1 and nutritional status (5, 6). This creates barriers to care in itself, given that many people with CF live large distances away from a CF centre, especially in areas of low population density such as in WA. Further, people with CF have competing lifestyle commitments and experience high treatment burden (71), limiting the time available for engagement with the CF team. Strategies aimed at reducing the barriers to accessing care are required.

With the challenges faced regarding access to care for people CF, the diagnosis of respiratory exacerbations becomes even more challenging. What constitutes a respiratory exacerbation in CF is a contentious issue, and there is no universally accepted definition (82, 83, 86, 87, 94, 95). A pragmatic approach is often taken within clinical practice and research. Similarly, the treatment provided for respiratory exacerbations (with oral, inhaled and IV antibiotics) varies between physicians and CF centres (84, 86), due to the lack of evidence supporting a specific treatment approach. Regardless, respiratory exacerbations increase HCU (41, 91) and have a profound and detrimental long-lasting impact on FEV_1 (17, 19, 54, 89), HRQoL (13, 109), physical activity (15), nutritional status (113) and ultimately survival (17).

The delayed identification of respiratory exacerbations and initiation of treatment has been associated with failure of FEV_1 to return to pre-exacerbation levels (19). Delayed identification

is often due to delayed presentation to a CF clinic by a person when their respiratory symptoms have worsened; with the reasons for this delay being multifactorial (20). Traditionally, people with CF are required to attend routine (at least 3-monthly) CF clinics to be assessed by the CF team (4), or they can contact the centre sooner if required, usually by phone. Given the busy lifestyle of people with CF, and the high treatment burden experienced, solutions are required to facilitate the faster identification of respiratory exacerbations and provision of antibiotic treatment.

The impact of telehealth technology in CF has been evaluated in interventions aimed at providing CF clinics (26, 143), identifying respiratory exacerbations via home monitoring (21, 24, 25, 96, 144, 150), improving adherence (148, 149), and promoting exercise, exercise testing and physical activity (27-29). Although adults with CF are likely to be comfortable with the use of mobile technologies, the effectiveness of telehealth at detecting respiratory exacerbations has previously been compromised by suboptimal adherence (i.e. 10 to 67%) (21, 22, 24, 25, 96). This is likely due to the high reporting burden experienced by participants, such as daily reporting of symptoms and/or regular spirometry. Minimising this burden in order to optimise adherence is an important consideration when designing telehealth technology.

This programme of research aimed to overcome some of these shortcomings by investigating the impact of the integration of modern technology with traditional CF care on health outcomes. First, videoconferencing for the provision of CF clinics was implemented for adults with CF living in rural and remote WA. Second, an app was developed for use by adults with CF to facilitate the early identification of symptoms suggestive of a respiratory exacerbation and allow the CF team to initiate treatment sooner.

CHAPTER 3

STUDY 1

This chapter details the methodology, results and discussion for Study 1 (described in Section 1.1) of this programme of research. Specifically, Study 1 investigated whether there was a difference in the magnitude of decline of forced expiratory volume in 1 second (FEV_1) between adults with cystic fibrosis (CF) living in the Perth metropolitan area and those living in rural and remote Western Australia (WA), over a 3-year period.

3.1 Study design

This study was an audit conducted retrospectively that investigated whether adults with CF living in metropolitan Perth, and those in rural and remote WA, have a different magnitude of decline in spirometry. While unique ethical approval was not sought for this study, all participants had previously consented to these data being used for research purposes via the Australia CF Data Registry. Approval was obtained from the Australia CF Data Registry prior to the extraction of data.

3.1.1 Participants

Adults with CF aged 18 years or more were included if they had i) attended the Sir Charles Gairdner Hospital (SCGH) CF Centre (both metropolitan and rural and remote) for the entire period from January 2010 to December 2012; and ii) had performed spirometry on at least two occasions during this time period (as this was the minimum required to conduct a regression analysis). A 3-year period was chosen to ensure the majority of participants attending the CF centre had two or more data points. There were no exclusion criteria.

3.1.2 Procedure and study measurements

All measures of spirometry (FEV_1, percentage predicted FEV_1 [$ppFEV_1$], forced vital capacity [FVC] and percentage predicted FVC [ppFVC]) for adults with CF attending the SCGH CF Centre were extracted retrospectively if they were originally collected between January 2010 and December 2012 inclusive. Spirometry was obtained at outpatient CF clinics, attended by each participant according to clinical need. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted $ppFEV_1$ and ppFVC. Data were extracted from the Australian CF Data Registry and verified with the participant's medical record and Medgraphics Breeze software program (MGC Diagnostics, Saint Paul, MN USA). In addition to spirometry, data were extracted on demographic information including age, sex, body mass index (BMI), pregnancy, *Pseudomonas aeruginosa* colonisation and CF-related diabetes (CFRD). All data points between these dates were extracted on 06/02/2014. The principal investigator collated all data pertaining to the measurements collected as part of this study.

Spirometry had been performed according to American Thoracic Society guidelines for repeatability and acceptability (152), and pre- and post-bronchodilator results were used where available. Health professionals who performed spirometry had previously received training from a certified respiratory technician, and the spirometer was calibrated at the commencement of each CF clinic. All spirometry was reviewed by respiratory scientist following completion. The magnitude of decline in spirometry over these 3 years was compared between adults with CF living in metropolitan Perth vs. those living in rural and remote WA (defined as living greater than 100km from the geographical centre of Perth).

3.1.3 Analyses

Statistical analyses were conducted by a statistician using Stata® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas, USA). Data are expressed as mean and standard deviation (SD) unless otherwise stated. Magnitude of decline (i.e. slope of line for variables plotted over time) in FEV_1, $ppFEV_1$, FVC and ppFVC was determined using mixed effects models. Adjusted mixed effects models were implemented to obtain FEV_1 and FVC outcomes by location and months since baseline visit, after adjusting for age, sex, BMI, pregnancy, *Pseudomonas aeruginosa* colonisation and CFRD. Further adjusted mixed effects models analysis was completed stratifying by age group (18 to 29 years, ≥ 30 years) (as age has been shown to impact the magnitude of decline in spirometry). Locally Weighted Scatterplot Smoothing (LOWESS) was used to present figures of $ppFEV_1$ and ppFVC data. Alpha was set at 0.05.

3.2 Results

A total of 156 participants met the study criteria and contributed data to the analyses (Table 3.1). In total, 2,748 ((mean [range] 219 (8 [2 to 24]) and (21 [3 to 58]))data points (spirometry) were available for participants living in Perth metropolitan (n = 130) and rural and remote (n = 26) areas, respectively.

3.2.1 Magnitude of decline of spirometry

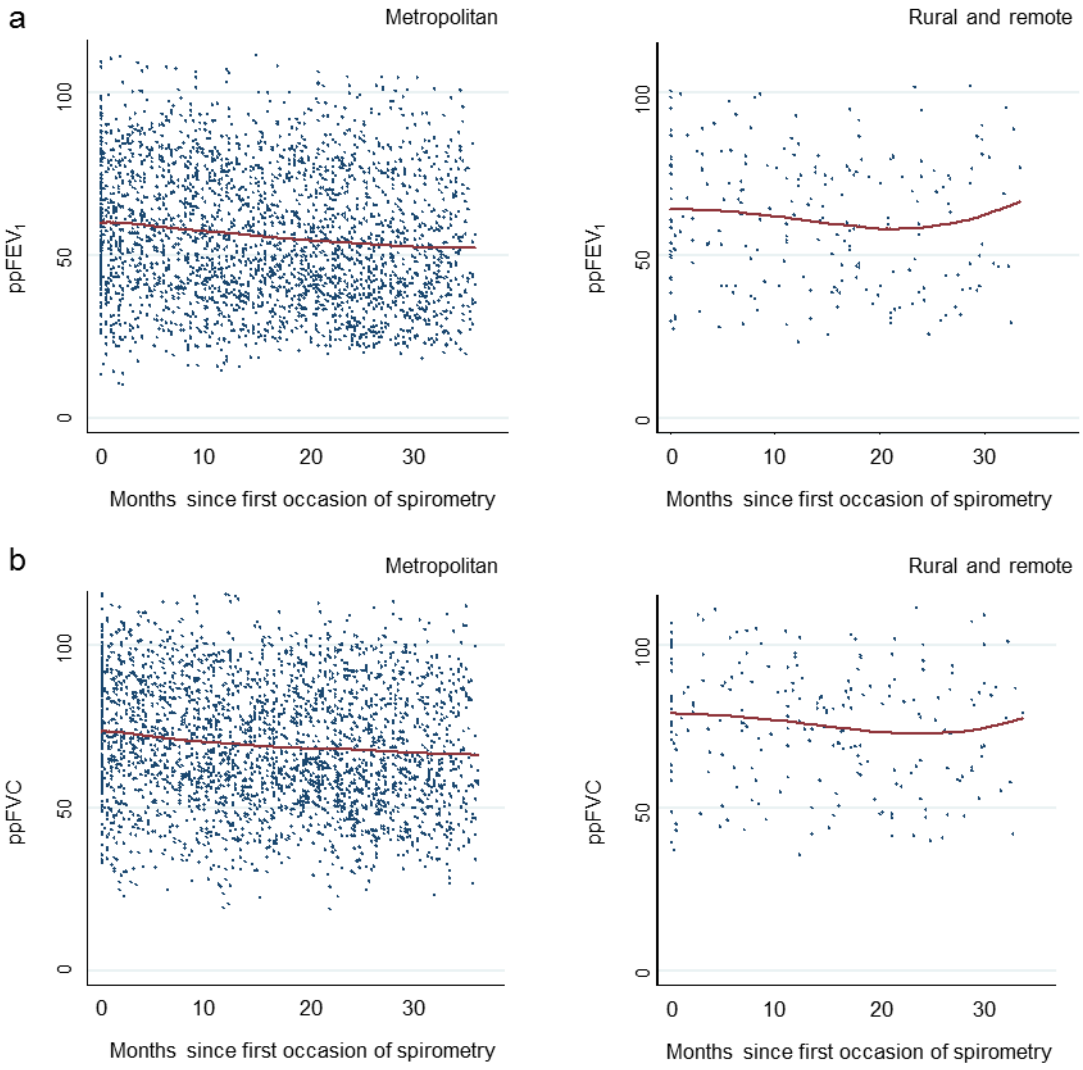
There was no clear difference between participants living in the Perth metropolitan and rural and remote areas for the magnitude of decline in FEV_1 (mean difference [95% CI] 0.00L [-0.01 to 0.01], p = 0.16), $ppFEV_1$ (0.07% [-0.07 to 0.21], p = 0.31), FVC (0.00L [-0.01 to 0.01], p = 0.31) or ppFVC (0.05% [-0.10 to 0.20], p = 0.53) (Figure 3.1). Results were unchanged when stratified for age (18 to 29 years or ≥ 30 years).

Table 3.1 Participant characteristics at the time of their first occasion of spirometry for those living in the Perth metropolitan area (n = 130) and rural and remote Western Australia (n = 26)

	Perth metropolitan	Rural and remote WA
Female, n (%)	57 (44)	16 (62)
Age, yr	27 (8)	30 (11)
BMI, kg/m^2	22.9 (3.7)	24.3 (6.5)
FEV_1, L	2.42 (0.97)	2.46 (1.00)
$ppFEV_1$	62 (20)	67 (19)
FVC, L	3.55 (1.19)	3.53 (1.19)
ppFVC	76 (18)	81 (17)
Pseudomonas aeruginosa, n (%)	120 (92)	23 (88)
CF-related diabetes, n (%)	19 (16)	1 (4)
Pregnancy during audit period, n (%)	3 (2)	0 (0)

Data are presented as mean (standard deviation) unless otherwise stated. BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, pp = % predicted. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted $ppFEV_1$ and ppFVC.

Figure 3.1 Locally Weighted Scatterplot Smoothing for percentage predicted forced expiratory volume in 1 second (a) and percentage predicted forced vital capacity (b) for participants living in metropolitan and rural and remote areas of Western Australia



$ppFEV_1$ = percentage predicted forced expiratory volume in 1 second, ppFVC = percentage predicted forced vital capacity. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted $ppFEV_1$ and ppFVC. All data points for each participant are provided, with timepoint '0' on the x axis indicating the first occasion of spirometry, with subsequent data points in months from baseline according to each participant's CF clinic appointments.

3.3 Discussion

This study aimed to determine whether there was a difference in the magnitude of decline in spirometry between adults with CF living in the Perth metropolitan and rural and remote areas in WA. The study design was pragmatic given the historical nature of the data, and it was beyond the scope of this research to undertake data collection prospectively. No clear effect on the magnitude of decline of spirometry was demonstrated between groups. Stratifying the analysis for age did not change the results.

While unexpected, the most likely reason no difference was detected in spirometry relates to the limited sample size available for these analyses. That is, data were available for only 26 participants living in rural and remote WA and these participants averaged only eight spirometry recordings over the 3-year study period. Further, some of these participants contributed as few as two (n = 2) or three (n = 4) data points (spirometry), of which the spirometry values were highly variable over the three-year period. Taken together, these factors made it difficult to estimate the true magnitude of decline in measures of spirometry in the rural and remote group, with any precision. This, in turn, compromised the power to detect between-group differences. Using data extracted retrospectively from the CF data registry may give rise to missing data points, however the SCGH CF centre had a dedicated employee entering the data (including spirometry) close to the time of each CF clinic, reducing the chance of this occurring.

It is also possible that there was no difference because of the relatively short time period (3 years) and a longer period of surveillance (i.e. 5 to 10 years) might be needed to detect a difference in the magnitude of decline in spirometry. Conducting a prospective study will likely improve the standardisation of data collection and potentially reduce variability in the results that was observed in the present study. Notwithstanding these considerations, the data presented in the current study draw attention to the lower disease surveillance in those people with CF living in rural and remote WA. This may impact health outcomes in a similar way to that observed in earlier work (5, 6).

The fewer available measures of spirometry (performed at CF clinics) amongst adults living in rural and remote WA highlights the reduced access to care experienced by this group. Programs aimed at improving access and engagement with the CF centre and multidisciplinary team need to be considered. Telehealth, in the form of videoconferencing, is a potential solution to some of the barriers (geography, time, financial) faced by adults with CF living in these areas.

CHAPTER 4

STUDY 2 (PART A, PART B)

This chapter details the methodology, results and discussion for Study 2 of this programme of research. Study 2 consists of two parts; Part A (described in Section 1.1) investigates the impact of providing cystic fibrosis (CF) clinics via videoconferencing on healthcare utilisation and other health outcomes in adults with CF living in rural and remote Western Australia (WA); and Part B (described in Section 1.2) is a sub-analysis of data from Part A, relating to absenteeism and presenteeism data collected using the World Health Organization (WHO) Health and Work Performance Questionnaire (HPQ). Part A has been published as original research in *Journal of Telemedicine and Telecare* in July 2016 (Appendix 2), and Part B as a letter to the editor in *Journal of Cystic Fibrosis* in July 2016 (Appendix 3). Data were collected for Study 2 from July 2013 to June 2015.

4.1 Part A Design

This was a single group study in which adults with CF who lived in rural and remote WA were invited to utilise telehealth clinics as part of routine care (i.e. attending a minimum of four clinics per year) over a 12-month period. Participants were recruited between July 2013 and August 2014. Approval was obtained from the Sir Charles Gairdner Osborne Park Healthcare Group (2012-209) and Curtin University (83/2013) Human Research Ethics Committees.

4.1.1 Participants

Adults with CF aged 18 years or more and living a minimum of 100km from the SCGH CF Centre were eligible to participate in this study. Exclusion criteria were pregnancy, previous lung transplantation or current listing for lung transplantation, as adults with CF meeting these criteria were already required to travel to Perth more frequently for medical care.

4.1.2 Telehealth clinics

This study aimed to provide telehealth clinics for participants approximately every three months, or sooner if clinically indicated, for reasons including self-reported acute deterioration in respiratory status or early follow-up after a course of intravenous (IV) antibiotics. Telehealth clinics were scheduled to suit the participants, CF team, regional telehealth coordinators, and a health professional local to the participant (physiotherapist, nurse or general practitioner).

On the day of the telehealth clinic, participants attended the nearest regional hospital. The participant's height, weight and spirometry were measured by a designated health professional before the telehealth clinic commenced. Telehealth clinics were held via a videoconferencing using Polycom HDX® series (Polycom, San Jose, USA) equipment at both SCGH and hospitals throughout rural and remote WA. During telehealth clinics, the participant chose whether to be reviewed by each member of the multidisciplinary CF team individually (i.e. consultant physician, nurse practitioner, physiotherapist and dietician) or by the whole team together in a group. A pharmacist and social worker were also available to provide input via telephone at a later date if requested by the participant

or the team. Following the telehealth clinic, prescriptions were faxed or medications were couriered to the participant's local pharmacy.

Traditional 'in-person' clinics at SCGH were still provided if requested by the participant (i.e. as a preference or if more convenient at that point in time), or if clinically indicated as previously described. Participants were encouraged to attend one in-person clinic during the intervention to allow for more comprehensive annual review of their clinical status. If a participant required admission to hospital at any time during the study, this was arranged at the SCGH CF Centre in Perth. Courses of home IV antibiotics were also commenced at the CF centre before the participant returned home. This allowed for intensive medical and allied health input to be provided, as well as access to specialist secondary services such as intravascular access, endocrinology, gastroenterology and immunology.

4.1.3 Study measurements

Participants completed the relevant measurements at baseline and at each CF clinic (telehealth or in-person) until the completion of the study period, unless otherwise stated. The principal investigator performed all assessments (including questionnaires) during CF clinics conducted at SCGH. For telehealth assessments, spirometry and weight were assessed by a health professional local to the participant, with the remaining measures collected by the principal investigator, unless otherwise stated.

4.1.4 Primary outcome

4.1.4.1 Uptake of telehealth

Uptake of telehealth was measured via the number of telehealth CF clinics attended throughout the study period. Clinic attendance data, recorded prospectively in the participant's medical record, were verified at the end of the 12-month study period and compared with the 12-month period preceding recruitment to the study.

4.1.5 Secondary outcomes

4.1.5.1 Participant satisfaction

Participant satisfaction with telehealth clinics was measured at the end of the study period using two questionnaires; the Telehealth Satisfaction Scale (TeSS) (153) and a purpose developed satisfaction survey. The TeSS is a 10-item questionnaire originally developed to assess patient satisfaction with telehealth in a rural memory clinic. For the purposes of this study, the term 'memory clinic team' was replaced with 'CF team' and the final statement requiring a response "How well the staff answered your questions about the equipment", was omitted as the participants in this study were not required to operate the telehealth equipment. The second survey contained six questions that were answered using a 5-point Likert scale (responses ranging from strongly agree to strongly disagree, with higher scores indicating stronger agreement), allowing the participant to provide further feedback on the telehealth clinics including preference for either telehealth or traditional in-person clinics. This survey was piloted in adults with CF (n = 5) living in the metropolitan area and minor changes were made to optimise its readability. The final version of this purpose-built survey and the modified TeSS are available as Appendix 4. The surveys were mailed to participants, and were returned by mail in pre-addressed, postage paid envelopes. The content of the surveys did not allow the researchers to identify the participants.

4.1.5.2 Healthcare utilisation

Healthcare utilisation data (HCU) (total number of CF clinics attended, courses and days of IV antibiotics, courses of inhaled and oral antibiotics, hospital admissions and admission days) were extracted from each participant's medical record at the end of the study period and compared with the 12-month period preceding recruitment to the study.

4.1.5.3 Spirometry

Spirometry (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]) was measured according to accepted guidelines (152) using either CPFS/D USB™ (MGC Diagnostics Corporation, St Paul, USA) or Easyone™ (NDD Medical Technologies, Andover, USA) spirometers.

The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted FEV_1 ($ppFEV_1$) and percentage predicted FVC (ppFVC). Health professionals who performed spirometry had previously received training from a certified respiratory technician.

4.1.5.4 Nutritional status

Height (Seca, Hamburg, Germany) and weight (A&D Company, Tokyo, Japan) were measured and used to calculate body mass index (BMI).

4.1.5.5 Health-related quality of life

Health-related quality of life (HRQoL) was measured using the Cystic Fibrosis Questionnaire – Revised (CFQ-R) (107) (discussed in Section 2.3.2.2) This self-completed questionnaire comprises 50 questions answered on a 4-point Likert scale, and covers 12 domains comprising physical, vitality, emotion, treatment burden, health, social, body, role, weight, respiratory, digestion and eating. The CFQ-R requires the user to recall information from the previous 2 weeks.

4.1.6 Analyses

Statistical analyses were conducted using Stata® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The distribution of data was checked for normality. Satisfaction data were reported using descriptive statistics. Healthcare utilisation data were compared pre- and during- the 12-month study period with Poisson or negative binomial regression. Paired t-tests and Wilcoxon signed rank tests were used to compare spirometry, weight, BMI, and HRQoL data pre- and during the 12-month study period as appropriate. As this study took the pragmatic approach of maximising the inclusion of all adults with CF living in rural and remote WA, with the primary aim of reporting the uptake of telehealth clinics amongst these people, no sample size calculations were undertaken. Alpha was set at 0.05. All data from participants who completed the study period were included in the analysis irrespective of their uptake of telehealth.

4.2 Part A Results

Twenty-three out of a possible 28 (82%) adults with CF living in rural and remote WA were recruited for this study (Table 4.1). Reasons for not participating were regular travel to Perth for other medical reasons (n = 3) and intention to move interstate or overseas within the study period (n = 2). The distance participants were required to travel to their nearest regional hospital was a median (range) of 5 (1 to 22) km (Table 4.1). Data from two participants were excluded from the analysis as they moved residence during the study period (one to Perth and one internationally). One other participant chose to travel to Perth for all CF clinics and did not utilise the telehealth intervention, therefore they were not asked to complete the satisfaction surveys.

4.2.1 Uptake of the telehealth clinics

The 21 participants included in the final analyses attended a total of 100 clinics during the study period, of which 66 (66%) were provided via telehealth (Table 4.2). Four participants (19%) utilised telehealth for all of their clinics, however three of these people also had hospital admissions at SCGH during the study period, and subsequent in-person contact with CF team at this time. The median (range) number of clinics per participant during the study period increased from 2 (0 to 6) in the preceding 12 months to 5 (2 to 8) ($p < 0.001$, Table 4.2). A total of 19 of the 21 participants (90%) attended four or more CF clinics (telehealth or in-person) during the study period, compared with 4 (19%) in the previous year. On two occasions, participants did not attend their scheduled telehealth clinic and failed to inform the CF team. Of the 34 in-person clinics where the participant attended the SCGH CF Centre, 19 (56%) were requested by the CF team for clinical indications.

4.2.2 Participant satisfaction

The TeSS and purpose developed participant satisfaction survey data were available for 17 (81%) participants. The participants' rated all nine items on the TeSS as either 'good' or 'excellent', with the exception of one participant's response to the item relating to the voice quality of the equipment (Table 4.3).

Table 4.1 Participant (n = 23) characteristics at commencement of the study

Participants, n	23
Female, n (%)	14 (61)
Age, yr	31.4 (10.2)
BMI, kg/m^2	21.1 (18.7 to 58.0) [a]
FEV_1, L	2.08 (0.78)
$ppFEV_1$, %	60 (20)
Distance from specialist CF centre, km	417 (100 to 2,567) [a]
Distance from nearest regional hospital, km	5 (1 to 22) [a]
Pseudomonas aeruginosa, n (%)	21 (91)
CF-related diabetes, n (%)	4 (17)
Pancreatic insufficiency, n (%)	21 (91)

Data are presented as mean (SD) unless otherwise stated. BMI = body mass index, CF = cystic fibrosis, FEV_1 = forced expiratory volume in 1 second, pp = percentage predicted. The Global Lung Function Initiative 2012 equations (151) were used to calculate $ppFEV_1$ and ppFVC.
[a] data are presented as median (range).

Table 4.2 Healthcare utilisation data for participants (n = 21) who completed the intervention, comparing the 12-month periods prior to and during telehealth

	Pre-telehealth		During telehealth				
	Nº	per participant	Nº	per participant	IRR	Std. err.	p
CF clinics	46	2 (0 to 6)	100	5 (2 to 8)	2.2	0.4	< 0.01
IV antibiotic courses	14	0 (0 to 3)	25	1 (0 to 4)	1.8	0.3	0.08
IV antibiotic days	170	8 (0 to 32) [b]	350	17 (0 to 61) [b]	2.3	0.8	0.03 [a]
Hospital admissions	8	0 (0 to 2)	19	1 (0 to 3)	2.4	1.0	0.04
Admission days	56	3 (0 to 15) [b]	209	10 (0 to 36) [b]	3.7	0.4	0.01 [a]
Oral antibiotic courses	24	1 (0 to 3)	29	1 (0 to 3)	1.2	0.3	0.5
Inhaled antibiotic courses	18	1 (0 to 2)	31	2 (0 to 3)	1.7	0.5	0.07

Data are presented as number (Nº) and median (range). IRR = incidence rate ratio, IV = intravenous, Std. err. = standard error. Analyses performed using Poisson regression or [a] negative binomial regression.
[b] data are presented as mean (range).

Table 4.3 Participant (n = 17) responses to questions from the Telehealth Satisfaction Scale

Overall, how satisfied were you with:	Score
The voice quality of the equipment	4 (1 to 4)
The visual quality of the equipment	4 (3 to 4)
Your personal comfort using the telehealth system	4 (3 to 4)
The ease of getting to the telehealth department	4 (3 to 4)
The length of time with the CF team	4 (3 to 4)
The explanation of your treatment by the CF team	4 (3 to 4)
The thoroughness, carefulness and skilfulness of the CF team	4 (3 to 4)
The courtesy, respect, sensitivity, and friendliness of the CF team	4 (3 to 4)
How well your privacy was respected	4 (3 to 4)

Data are presented as median (range). Questions were answered using a 4-point scale: Excellent = 4, Good = 3, Fair = 2, Poor = 1.

Results from the purpose developed satisfaction survey (Table 4.4) demonstrated that 16 (94%) participants strongly agreed or agreed that telehealth clinics were a good way to manage CF care. Ten (59%) participants preferred telehealth clinics for their CF clinics.

4.2.3 Healthcare utilisation

During the study period, there was an increase in the number of IV antibiotics days, hospital admissions and admission days per participant (Table 4.2) (all $p < 0.05$). The number of courses of IV antibiotics, oral antibiotics, and inhaled antibiotics per participant also increased, however these differences were not clear (Table 4.2). Of the 25 respiratory exacerbations requiring IV antibiotics during the study period, 20 (80%) were detected during telehealth clinics.

4.2.4 Spirometry

No changes were seen in spirometry (FEV_1, $ppFEV_1$, FVC and ppFVC) following the intervention (Table 4.5).

4.2.5 Nutritional status

In the 20 participants for whom weight gain was a goal, there was an increase in median (interquartile range) BMI from 20.9 (4.7) to 21.7 (3.4) at the end of the study period, however this was not significant ($p = 0.12$). One participant was excluded from the BMI analysis as they were morbidly obese and weight loss was being encouraged. Fourteen (70%) participants gained weight during the intervention, with a mean (standard deviation) increase of 2.2 (2.1) kg, or 3.7 (3.6) %.

4.2.6 Health-related quality of life

There was an improvement in the vitality domain ($p = 0.04$) of the CFQ-R, and a trend toward improvement in the weight domain ($p = 0.06$) (Table 4.6). No clear changes were observed in other domains of the CFQ-R.

Table 4.4 Participant (n = 17) responses to questions from the purpose developed satisfaction survey, with data presented as number (percentage) of participants

	SA	A	U	D	SD
The organisation of the clinics met my expectations	5 (29)	11 (65)	1 (6)	0 (0)	0 (0)
The timing of the telehealth clinic appointments were convenient for me	8 (47)	9 (53)	0 (0)	0 (0)	0 (0)
The healthcare I received during the telehealth clinics met my expectations	6 (35)	10 (59)	1 (6)	0 (0)	0 (0)
I was able to communicate effectively with the CF team using this technology	6 (35)	10 (59)	1 (6)	0 (0)	0 (0)
I prefer telehealth clinics over traditional 'face to face' clinics	3 (18)	7 (41)	5 (29)	2 (12)	0 (0)
Telehealth clinics are a good way to manage my CF care	3 (18)	13 (76)	1 (6)	0 (0)	0 (0)

Data are presented as number (percentage). Questions were answered using a 5-point Likert scale: SA = Strongly Agree, A = Agree, U = Unsure, D = Disagree, SD = Strongly Disagree.

Table 4.5 Spirometry measured prior to telehealth and at the end of the 12-month telehealth study period for participants (n = 21) who completed the study

	Prior to telehealth	Following telehealth	Difference	95% CI
FEV_1 (L)	2.02 (0.76)	1.96 (0.69)	-0.06	-0.19 to 0.08
ppFEV_1 (%)	58 (19)	56 (18)	-2	-4.91 to 1.87
FVC (L)	3.18 (0.90)	3.15 (-0.03)	-0.03	-0.17 to 0.11
ppFVC (%)	75 (17)	74 (15)	-1	-3.44 to 2.78

Data are presented as mean (standard deviation). CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, pp = percentage predicted. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted ppFEV_1 and ppFVC.

Table 4.6 Participant (n = 21) responses to the Cystic Fibrosis Questionnaire-Revised prior to and following telehealth intervention

CFQ-R domain	Prior to telehealth	Following telehealth	Mean diff. (95% CI)	p
Physical functioning [a]	71 (33 to 42)	75 (42 to 90)	-	0.64 [b]
Vitality	44 (21)	55 (20)	11 (1 to 22)	0.04
Emotional functioning	69 (23)	71 (19)	2 (-9 to 12)	0.75
Eating [a]	100 (61 to 100)	100 (67 to 100)	-	0.43 [b]
Treatment burden	58 (17)	56 (20)	-2 (-9 to 4)	0.51
Health perceptions	53 (23)	58 (19)	5 (-7 to 17)	0.39
Social	63 (20)	61 (18)	-2 (-8 to 5)	0.56
Body image	71 (26)	68 (28)	-3 (-14 to 8)	0.56
Role	78 (16)	77 (21)	-1 (-10 to 9)	0.86
Weight [a]	67 (33 to 100)	100 (50 to 100)	-	0.06 [b]
Respiratory symptoms	55 (24)	64 (19)	9 (-3 to 20)	0.13
Digestive symptoms [a]	89 (67 to 100)	89 (67 to 100)	-	0.97 [b]

Data are presented as mean (standard deviation) for normally distributed data, or [a] median (IQR) for non-normally distributed data. An increase in score represents improvement, with a maximum score of 100. Analysis performed using paired t test or [b] Wilcoxon signed rank test. CI = confidence interval, diff = difference.

4.3 Part A Discussion

This study appears to be the first in Australia to evaluate the uptake of telehealth clinics implemented as part of routine care in people with CF living in rural and remote areas. The results have demonstrated that telehealth technology increases access to care for adults with CF and resulted in 90% of participants meeting the recommended number of CF clinic attendances (33) during the study period. Although both telehealth and traditional in-person CF clinics were offered, participants utilised telehealth for more than two-thirds of their clinics. One participant did not attend the CF centre (for an in-person clinic or hospital admission) as it was not convenient for them during the study period. This is a potential limitation of telehealth, as certain assessments (e.g. bone mineral density, general respiratory function testing and chest computed tomography) are not readily available in all rural and remote areas. While one participant chose not to utilise telehealth, the inclusion of their data in measures related to HCU provides a more conservative and real-world estimate of the effect telehealth had on these outcomes.

The observed increase in antibiotic use and hospital admissions reflects increased surveillance of the participants, and a corresponding increased detection of respiratory exacerbations. Although this short-term increase in HCU was observed, the increased frequency of CF clinics attended and contact with the clinical team as a result of this intervention may lead to increased treatment adherence and improved longer-term health outcomes. Specifically, more frequent contact with the CF team (154) and earlier detection of respiratory exacerbations that will allow treatment to be initiated sooner (19), and it is a broadly held view of clinicians that this may slow the magnitude of decline of FEV_1, and potentially improve nutritional status and HRQoL.

Recruitment for this study was good (over 80%), with only five potential participants not enrolling because they were required to travel to Perth for other medical reasons, or had intentions to move during the study period. The most likely explanation for the high recruitment rate is that potential participants could envisage the reduction in travel burden that would result from telehealth, as most of the participants were required to travel many hours by car or plane to

Perth to attend in-person clinics. It is also likely that recruitment was influenced by the mean age (31.4 years) of the study sample, as younger adults may be more open to the idea of integrating modern technology into their care. This study adds support to previous studies reporting that people with CF are willing to utilise telehealth technology (142).

Responses to the TeSS reflected an excellent level of satisfaction with telehealth clinics. The only item given a score less than three (out of 4) by a participant was regarding the voice quality of the equipment, which could be attributed to the voice delay occasionally experienced with the system. The TeSS responses demonstrated that participants perceived telehealth clinics to be a highly acceptable method to provide regular healthcare review. However, responses to the purpose developed participant satisfaction survey indicated that some participants (12%) preferred in-person clinics over telehealth and some had no preference (29%). This is understandable given that in-person clinics have been offered for many years and have advantages such as the ability for physical examination, access to on-site specialist secondary services (e.g. intravascular access, endocrinology, immunology and hepatology) and immediate admission to hospital if required.

In keeping with the high level of satisfaction observed in this study, a meta-analysis of telehealth for chronic obstructive pulmonary disease found that people were largely satisfied with receiving care via telehealth at home, as long as face to face consultations were still available on request (154). The positive view of telehealth amongst participants in this study is consistent with previous telehealth studies in CF (142), and provides merit to the continuation of its use as part of routine CF care.

It is difficult to make comparisons between the HCU results of this study and other telehealth studies in CF due to the differences in the interventions and study designs. In another study, weekly videoconferencing with the CF team has previously been utilised by a small number of people with CF (n = 7) awaiting lung transplantation over a six-month period, and no differences in HCU were found when compared to usual care (26). Videoconferencing has also been used effectively as a means of assessing functional exercise capacity (27). In 19 people

with CF from adult and paediatric centres, the monitoring of spirometry and respiratory symptoms on a daily basis at home over a 6-month period resulted in no difference in the number of respiratory exacerbations per participant when compared to the same period prior to the study; however an increase in courses of oral antibiotics was noted during the intervention (25). Another intervention comparing daily monitoring of spirometry and oximetry (n = 17) to usual care (n = 28) over seven months found no difference in the rate of hospitalisation, but an increase in CF clinic attendance during the study period was observed (21). Thus, despite the differences in study designs across these studies, many observed an increase in certain measures of HCU.

As this study was unlikely to be powered to detect small differences in the change in magnitude of spirometry (FEV_1 and FVC), the lack of difference in these measures were not unexpected. Future studies may address this lack of demonstrated change in spirometry with larger sample sizes and/or longer surveillance periods, given the variability of this outcome seen in people with CF. The increased treatment of respiratory exacerbations may explain the improvement seen in the vitality domain of the CFQ-R, which consists of four questions relating to energy levels. Although the minimal clinically important difference for the vitality domain of the CFQ-R has not been established, the magnitude of change in this domain demonstrated in our study (11 out of 100 points) exceeded the magnitude of change (8 points) reported following 28 days of inhaled Aztreonam Lysine in people with CF colonised with *Pseudomonas aeruginosa* in another study (156). As the change in HRQoL alongside the improvement in lung function was considered to be clinically meaningful to the participants in this other study, it is likely that the improvement seen in the present study would also be perceived as clinically meaningful (157). The trend towards improvement in the weight domain of the CFQ-R, alongside the weight gain in 14 (67%) of the participants, may reflect an increase in dietetic input delivered during the study period, as well as the improved management of respiratory exacerbations. It is well established that in people with CF, a loss of appetite and weight are associated with respiratory exacerbations (87) and earlier management of such episodes may have minimised weight loss during the study period.

This study demonstrated that telehealth clinics are a feasible way to deliver care for people with CF living in rural and remote areas, and as a result this service will continue to be offered to adults with CF living in WA. Adults with CF in these areas are willing to utilise this technology and most prefer telehealth over in-person clinics offered at the SCGH CF Centre. There were limitations to this study, such as a small sample and lack of control group, which are also common limitations among many of the published telehealth studies in CF to date (142). Furthermore, other clinical measures commonly used in CF care such as sputum microbiology, inflammatory and diabetic markers, and chest radiography were not included as outcomes as they were beyond the scope of this study.

Given the differences in geography, CF centre resources and government health service provision between states and countries throughout the world, it would be difficult to conduct a multicentre randomised controlled trial in this area. Therefore, future studies for similar cohorts should consider focusing on the evaluation of the longer-term implementation of telehealth services as part of routine care, and their impact on a wider range of health outcomes.

4.4 Part B Design

The study was a sub-analysis of data collected during Study 2, relating to absenteeism and presenteeism data collected from the WHO HPQ (158).

4.4.1 Study measurements

The principal investigator collated all data pertaining to the measurements presented in this study, which were collected at the same time as the measurements described in Part A of this chapter.

4.4.1.1 Absenteeism and presenteeism

During CF clinics (telehealth and in-person) throughout a 12-month period, participants completed the absenteeism and presenteeism questions of the WHO HPQ (158). This self-reported 11-item questionnaire collects information regarding; i) expected and actual hours worked during the previous 7 and 28 days; ii) part or entire days of work missed (for health or holiday); iii) overtime worked; and, iv) perceived work performance (rated out of 10) for the participant and colleagues undertaking similar work. Responses were used to calculate relative absenteeism and relative presenteeism. Relative absenteeism is the proportion of time absent from work. A maximum score of 1 indicates 100% absenteeism; a score of 0 indicates no absenteeism. Negative scores indicate the hours worked exceeded employer's expectations. Relative presenteeism is work performance compared to others in similar employment. A score of 1 represents equal performance, 0 represents worst performance, and a maximum score of 2 represents performance at least twice as good as colleagues.

4.5 Part B Results

Twenty-three adults with CF completed the study (Table 4.1). Data were collected during a total of 91 CF clinics attended. Participants were engaged in paid work on 61 (67%) of these occasions. Twenty-two (96%) participants were employed on at least one occasion, and 11 (48%) were employed on all occasions throughout the entire 12 months. Only one participant, a fulltime carer, had no paid work in this time.

For those employed, the median (range) number of hours worked per week was 38 (10 to 80). The mean (range) number of entire work days missed in the previous 28 days because of problems with physical or mental health was 2 (0 to 21) days, while the number of partial work days missed in this period for the same reason was to 1 (0 to 11) days. Participants worked longer hours than expected on 2 (0 to 28) days during the previous 28 days. Overall, relative absenteeism (mean [range]) in those employed was 0.1 (-1.2 to 0.9).

Participants reported that their work performance over the past one to two years was median (range) 8 (5 to 10) out of 10, which was similar to how they rated the performance of colleagues in similar employment, also being 8 (5 to 10). However, when asked to rate their work performance over the past 28 days, the participants' responses were more variable (8 [0 to 10]). Overall, median (range) relative presenteeism in those employed was 1.0 (0.0 to 1.8).

4.6 Part B Discussion

These data provide evidence of the potential impact of CF on a person's ability to work. Despite having a chronic disease that is associated with a significant treatment burden, most adults with CF living in rural and remote WA engaged in paid work during the 12-month study period. Absenteeism scores were variable, and demonstrated that CF affected the work attendance of many, but not all participants. Presenteeism scores, while also variable, demonstrated that on average participants felt they performed as well as their colleagues at work. However, with many reporting that CF does have has a large impact on their work performance, further research is required in larger samples including both metropolitan and rural and remote areas to understand the full impact of CF on presenteeism. Measuring absenteeism and presenteeism using the HPQ provides a useful insight into the disease-related impact on work attendance and performance in adults with CF, and this outcome measure should be considered for use in future studies in this population.

CHAPTER 5

STUDY 3 (PART A, PART B)

This chapter presents the methodology, results and discussion for Study 3 (described in Section 1.3), which investigates the usability of a smartphone application (app) amongst adults with cystic fibrosis (CF) (Part A), and the agreement of clinical decision making between clinicians (experienced in providing CF care) interpreting the app data (Part B). These are preliminary studies undertaken to demonstrate feasibility prior to the commencement of Study 4 (Chapter 6). The methods and results for Parts A and Part B are presented separately, followed by a combined discussion relevant to both parts. Study 3 was published as original research in the *Journal of Telemedicine and Telecare* in November 2017 (Appendix 5).

5.1 Part A Design

This was a single group study exploring usability over four weeks duration, conducted at the Sir Charles Gairdner Hospital (SCGH) CF Centre. Approval was obtained from the Sir Charles Gairdner Osborne Park Healthcare Group (2015-209) and Curtin University (HR123/2015) Human Research Ethics Committees.

5.1.1 Recruitment

While attending a CF clinic, 10 adults with CF who owned a smartphone with iOS or Android operating systems were invited to participate. Recruitment was consecutive and targeted (ceasing recruitment of each sex at five participants) to ensure equal numbers of male and female participants. In total, 190 adults with CF attended the centre at the commencement of the study, and at this time 183 (96%) owned a smartphone.

5.1.2 Smartphone application

Experienced clinicians who were also the investigators in this study formulated the 12 questions used in the app (described further below). Members of the research team reviewed the questions for face validity including completing the questions several times to assess readability. Eight of the respiratory symptom questions were derived from exacerbation scales previously used in CF research (18, 83) (Table 5.1) (see Section 2.3.1) and two further symptom questions (i.e. those pertaining to wheeze and chest tightness) were included as these symptoms have been identified by adults with CF as indicators of a respiratory exacerbation (95). Finally, two questions pertaining to emotional wellbeing were included, because in people with CF, greater feelings of anxiety and depression have been associated with the greater respiratory symptoms, as well as poorer lung function, HRQoL and physical functioning (159). All of the app questions were answered yes or no, and each time an answer was selected the app automatically moved to the next question. The font size of the text in the app was set at a minimum of 18 to ensure all users could read the questions.

Table 5.1 Smartphone application questions

In the past week, have you had:
An increase in or sputum volume or change in colour?
New or increased blood in your sputum?
Increased cough, or new pain on coughing?
New or increased wheeze?
New or increased chest tightness?
Increased shortness of breath or difficulty breathing?
Increased fatigue or lethargy?
Fever?
Loss of appetite or weight?
Sinus pain or tenderness?
In the past week, have you felt:
Low in mood?
Worried?

A prototype of the app was designed by a software engineer, and internal testing was then undertaken by several members of the research team to ensure the application was functioning as intended. The final version of the app was then made available free of charge on iTunes and the Google Play Store, allowing participants to install it on their smartphone after enrolment in the study.

5.1.3 Procedure

At enrolment in the study, participants installed the app and practised answering the questions once in the presence of the principal investigator. They were then required to answer the questions once a week over four consecutive weeks. Four occasions (over a 4-week period) of use was considered sufficient by the research team, given another study that explored the usability of a telehealth system in CF based their conclusion on a single use (27). Participants in the current study were asked to set a recurring alert on their smartphone, which prompted them to answer the questions on a pre-specified day and time each week of their choosing. To login securely, each participant had a unique four-digit user code. Once all questions were answered, the responses were emailed in binary code (1 = yes, 0 = no), along with the user code, to an account established for the purpose of the study. To maintain data security, only the principal investigator could identify each participant based on their user code. Participants were informed that for the purpose of this study, symptom responses were not being used by the CF team to detect respiratory exacerbations, and they were instructed to contact the CF clinic by phone if they required an appointment. Participants were not reviewed in the CF clinic during the four-week period, and therefore no comparison was undertaken regarding the app answers and clinical status.

5.1.4 Study measurements

The principal investigator administered all assessments at the follow-up visit, 4 weeks following enrolment.

5.1.4.1 System usability

Usability was measured at the end of the study period with the System Usability Scale (SUS) (160). This scale comprises 10 items that ask about the usability aspects of the new technology, such as its complexity and functionality, and the participant's confidence in using it. Each item was answered using a 5-point Likert scale with responses that ranged from 5 (strongly agree) to 1 (strongly disagree). Scores from each of the 10 items were scaled to provide a score out of four, then combined and multiplied by 2.5 to provide a total score out of 100. Scores from the SUS were also grouped into two subscales: usability (8 items) and learnability (two items), both of which were also scored out of 100. The SUS has been widely used in the information technology industry, and more recently in studies evaluating the usability of telehealth technologies in CF (27) and chronic obstructive pulmonary disease (137).

5.1.4.2 Participant satisfaction

Participant satisfaction was assessed at the end of the study period using a purpose-developed survey which comprised seven items relating to the design and use of the app. Items alternated between positive and negative wording, and were answered with a 5-point Likert scale with responses that ranged from 5 (strongly agree) to 1 (strongly disagree).

5.1.5 Analyses

Statistical analyses were conducted using SPSS® (Statistical Package for Social Sciences, version 22.0, IBM corp., New York, USA). Data from both the System Usability Scale and satisfaction survey were reported using descriptive statistics.

5.2 Part A Results

Ten participants with CF completed the study (Table 5.2). Each participant used the app once per week over the four-week study period. Seven (70%) participants used iPhones, and three (30%) used phones with Android operating systems. At recruitment, the observed time taken to complete the app questions following installation was less than 2 minutes for all participants.

5.2.1 System usability

The mean (standard deviation) raw SUS score was 94 (6) (Table 5.3). When summed as subscales, participants scored the smartphone application as 92 (7) and 100 (0) for usability and learnability, respectively.

5.2.2 Participant satisfaction

Nine (90%) participants responded that they believed the app was a good method for reporting symptoms to the CF team. All participants (100%) found the instructions in the app easy to follow (Table 5.4).

Table 5.2 Participant (n = 10) characteristics

Male, n (%)	5 (50)
Age, yr	32 (11)
BMI, kg/m^2	23 (5)
$ppFEV_1$, %	49 (27)
Rural or remote, n (%)	2 (20)

Data are presented as number (percentage) or mean (standard deviation). BMI = body mass index; $ppFEV_1$ = percentage predicted forced expiratory volume in one second. The Global Lung Function Initiative 2012 equations (151) were used to calculate percent predicted $ppFEV_1$.

Table 5.3 Participant (n = 10) responses to items of the System Usability Scale

Item	SA	A	U	D	SD
I think that I would like to use this system frequently	5 (50)	4 (40)	1 (10)	0 (0)	0 (0)
I found the system unnecessarily complex	0 (0)	0 (0)	0 (0)	1 (10)	9 (90)
I thought the system was easy to use	9 (90)	1 (10)	0 (0)	0 (0)	0 (0)
I think that I would need the support of a technical person to be able to use this system	0 (0)	0 (0)	0 (0)	0 (0)	10 (100)
I found the various functions in this system were well integrated	4 (40)	3 (30)	3 (30)	0 (0)	0 (0)
I thought there was too much inconsistency in this system	0 (0)	1 (10)	0 (0)	2 (20)	7 (70)
I would imagine that most people would learn to use this system very quickly	10 (100)	0 (0)	0 (0)	0 (0)	0 (0)
I found the system very cumbersome to use	0 (0)	0 (0)	0 (0)	2 (20)	8 (80)
I felt very confident using the system	9 (90)	0 (0)	1 (10)	0 (0)	0 (0)
I needed to learn a lot of things before I could get going with this system	0 (0)	0 (0)	0 (0)	0 (0)	10 (100)

Data are presented as number (percentage of participants). Each item is answered using a 5-point Likert scale: SA = Strongly Agree, A = Agree, U = Unsure, D = Disagree, SD = Strongly Disagree.

Table 5.4 Participant (n = 10) responses to the purpose developed satisfaction survey

Item	SA	A	U	D	SD
I liked the graphic design (layout, colours etc.) of the app	0 (0)	8 (80)	2 (20)	0 (0)	0 (0)
It was easy to follow the instructions on the app	8 (80)	2 (20)	0 (0)	0 (0)	0 (0)
It was difficult to know what the app was asking me to do next	0 (0)	0 (0)	0 (0)	6 (60)	4 (40)
The questions I was asked about my symptoms were easy to understand	5 (50)	3 (30)	0 (0)	2 (20)	0 (0)
The questions I was asked about how I felt were difficult to understand	0 (0)	1 (10)	0 (0)	5 (50)	4 (40)
Using the app was a good way for me to report my symptoms to the CF team	4 (40)	5 (50)	1 (10)	0 (0)	0 (0)
Using the app to report my symptoms was an inconvenience or intrusion into my daily life	0 (0)	0 (0)	0 (0)	3 (30)	7 (70)

Data are presented as percentage of participants. SA = Strongly Agree, A = Agree, U = Unsure, D = Disagree, SD = Strongly Disagree.

5.3 Part B Design

This was an observer agreement study, investigating the agreement between experienced senior clinicians interpreting scenarios containing simulated app responses.

5.3.1 Study measurements

The principal investigator collated all data pertaining to the measurement collected as part of this study.

5.3.1.1 Observer agreement

A physician and nurse practitioner, both of whom were experienced in providing CF care, were presented with an identical set of 45 clinical scenarios, developed by the principal investigator. A nurse practitioner was included to reflect the growing utilisation of this role as a first point of contact in CF centres internationally. These scenarios were created by pairing one of three case studies, with one of 15 different combinations of app responses (45 in total). The three case studies described clinical presentations of an adult with mild, moderate or severe CF (i.e. each clinical presentation provided 15 differing combinations of app responses) and were reviewed for authenticity by a respiratory physician with extensive experience in CF, who was not otherwise involved in the study. Each scenario contained a different combination of possible responses to the app questions used in Part A. For each scenario, the two clinicians were asked to indicate whether or not they would; i) initiate telephone contact to discuss symptoms further, and/or ii) request the person attend an outpatient clinic for further assessment. The clinicians were blinded to each other's responses. An example scenario is provided as Appendix 6.

5.3.2 Analyses

Observer agreement between clinicians was assessed using a Cohen's kappa statistic. A sample size of 45 responses was adequate to detect a difference in proportion between chance and anticipated agreement of 0.5, assuming a relative error of 30%. Alpha was set at 0.05.

5.4 Part B Results

5.4.1 Observer agreement

Observer agreement between clinicians was perfect for the question regarding whether or not to initiate contact with the person to further discuss symptoms ($\kappa = 1.0$, $p < 0.001$). Specifically, both clinicians indicated that they would initiate contact for 42 (93%) scenarios, but not for three (7%) scenarios. There was near-perfect agreement for whether or not the person should be advised to attend the CF clinic ($\kappa = 0.86$, $p < 0.001$). Specifically, both clinicians indicated that they would request the person attend the CF clinic for 24 (53%) scenarios, but not for 18 (40%) scenarios. The two clinicians disagreed on the same scenario across all three case studies; this scenario contained a 'yes' response to only one question, which asked "in the past week have you had increased cough or new pain on coughing?"

5.5 Part A and Part B Discussion

This study has shown that an app that can be used to report symptoms that may be suggestive of a respiratory exacerbation had excellent usability in adults with CF. Furthermore, the symptom responses from the app were interpreted in a similar way by different senior clinicians in the process of clinical decision making.

The integration of telehealth with traditional care in CF is an expanding area of research. To date, feasibility in CF has been demonstrated in interventions such as using Skype and WhatsApp as a method of communication (143), monitoring of lung function and symptoms at home (21, 22, 97, 145), assessing exercise capacity (27), and promoting exercise (28, 147) and physical activity (29). While the evidence supporting the role of telehealth in CF is relatively limited, the aim of such interventions in the longer-term will be to improve health outcomes the earlier detection of respiratory exacerbations and increased treatment adherence. Strategies similar to those used in CF have also been employed in chronic diseases such as type 1 diabetes mellitus (161), with demonstrated improvements in access to routine care. A systematic review into mobile health interventions in diabetes mellitus and other cardiovascular and respiratory diseases found mixed evidence supporting the effectiveness of these interventions on treatment adherence and health outcomes (162).

The use of out-of-hospital monitoring systems to detect changes in symptoms and physiological parameters suggestive of a respiratory exacerbation in CF is a growing area of interest (21, 22, 96, 145). One shortcoming of these previous studies was poor adherence to the monitoring system, which resulted, at least in part, from the equipment being large and bulky. The app described in the present study overcame this limitation, as it was small and portable, and integrated easily with the lifestyle of adults with CF. Further, in contrast with earlier work which required daily use of the monitoring system by all participants, those in the current study were asked to use the system less frequently (i.e. once a week); a factor which may also have contributed to the excellent adherence observed. While the optimal frequency of reporting in order to detect a respiratory exacerbation is unknown, daily reporting in other studies probably

contributed to the observed poor adherence. Therefore, weekly reporting appears to be a pragmatic alternative which was well tolerated in this small study. In clinical practice, to minimise the possibility of missing the onset of a respiratory exacerbation that occurred between the weekly use of the app, people with CF could be instructed to use the app at any time between scheduled uses if they felt their respiratory symptoms had worsened.

The high SUS scores indicated that the app achieved an 'A' rating for usability. This rating is at the top of the "acceptable" usability range, and is described on the SUS adjective rating scale as "best imaginable" usability (163). In addition, raw scores of over 90 on the SUS indicate that a system is in the 99th percentile of usability for the tested demographic. Finally, a very high score like this also indicates that users would be more likely to recommend this technology to a friend.

The SUS scores observed in this study were similarly high to those reported for interventions in adults with CF investigating the feasibility of an internet based tool to promote physical activity (29), and using a videoconferencing system to assess exercise capacity (27). This was not surprising given the uncomplicated design and functionality of the app, including asking for yes/no responses to questions and requiring minimal time to answer the questions (less than 2 minutes). Similarly, participant satisfaction, as measured using the purpose developed survey was very high. All of the participants owned smartphones prior to the study, and therefore the high level of usability and satisfaction observed may be a function of their pre-existing comfort with such technology. This was expected, as 74% of adults in Australia owned a smartphone in 2015 at the time of this study (164).

Although the sample size for Part A of this study was modest, participants were recruited across a broad range of ages and severity of lung function, and there was equal representation from both genders. Participants living in rural and remote areas (n = 2) also participated in the study. Seven (70%) had received treatment for a respiratory exacerbation in the 12 months prior to commencing the study. Participants were employed in a wide variety of occupations, including administration, retail, information technology and healthcare, and one was a fulltime university

student. This allowed the investigators to gather usability data from people who were representative of the broader adult CF population.

In Part B, near-perfect agreement was observed in clinical decision making between two experienced clinicians. This suggests that others may be able to use this app to arrive at similar clinical decisions regarding whether the person requires further assessment for a potential respiratory exacerbation. However, having only two clinicians participating in the observer agreement study was a limitation. It is also a limitation that the scenarios were also simulated and did not reflect true clinical practise. It is possible that for the question with poor agreement, the ambiguity related to asking the clinician to interpret responses regarding two different symptoms (increased cough and new pain on coughing). This ambiguity might be overcome by dividing this into two separate questions: one regarding increased cough and a second regarding chest pain. This will allow people with CF to report chest pain irrespective of whether it is related to coughing.

This app, while designed to detect respiratory exacerbations, clearly did not include spirometry. This is a potential limitation as FEV_1 is regarded as one of the key measures of clinical status in CF (52). However, the provision of a spirometer would have greatly increased cost and reduced the portability of the reporting system. A system was developed that required no additional equipment to the participant's own smartphone, leading to high usability. The app questions, which provided the participant with a means to report respiratory symptoms, will allow the CF team to determine whether spirometry is required. It is acknowledged however, that the inclusion of home spirometry as part of this system may provide more accurate diagnosis of a respiratory exacerbation prior to the person being contacted by the CF team or attending the CF clinic.

The results of this study have demonstrated that amongst adults with CF, an app used to report symptoms suggestive of a respiratory exacerbation has excellent usability, and provides symptom responses that can be interpreted consistently between clinicians who are experienced in the management of this clinical population. A randomised controlled trial is now warranted to

investigate whether the use of this app can reduce the delay in time taken by an adult with CF to report respiratory symptoms to a CF team, and measure its impact on health-related outcomes.

CHAPTER 6

STUDY 4

This chapter presents the methodology, results and discussion for Study 4 (described in Section 1.3), which was a prospective randomised controlled trial (RCT) investigating the impact of the weekly use of the smartphone application (app) on healthcare utilisation and other health outcomes in adults with cystic fibrosis (CF). The methods from Study 4 were published as a protocol in the *BMJ Open* in April 2018 (Appendix 7). After completion, Study 4 was published in the *Journal of Cystic Fibrosis* in September 2019 (Appendix 8). Further, baseline data from Study 4 was published in *Respiratory Care* in March 2019 by a different author following an Honours degree project (see 'Publications arising using data from this thesis'). Additional results and discussion regarding unpublished data relating to secondary outcome measures have been incorporated into this chapter.

6.1 Study design

This was a prospective 12-month, single blinded RCT. Ethical approval was obtained from the Sir Charles Gairdner Osborne Park Healthcare Group (2015 - 030) and Curtin University (HR212/2015) Human Research Ethics Committees. This trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615000599572), and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (165) (Appendix 7).

6.1.1 Participant screening and selection

Eligible participants were identified at routine outpatient clinic appointments at the Sir Charles Gairdner Hospital (SCGH) CF Centre in Perth.

6.1.1.1 Inclusion criteria

Adults who met the following criteria were eligible to participate: diagnosis of CF; age ≥ 18 years; under the care of the SCGH CF Centre; had a respiratory exacerbation requiring treatment with intravenous (IV) antibiotics in the preceding 12 months; were in a period of clinical stability, defined as no signs of a respiratory exacerbation for the previous 2 weeks; and were able to understand written and spoken English.

6.1.1.2 Exclusion criteria

Criteria to exclude people from participating were: previous lung transplantation or current listing for lung transplantation; inability to undertake a prescribed treatment regimen due to cognitive reasons, or inability to use or not being in possession of a smartphone.

6.1.2 Randomisation and allocation concealment

Participants were randomly allocated to the intervention (usual care plus experimental intervention) or control (usual care) group using the University of Sydney National Health Medical Research Council Clinical Trials Centre randomisation service. Randomisation was stratified according to sex, location (metropolitan vs. rural and remote) and whether or not the participant was prescribed Ivacaftor or Lumicaftor/Ivacaftor, as these medications can reduce

the rate of respiratory exacerbations and improve lung function, weight and health-related quality of life (HRQoL) (39, 166).

6.1.3 Study measurements

Participants had assessments performed prior to randomisation (i.e. at baseline), and at 6 and 12 months (i.e. final), unless otherwise stated. Assessments were performed when the participant was in a period of clinical stability, defined as no signs of a respiratory exacerbation for the previous 2 weeks. If the participant had signs of a respiratory exacerbation at their scheduled follow-up time, the assessments were completed at the subsequent CF clinic when they were clinically stable. The principal investigator performed all assessments during follow-up visits conducted at SCGH. For telehealth assessments, spirometry and weight were assessed by a health professional local to the participant, with the remaining measures collected by the principal investigator.

6.1.4 Primary outcome

6.1.4.1 Number of courses of intravenous antibiotics and intravenous antibiotic days

Information regarding the use of IV antibiotics was obtained from the medical records of the participants by a pharmacist blinded to group allocation and verified against SCGH pharmacy dispensing records. This was collected at the final assessment only.

6.1.5 Secondary outcomes

6.1.5.1 Other measures of healthcare utilisation

At the final assessment only, the participant's medical record was reviewed to extract information pertaining to healthcare utilisation (HCU). This included: time (in days) from randomisation to the detection of the first respiratory exacerbation requiring oral and/or IV antibiotics; number of hospital admissions and days; number of courses and days of oral and inhaled antibiotics; number of CF clinics attended; estimated cost of IV, oral and inhaled antibiotic treatment; and estimated cost of hospital admissions. Costs related to HCU were estimated using information provided from the SCGH Pharmacy and Finance departments. All

potential participants received their care at the SCGH CF Centre or via shared care with an external respiratory physician (but not from a general practitioner). Prescribed antibiotic use was documented in the medical record, and participants were not required to keep a diary of antibiotic use. Non-clinical costs relating to participants' travel, parking, time off work and telephone calls were not recorded.

6.1.5.2 Smartphone application adherence

Adherence to the weekly use of the app for participants in the intervention group, expressed as a percentage, was calculated by dividing the number of weeks successfully reported by the total number of weeks enrolled in the study (expected to be 52 weeks), and multiplying this number by 100.

6.1.5.3 Smartphone application symptom responses

Participant responses to the symptom questions were collated and reported at the completion of the study period.

6.1.5.4 System usability – System Usability Scale

The System Usability Scale (SUS) (160) is an assessment tool comprising 10 questions regarding the usability of technological systems, and is answered on a 5-point Likert scale (discussed in Section 5.1.4.1).

6.1.5.5 Spirometry

Spirometry (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]) was measured using a Medgraphics USB spirometer (MGC Diagnostics, Minnesota, USA), or Easyone spirometer (ndd Medical Technologies, Massachusetts, USA). Each participant performed up to eight maximal forced expiratory manoeuvres to ensure the two best attempts met published standards (152). The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted FEV_1 ($ppFEV_1$) and percentage predicted FVC (ppFVC).

6.1.5.6 Nutritional status - body mass index

Participants had their height (CE0123, Seca, Hamburg) and weight (UC-321, A&D Company, Tokyo) measured and body mass index (BMI) was calculated.

6.1.5.7 Health-related quality of life – Cystic Fibrosis Questionnaire – Revised

This self-completed questionnaire comprises 50 questions answered on a 4-point Likert scale. It covers 12 domains comprising physical, vitality, emotion, treatment burden, health, social, body, role, weight, respiratory, digestion and eating (107).

6.1.5.8 Feelings of anxiety and depression – Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (108) contains 14 self-reported questions, evenly divided into anxiety and depression scales (7 each). A 4-point Likert scale (0 to 3) is used to answer questions based on a recall period of 7 days.

6.1.5.9 Treatment adherence – Treatment Adherence Questionnaire – Cystic Fibrosis

Adherence to routine CF treatments was assessed using the Treatment Adherence Questionnaire – Cystic Fibrosis (TAQ-CF) (167). This measure has 12 treatment items and asks the user to report on the frequency of each treatment on a 7-point Likert scale (ranging from “not at all” to “3 or more times per day”), and the duration of treatment on a 6-point Likert scale (“0” to “25+” minutes). The TAQ-CF also asks the participant to report on the barriers to individual treatments. The wording of certain medications and barriers was adjusted to be relevant to an Australian CF cohort (Appendix 10).

6.1.5.10 Absenteeism/presenteeism – World Health Organisation’s Heath and Work Performance Questionnaire

Absenteeism is defined as being absent from work or study due to illness whereas presenteeism is defined as the loss of productivity associated with attending work or study when unwell (168). This questionnaire uses the absenteeism and presenteeism questions of the World Health Organisation’s Heath and Work Performance Questionnaire (HPQ) (158) (discussed in Section 4.4.1.1).

6.1.6 Intervention group

An app was developed for use by participants in the intervention group to report respiratory symptoms on their own smartphones. The application contained 14 questions (Table 6.4) that are required to be answered 'yes' or 'no'. Twelve questions relate to respiratory symptoms; 10 questions were derived from the Fuchs exacerbation scale (18), with the addition of two symptoms (wheeze and chest tightness) commonly identified by adults with CF as indicators of a respiratory exacerbation (95) and considered important by the research team. The application also asked the participant to answer two questions relating to their feelings of anxiety and depression. The data were then transmitted securely via password protected email to members of the research team. The app was demonstrated to have high system usability in people with CF, as well as good observer agreement between experienced clinicians interpreting the app data (Chapter 5, Study 3).

Participants were asked to use the app once per week on a set day and time of their choosing, for a period of 12 months. A smartphone calendar alert was set by each participant to remind them to answer the symptom questions. Participants could also use the app earlier than the next weekly reporting time if they felt their respiratory symptoms had worsened. If the participant missed one of their weekly reporting times, they were messaged at the end of the week to remind them to answer the app questions the following week. If the participant responded 'yes' to any of the symptom questions, the principal investigator alerted the nurse practitioner, who then phoned the participant to discuss their respiratory symptoms and whether treatment (i.e. antibiotics) were required, in consultation with a physician. The nurse practitioner also determined if a formal review in the CF clinic was required. Both the nurse practitioner and physician were blinded to group allocation. If the participant's respiratory disease had been stable for 3 months (i.e. no increase in any respiratory symptoms), they were asked to attend a CF clinic as per standard of care guidelines (4).

6.1.7 Control group

Participants in this group continued to receive usual care, involving routine CF clinic appointments (approximately 3-monthly). Participants were able to contact the nurse practitioner via telephone sooner if there was a change in their clinical status.

6.1.8 Analyses

Statistical analyses were undertaken with Stata (StataCorp, Stata Statistical Software Release: V.14) in accordance with the intention-to-treat principle (169). Categorical data are presented as frequencies and proportions. Continuous data and count are presented as medians and ranges due to skewed distributions. General linear mixed models were used to examine continuous outcomes with normal distributions. Healthcare utilisation data are presented as count data with skewed distributions. Negative binomial regression was used to examine differences between groups for HCU, with this model chosen over Poisson as the data were over dispersed. Models were adjusted for baseline variables of sex, $ppFEV_1$, and courses of IV antibiotics in the preceding 12 months. Kaplan-Meier and Cox regression were used to compare time to detection of respiratory exacerbation. Where possible, point estimates are reported with their corresponding 95% confidence interval (CI). Alpha was set at 0.05.

6.1.8.1 Sample size calculation

To detect a between-group difference ($\alpha = 0.05$, $1 - \beta = 0.8$) in the number of IV antibiotic courses of one per participant, assuming a standard deviation (SD) of 1.21 (based on IV antibiotic usage at the SCGH CF Centre during 2013 and 2014), a sample size of 23 in each group was required. To account for any loss to follow-up or drop out, it was proposed to recruit seven additional participants to each group, for a total sample size of 60.

6.1.9 Data privacy

Data from the app were transmitted securely via password-protected email to members of the research team at SCGH, and not kept in ‘cloud’ storage. After transmission from the participant’s phone or tablet, the data were automatically deleted, preventing any potential

breach of privacy if the device was lost or stolen. The application also requested the user to enter a unique, 4-digit passcode before being able to access the app questions.

6.2 Results

6.2.1 Participant characteristics

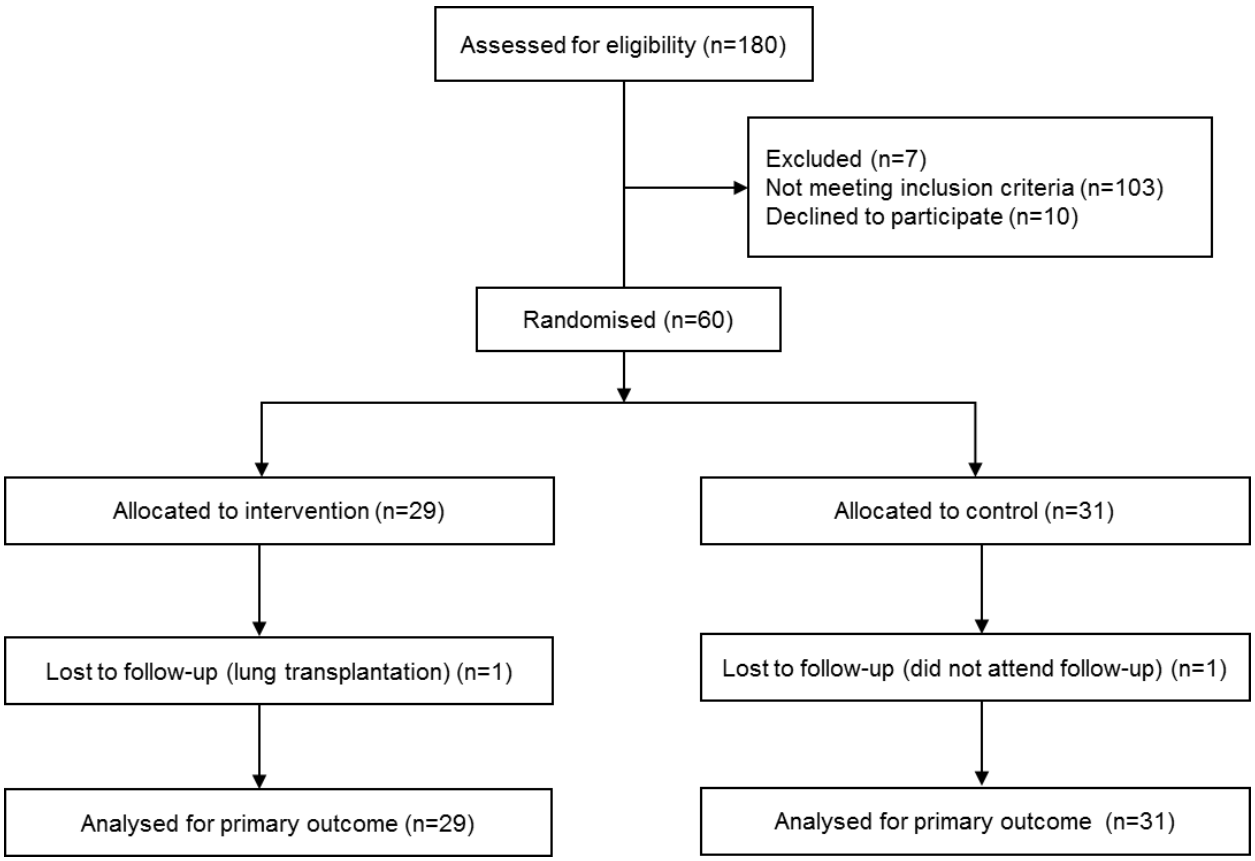
Of the 180 patients attending the CF centre at the commencement of the study, 70 (39%) met the inclusion criteria and were invited to participate in the study. The most common reason for a potential participant to be ineligible for the study was not having had a respiratory exacerbation requiring IV antibiotics in the preceding 12 months. Sixty participants were enrolled in the study (Table 6.1), with 29 (48%) allocated to the intervention group. One (3%) participant in the control group did not attend the 6- or 12-month study visits, and one participant in the intervention group received lung transplantation prior to the 12-month assessment (Figure 6.1).

Table 6.1 Participants' characteristics at baseline (n = 60)

	Intervention	Control
Participants, n (%)	29 (48)	31 (52)
Female, n (%)	17 (59)	12 (39)
Age, yr	31 (10)	31 (8)
FEV_1 (L)	2.07 (0.85)	2.41 (0.82)
$ppFEV_1$	58 (18)	61 (17)
FVC (L)	3.06 (1.04)	3.68 (1.03)
ppFVC	71 (16)	78 (14)
BMI, kg/m^2	22.4 (5.0)	23.4 (2.9)
CFQ-R respiratory domain	67 (17)	71 (16)
IV antibiotics courses in past 12 months, n	60	45
Living in a rural / remote region, n (%)	4 (14)	6 (19)
Pseudomonas aeruginosa, n (%)	29 (100)	30 (97)
CF-related diabetes, n (%)	5 (17)	13 (42)
Pancreatic insufficiency, n (%)	23 (79)	29 (93)
Ivacaftor or Lumacaftor/Ivacaftor, n (%)	8 (28)	9 (29)

Data are presented as mean (SD) unless otherwise stated. BMI = body mass index, CFQ-R = Cystic Fibrosis Questionnaire – Revised, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IV = intravenous, pp = % predicted. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted $ppFEV_1$ and ppFVC.

Figure 6.1 Consolidated Standards of Reporting Trials (CONSORT) diagram



6.2.2 Number of courses of intravenous antibiotics and intravenous antibiotic days

Following adjustment for the courses of IV antibiotics in the preceding 12 months, sex, and $ppFEV_1$, there was no clear effect of the intervention on the number of courses and days of IV antibiotics per participant over the 12 month study period (Table 6.2).

6.2.3 Secondary outcomes

6.2.3.1 Other measures of healthcare utilisation

Over the 12 month study period, there was no clear effect of the intervention on the time to detection of a respiratory exacerbation requiring IV antibiotics, being a median (interquartile range [IQR]) of 186 (298) vs. 273 (184) days in the control group (p = 0.20; Figure 6.2). The time to detection of a respiratory exacerbation requiring oral or IV antibiotics was shorter in the intervention group compared to the control group with a median (IQR) of 70 (123) versus 141 (140) days, respectively (p = 0.02; Figure 6.2).

There was evidence to support an increase in the prescription of oral antibiotics in the intervention group, but not in the prescription of inhaled antibiotics (Table 6.2). There was no clear effect of the intervention on the number of hospital admissions, admission days and number of CF clinics attended (Table 6.2). Participants in the intervention group communicated via phone with the nurse practitioner a median (IQR) of 7 (8) times during the study, compared to 3 (4) times (p = 0.01) for participants in the control group. After adjusting for baseline variables, there was no clear evidence to support a difference in HCU costs (antibiotics, admission days and CF clinics) between the two groups (Table 6.3).

Table 6.2 Participants' (n = 60) healthcare utilisation data

	Intervention (n = 29)		Control (n = 31)			
	Nº	per participant	Nº	per participant	IRR	95% CI
IV antibiotic courses	42	1 (0 to 4)	30	1 (0 to 6)	1	0.6 to 1.7
IV antibiotic days	609	14 (0 to 64)	468	14 (0 to 105)	1.1	0.5 to 2.6
Oral antibiotic courses	71	2 (0 to 8)	46	1 (0 to 5)	1.5	1.0 to 2.2
Inhaled antibiotic courses	24	0 (0 to 4)	18	0 (0 to 4)	1	0.7 to 1.4
Hospital admissions	27	1 (0 to 4)	21	0 (0 to 5)	1	0.5 to 2.0
Admission days	244	4 (0 to 44)	214	0 (0 to 57)	0.9	0.5 to 2.0
CF clinics attended	249	9 (1 to 21)	216	6 (1 to 22)	1.1	0.8 to 1.4

Data are presented as number (Nº) and median (range) per participant. Analyses performed using negative binomial regression, adjusted for sex, forced expiratory volume in 1 second percentage predicted, and courses of IV antibiotics in the preceding 12 months, measured prior to randomisation. CI = confidence interval. IRR = incidence rate ratio. IV = intravenous.

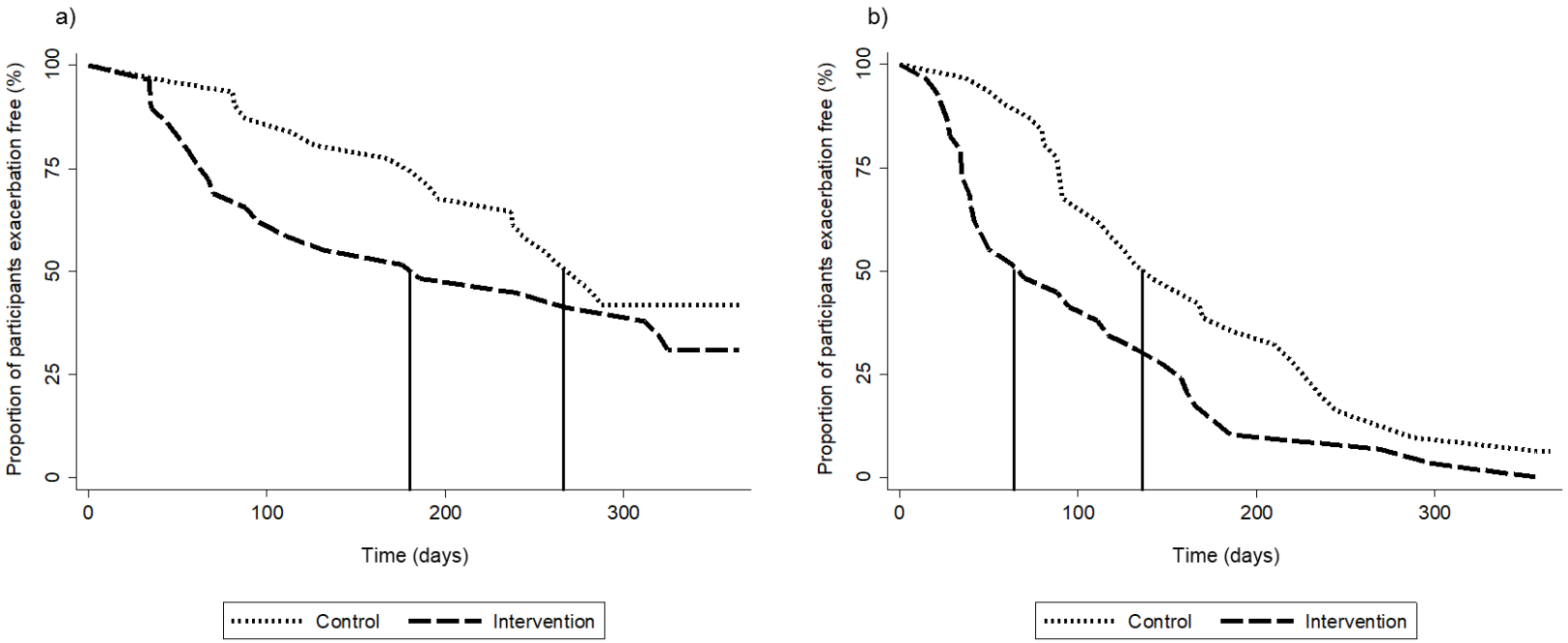


Figure 6.2 Time to detection of respiratory exacerbation requiring a) intravenous antibiotics; and b) oral or intravenous antibiotics plotted against time (days).

Data are presented as the proportion (%) of participants. Analyses performed using Kaplan-Meier, Cox regression.

a) No difference in time to detection of respiratory exacerbation requiring intravenous (IV) antibiotics between the intervention (n = 29) and control (n = 31) groups (median ([IQR] of 186 [298] vs. 273 [184] days, respectively), p = 0.20;

b) Shorter time to detection of respiratory exacerbation requiring oral or IV antibiotics between the intervention and control groups (median [IQR] of 70 [123] vs. 141 [140] days, respectively), p = 0.02.

Table 6.3 Healthcare utilisation costs

	Intervention (n = 29)		Control (n = 31)			
	Cost	per participant	Cost	per participant	IRR	95% CI
Antibiotics	$111,871	$3,858 ($6 to $29,452)	$48,939	$1,579 ($0 to $12,598)	1.1	0.6 to 2.1
Admission days	$319,303	$11,010 ($0 to $57,579)	$280,044	$9,034 ($0 to $75,591)	0.8	0.3 to 2.2
CF clinics	$164,741	$5,681 ($662 to $13,894)	$142,908	$4610 ($662 to $14,555)	1.0	0.7 to 1.4

Data are presented as total or mean (range) in Australian dollars. Antibiotic costs were provided by the Sir Charles Gairdner Hospital (SCGH) Pharmacy Department. Admission days and CF clinic costs were provided by the SCGH Department of Activity Based Costing. Analyses performed using Poisson regression, adjusted for sex, forced expiratory volume in 1 second and courses of intravenous antibiotics in the preceding 12 months, measured prior to randomisation. CI = confidence interval, IRR = incident rate ratio.

6.2.3.2 Smartphone application adherence

Adherence to the weekly use of the app was a mean (range) of 77 (25 to 100)%, with 1,136 of a possible 1,483 reporting occasions completed. Subgroup analysis demonstrated an increase in oral antibiotic prescription and reduction in IV antibiotic prescription compared with the 12 months preceding the study for participants in the intervention group with adherence ≥ 80% (n = 15) (Figure 6.3).

6.2.3.3 Smartphone application symptom responses

Of the completed reporting occasions whilst using the app, participants in the intervention group reported an increase in at least one symptom 399 (35%) times (median [range] 10 [1 to 44]) per participant). Oral or IV antibiotics were subsequently prescribed on 113 (28%) of these occasions. The most commonly reported symptoms were increased cough, increased fatigue or lethargy, and worsening sputum volume or colour (Table 6.4).

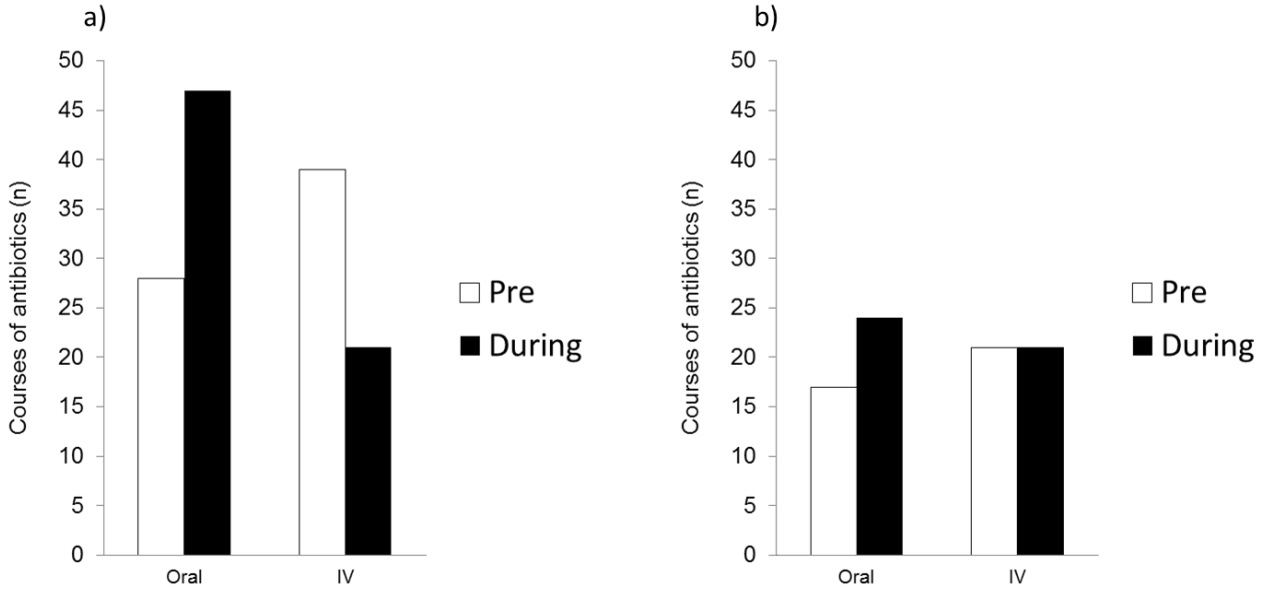


Figure 6.3 Intravenous and oral antibiotic use in the 12 months prior to randomisation and during the study for a) participants in the intervention group who were ≥ 80% (n = 15); and b) < 80% adherent (n = 14) to the weekly use of the smartphone application

Data are presented as the total number of courses. Analyses performed using negative binomial regression. IV = intravenous.

a) An increase in oral antibiotic prescription (p = 0.02) and reduction in IV antibiotic prescription (p = 0.03) was observed during the intervention;

b) No change in oral or IV antibiotic prescription during the intervention.

Table 6.4 Smartphone application questions and response data for participants in the intervention group (n = 29)

In the past week, have you had:	Nº	per participant
Worsening sputum volume or change in colour?	144	3 (0 to 22)
New or increased blood in your sputum?	50	0 (0 to 10)
Increased cough?	184	5 (1 to 28)
New or increased chest pain?	53	1 (0 to 20)
New or increased wheeze?	101	2 (0 to 25)
New or increased chest tightness?	124	2 (0 to 20)
Increased shortness of breath or difficulty breathing?	124	3 (0 to 19)
Increased fatigue or lethargy?	171	4 (0 to 28)
A fever?	39	0 (0 to 18)
Loss of appetite or weight?	52	1 (0 to 7)
Sinus pain or tenderness?	75	1 (0 to 19)
In the past week do you feel that your health has worsened?	143	4 (0 to 22)
In the past week, have you felt:		
Low in mood?	78	1 (0 to 19)
Worried?	79	1 (0 to 24)

Questions required a 'yes/no' response. Data are presented as the total number (Nº) of times each question had a 'yes' response, and the median (range) per participant.

6.2.3.4 Other secondary outcomes

The mean (SD) SUS score for the app at 6 and 12 months was 87 (13) and 89 (13), respectively. There was no clear evidence that use of the app affected spirometry (Table 6.5), nutritional status (Table 6.5), HRQoL (Table 6.6), or feelings of anxiety and depression (Table 6.7).

There was no clear evidence that use of the app affected treatment adherence (Table 6.8). The most common reasons reported by all participants for ‘What is getting in the way?’ of treatment were “I couldn’t find the time” (34 [57%]), “I forgot to do it” (34 [57%]), “I don’t think I need it” (18 [30%]), “I don’t want to do it” (12 [20%]) and “I experience side effects” (9 [15%]).

There was no clear evidence that use of the app affected absenteeism and presenteeism (

Table 6.9). Most participants (87%) were engaged in employment on at least one occasion throughout the 12-month study period. The proportion of participants engaged in employment on at least one occasion was similar between the intervention (90%) and control groups (84%).

Table 6.5 Spirometry and body mass index measured prior to randomisation and 12 months following randomisation

	Intervention		Control		
	Prior to randomisation (n = 29)	12 months following randomisation (n = 28)	Prior to randomisation (n = 31)	12 months following randomisation (n = 30)	Mean diff. in change (95% CI)
FEV_1, L	2.07 (0.85)	2.03 (0.88)	2.41 (0.82)	2.28 (0.86)	0.08 (-0.08 to 0.15)
$ppFEV_1$	58 (18)	56 (19)	61 (17)	58 (18)	1 (-2 to 4)
FVC, L	3.06 (1.04)	3.07 (1.11)	3.68 (1.03)	3.50 (1.11)	0.17 (-0.05 to 0.27)
ppFVC	71 (16)	71 (16)	77 (14)	74 (15)	3 (-1 to 6)
BMI, kg/m^2	22.4 (5.0)	21.9 (6.3)	23.4 (2.9)	24.0 (2.7)	-1.1 (-2.4 to 0.2)

Data are presented as mean (SD). Analyses performed using general linear mixed models. BMI = body mass index, CI = confidence interval, diff. = difference, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, pp = percentage predicted. The Global Lung Function Initiative 2012 equations (151) were used to calculate percentage predicted $ppFEV_1$ and ppFVC.

Table 6.6 Participant responses to the Cystic Fibrosis Questionnaire-Revised measured prior to randomisation and 12 months following randomisation

	Intervention		Control		
	Prior to randomisation (n = 29)	12 months following randomisation (n = 28)	Prior to randomisation (n = 31)	12 months following randomisation (n = 30)	Mean diff. in change (95% CI)
Physical functioning	70 (26)	73 (22)	70 (26)	74 (25)	-3 (-11 to 5)
Vitality	55 (16)	55 (17)	58 (17)	52 (20)	6 (-3 to 15)
Emotional functioning	79 (14)	82 (14)	77 (17)	79 (15)	1 (-6 to 7)
Eating	92 (13)	92 (16)	93 (12)	96 (11)	-3 (-8 to 2)
Treatment burden	56 (22)	58 (19)	57 (16)	58 (18)	1 (-8 to 9)
Health perceptions	62 (19)	64 (18)	63 (20)	63 (19)	2 (-7 to 9)
Social	75 (15)	71 (16)	65 (16)	67 (18)	-6 (-13 to 1)
Body Image	66 (29)	67 (29)	75 (24)	80 (24)	-4 (-12 to 4)
Role	83 (14)	84 (17)	79 (20)	81 (18)	-1 (-9 to 6)
Weight	67 (41)	62 (42)	82 (28)	89 (20)	-12 (-22 to 3)
Respiratory symptoms	67 (17)	65 (17)	71 (16)	65 (18)	4 (-5 to 11)
Digestive symptoms	82 (19)	85 (15)	86 (15)	88 (12)	1 (-8 to 9)

Data are presented as mean (SD). An increase in score represents improvement, with a maximum score of 100. Analyses performed using general linear mixed models. CI = confidence interval, CFQ-R = Cystic Fibrosis Questionnaire – Revised, Diff. = difference.

Table 6.7 Participant responses to the Hospital Anxiety and Depression Scale prior to randomisation and 12 months following randomisation

	Intervention		Control		
	Prior to randomisation (n = 29)	12 months following randomisation (n = 28)	Prior to randomisation (n = 31)	12 months following randomisation (n = 30)	Mean diff. in change (95% CI)
Feelings of anxiety	5 (6)	3.5 (6)	4 (5)	4.5 (4)	2 (-2 to 1)
Feelings of depression	2 (4)	2 (3)	3 (4)	2 (4)	-1 (-1 to 1)

Data are presented as mean (SD). A decrease in score represents improvement, with a maximum score of 21. Analyses performed using general linear mixed models. BMI = body mass index. CI = confidence interval, diff. = difference.

Table 6.8 Treatment Adherence Questionnaire – Cystic Fibrosis scores for participants with complete data prior to and 12 months following randomisation

	Intervention (n = 26)		Control (n = 30)		
	Prior to randomisation	12 months following randomisation	Prior to randomisation	12 months following randomisation	Mean diff. in change (95% CI)
Treatments/week (n)	89 (25 to 132)	85 (17 to 133)	85 (42 to 161)	77 (23 to 133)	4 (-9 to 15)
Total time/week (min)	1582 (0 to 6290)	1858 (20 to 4340)	1640 (260 to 7765)	1332 (60 to 3465)	584 (-283 to 1446)

Data are presented as number (range) or minutes (range). Treatments/week represents the total number of treatments completed over a one-week period. Total time/week represents the number of treatments per week multiplied by the time taken to complete each treatment according to participants' responses. Analyses performed using general linear mixed models.

Table 6.9 Absenteeism and presenteeism scores for participants with complete data prior to and 12 months following randomisation

	Intervention (n = 26)		Control (n = 26)		
	Prior to randomisation	12 months following randomisation	Prior to randomisation	12 months following randomisation	Mean diff. in change (95% CI)
Relative absenteeism	0.0 (0.8)	0.0 (0.8)	0.1 (0.3)	0.1 (0.2)	0.0 (-0.5 to 0.4)
Relative presenteeism	1.1 (0.4)	1.0 (0.1)	1.1 (0.4)	1.1 (0.2)	-0.1 (-0.4 to 0.0)

Data are presented as mean (SD). Relative absenteeism is the percentage of time absent from work. A maximum score of 1 indicates 100% absenteeism; a score of 0 indicates no absenteeism. Negative scores indicate the hours worked exceeded employer's expectations. Relative presenteeism is self-rated work performance compared to others in similar employment. A score of 1 represents equal performance, 0 represents worst performance, and a maximum score of 2 represents performance at least twice as good as colleagues. Analyses performed using general linear mixed models. CI = confidence interval, diff. = mean difference.

6.3 Discussion

For adults with CF, a novel app was developed for reporting symptoms suggestive of a respiratory exacerbation its effect on the number of respiratory exacerbations requiring IV antibiotics and other health outcomes was investigated. Adherence to the weekly use of the app by participants in the intervention group was much greater than reported in previous telehealth studies in people with CF (21, 22, 24, 25, 96), and system usability was maintained above 85% at both 6 and 12 months. The 95% CI for between-group differences in the number of respiratory exacerbations requiring IV antibiotics suggested there was no effect of the intervention on this outcome. However, respiratory exacerbations requiring oral or IV antibiotics were detected earlier, and there was an increased prescription of oral antibiotics in the intervention group. There was no clear effect of the use of the app on other aspects of HCU, spirometry, nutritional status, HRQoL or feelings of anxiety and depression, treatment adherence or absenteeism and presenteeism.

The level of adherence (77%) to the use of the app was somewhat better than earlier work that has investigated home monitoring interventions for people with CF, in which adherence has ranged from 10% to 67% (21, 22, 24, 25, 96). Any intervention that is inconvenient and time consuming will likely have poorer adherence, given it is in addition to the already large treatment burden that people with CF experience (71). Adherence in the present study did vary though, with 14 (48%) participants using the app less than 80% of the required weeks. Sub-group analyses suggested that those participants in the intervention group who were more adherent (≥ 80%) to the weekly use of the app experienced an increase in oral antibiotic use and a concurrent reduction in IV antibiotic use. Further investigation is needed to determine the characteristics of participants likely to have better adherence to apps and other monitoring interventions so that prospective studies can determine the effectiveness in this sub-group.

The high usability of this app is further supported by the low attrition from the intervention group (3%). This is considerably less than earlier studies of telehealth interventions in a CF population, in which attrition ranged from 24% to 63% (21, 22, 24, 25). The level of adherence

and low attrition in this study is likely attributed to the use of smartphones, a small and portable technology already incorporated into the lifestyle of the participants, and the once weekly reporting requirement. The usability scores at both 6 and 12 months reflected those observed in the previous usability study for this app (Chapter 5, Study 3, Part A). High usability was maintained through to 12 months, indicating that the app is a potential longer-term solution within routine clinical care.

The earlier detection of respiratory exacerbations and increased provision of oral antibiotics in the intervention group did not translate into an important reduction in the number of courses of IV antibiotics. The greater number of courses of IV antibiotics prescribed in the intervention group was consistent with the number of courses seen in the preceding 12 months, and was adjusted for in the analysis. This does raise the question as to whether the early provision of oral antibiotic treatment alone can translate into a reduction in the need for IV antibiotics, and also highlights the limited treatment options available for clinicians when treating respiratory exacerbations. Likewise, as noted for the difference in IV antibiotics, these data demonstrate no differences between groups in secondary outcomes such as aspects of healthcare costs, spirometry, nutritional status, HRQoL, feelings of anxiety and depression, treatment adherence and absenteeism and presenteeism. Despite this finding, it is encouraging that the app provided a means of earlier detection of respiratory exacerbations, and if implemented over a longer surveillance period (e.g. 3 years), this may provide clearer answers regarding the potential longer-term benefits such as slowing the magnitude of decline in lung function.

The most common respiratory symptoms reported in the present study were cough, sputum, fatigue, shortness of breath and chest tightness, mirroring those previously reported as being triggers for seeking treatment for a respiratory exacerbation by children and adults with CF (95). Most of the symptoms included in the app questions were adapted from Fuchs exacerbation scale (18), but of note the symptom ‘chest tightness’ was included as it has been previously reported by people with CF as being commonly associated with respiratory exacerbations (95). As there is no universal agreement on how to diagnose a respiratory exacerbation in this

population (82, 83, 86), the pragmatic decision was made to mirror clinical practice and rely on symptom reporting alone as the first line of detection.

It was surprising to see that, when compared with the 12 months preceding enrolment, there was a reduction in the number of courses of IV antibiotics in both groups during the 12-month study period. While this may simply reflect a spurious finding, it is likely that participating in a study of this kind led to increased contact with the CF centre and potentially offered greater opportunity for people to collect prescriptions from the hospital pharmacy. Participants in both groups attended a higher number of CF clinics than are currently recommended (i.e. 4 per year) (4); therefore involvement in the study seems to have improved access to care for all participants. The single centre design of this study is a limitation in the ability to generalise the results to other CF centres, and a larger multicentre study is now warranted.

Monitoring with smartphone spirometry was not included because of the increased burden on the participant, which would most likely have compromised adherence. Future studies planning to add additional technology to supplement data obtained from the app must carefully consider the benefit vs. the risk to adherence. The use of other readily available smartphone technologies, such as measurements of daily steps may be a useful addition as physical activity may decline during respiratory exacerbations, and these data can be collected with minimal additional burden to the user.

It is also possible that once weekly reporting of symptoms was insufficient and that increased frequency may be helpful. That is, with more frequent reporting of symptoms, respiratory exacerbations may be detected earlier than in the present study. Given the high level of adherence observed with weekly reporting, there is scope to increase this to two or three times per week; however, the impact of increasing the frequency of reporting on adherence will need careful evaluation.

In summary, this is the first app used by adults with CF to report their respiratory symptoms directly to the CF team. The high level of adherence is attributed to the low reporting burden and use of technology already owned by participants. Provision of the app facilitated the earlier

detection of respiratory exacerbations and treatment in the form of oral antibiotics. While the data did not demonstrate an effect on the number of courses of IV antibiotics for the participants over a 12-month period, this study supports the continued development and investigation of similar apps and technologies used to identify respiratory exacerbations, with the aim of improving long-term health outcomes.

CHAPTER 7

SUMMARY AND CONCLUSIONS

This chapter summarises the findings and draws conclusions from the studies conducted within this programme of research. The summary and conclusions are presented in three sections, corresponding with those presented in the Introduction (Chapter 1). Finally, future directions and the implications for further research in this field are discussed.

7.1 Telehealth for adults with cystic fibrosis living in rural and remote Western Australia

In this study, the difference in magnitude of decline in forced expiratory volume in 1 second (FEV_1) was investigated between adults with cystic fibrosis (CF) living in rural and remote Western Australia (WA) and their metropolitan counterparts. An audit was conducted over a 3-year period for all eligible adults with CF living in WA (n = 156), with the magnitude of decline calculated based on spirometry collected at CF clinic attended during this period.

No clear effect on the magnitude of decline of spirometry measures was demonstrated, however this was most likely explained by the modest sample size (n = 156), especially for those living in rural and remote WA (n = 26). Despite this, the results of this study highlighted the poor access to care and clinic attendance amongst adults with CF in rural and remote WA, with the mean (range) number of CF clinics attended per participant over 3 years (8 [2 to 24]) falling well below the Australian CF Standards of Care guideline of a minimum of four CF clinics per year (i.e. 12 over 3 years) (4). In contrast, for those living in the Perth metropolitan area, this recommendation was exceeded with the number of CF clinics attended per participant over 3 years (21 [3 to 58]). The reduced level of surveillance observed for those in rural and remote areas may lead to the CF team missing opportunities to identify respiratory exacerbations and provide essential antibiotic treatment. This provides a sound argument for the need for improved access to care and disease monitoring via telehealth in adults with CF living in rural and remote WA.

Telehealth clinics (via videoconferencing) were implemented as part of the routine outpatient care for people with CF living in rural and remote WA, and uptake and satisfaction was evaluated. Uptake was high, with CF clinic attendance increasing during the study period (median = 5) to meet the recommended standards of care. Satisfaction was also high amongst participants, and most expressed a desire to continue using telehealth as part of routine clinical care. This is not surprising, given the reduced travel burden and time away from home associated with utilising telehealth in this manner.

Telehealth facilitated improved surveillance of participants, resulting in increased antibiotic use and hospital admissions. Rather than telehealth being of detriment to the participants, these data reflected the increased ability of the CF team to detect respiratory exacerbations. The improved detection of respiratory exacerbations may lead to improved longer-term health outcomes (FEV_1, nutritional status and health-related quality of life [HRQoL]) if maintained over a much longer timeframe (i.e. 5 to 10 years).

People with CF have been previously found to be willing to utilise telehealth technology (142), which is supported by the results of this study. Nevertheless, clinicians need to recognise that services provided by telehealth are unable to replicate all aspects of an in-person clinic. First, telehealth removes the ability of the clinician to perform physical assessments such as palpation and auscultation. Second, participants in rural and remote areas have historically had limited access to on-site specialist secondary services (e.g. intravascular access, endocrinology, immunology and hepatology), and may also have no access to imaging equipment such as computed tomography and magnetic resonance imaging. Third, a service that can provide spirometry may not be available in many areas of low population density throughout the world, potentially limiting the information available for clinical decision making.

Telehealth has a promising role in the delivery of care to people with CF in rural and remote areas. By removing the need to travel to the CF centre for all CF clinics, people with CF can reduce their travel, time and financial burden. If utilised by the CF team in a manner that recognises both the strengths and limitations of this type of system, the use of telehealth in the provision of CF clinics will be beneficial to both people with CF and the healthcare system.

7.2 The working profile of adults with cystic fibrosis living in rural and remote Western Australia

This study was an opportunistic sub-analysis of data collected from those participants who enrolled in the study investigating the provision of CF clinics via telehealth. The results demonstrated that most adults with CF living in rural and remote WA engaged in paid work during the 12-month study period.

The impact of CF on work attendance (absenteeism) and performance (presenteeism) was variable. While this may be due to the variable impact of CF on the participants in general, the results may also have been affected by the small sample size and variability in employment undertaken (e.g. administration, retail, information technology, and healthcare). It is encouraging that, on average, participants felt that they performed as well as their colleagues when at work. It would be useful to know further details about the impact of CF on the participants who reported high absenteeism and low presenteeism.

The use of absenteeism and presenteeism is a novel outcome measure in CF, and its measurement can provide a useful insight into the disease-related impact on work attendance and performance. If appropriate, future studies should consider capturing these data to measure the impact of interventions on the ability of people with CF to engage in employment, especially considering the increasing proportion of adults living with CF (31, 33).

7.3 A smartphone application for reporting respiratory symptoms in adults with cystic fibrosis

Studies that have explored the effect of home monitoring interventions in CF have been plagued by sub-optimal adherence to the monitoring system. This has been a result of the high reporting burden (up to daily), and the monitoring equipment being large and not mobile outside of the home. The smartphone application (app) described in this study overcame this limitation, as it was small and portable, required only weekly use, and integrated easily with the lifestyle of adults with CF. The system did not include spirometry which may improve the accuracy of diagnosis of respiratory exacerbations, however this would have increased costs, and increased the reporting burden amongst participants. The inclusion of spirometry may potentially compromise adherence in future versions of the system.

The usability of the app was rated as high by participants, and importantly, the symptom responses from the app were interpreted in a similar way by clinicians experienced in the process of clinical decision making within CF care.

The use of an app for the purpose of reporting symptoms suits the demographic profile of the adult CF population. A quick-to-use, convenient and low-burden tool is also ideal given the heavy treatment and lifestyle burden that people with CF already experience. While the usability study was of short duration with a small sample, the results provided encouragement for further investigation of the impact of the app on health outcomes. Specifically, it was important to ascertain whether using the app can improve the detection of respiratory exacerbations and reduce the time taken to provide antibiotic treatment.

The randomised controlled trial (RCT) undertaken was the first to examine the impact of an app used by adults with CF to report respiratory symptoms to the CF team. The aim was to improve the detection of respiratory exacerbations, facilitating the earlier provision of treatment, which in turn may reduce the severity of exacerbations. Despite good adherence (77%) to the weekly use of the app, and the faster detection of respiratory exacerbations requiring oral or IV antibiotics for those in the intervention group, there was no effect of the intervention on the

number of exacerbations requiring IV antibiotics. The question needs to be raised as to whether the provision of oral antibiotic treatment alone as the first line of respiratory exacerbation treatment can translate into a reduction in the need for IV antibiotics and improved health outcomes in the longer-term. There was also no clear effect of the app on other outcomes including other aspects of HCU, spirometry, nutritional status, HRQoL or feelings of anxiety and depression, treatment adherence or absenteeism and presenteeism.

The level of adherence observed with use of the app was somewhat higher than that seen in earlier work in this area, and this matched the high levels of usability demonstrated throughout the entire study period. Further, attrition was extremely low in the intervention group (3%), highlighting that this system was low-burden and acceptable to the adults with CF using it. The app questions took approximately two minutes to complete, and therefore it is unlikely that the perceived reporting burden associated with this would increase in the future. The optimal frequency of reporting has not been determined, and twice per week may be warranted, however care should be taken not to compromise adherence by increasing the required frequency.

The app questions were formulated from respiratory exacerbation criteria used in a previous clinical trial (18) in combination with clinician and patient reported outcomes (95). The definition of a respiratory exacerbation is a contentious issue and not universally agreed (82, 83, 86, 87), and the pragmatic approach taken with this app, and criteria used to define a respiratory exacerbation, mirrors clinical practice around the world (84, 86).

This is the first app designed for use by adults with CF to report their respiratory symptoms directly to the CF team. While the data did not demonstrate a clear effect on the number of courses of IV antibiotics for the participants over a 12-month period, this study supports the continued development and investigation of similar apps and technologies used to identify respiratory exacerbations, with the aim of improving long-term health outcomes.

7.4 Limitations

The studies comprising this work have several limitations that could be addressed for future research efforts. The sample sizes are generally small and the research is single centre in nature. In the present work this was difficult to address given the pragmatic approach and unique CF model of care in Western Australia. The telehealth interventions investigated had better adherence than previously seen in CF studies, and show promise technologies that can be incorporated into routine clinical care; however, they need to be explored in much larger numbers of participants and in different CF clinics, countries and cultures. The level of adherence to the interventions may have been improved by the fact this was research, and that the investigators had a prior relationship with the participants. Longer term studies conducted over several years will provide further clarification on the adherence to, and effectiveness of these interventions in a setting that reflects real life more closely.

The detection of respiratory exacerbations is CF is a contentious topic given the lack of consensus around the definition of an exacerbation. Given that the identification and treatment of an exacerbation in CF is clinician driven, this will influence the interpretation of outcome sin both clinical practice and research. It is therefore important to continue this work in different CF clinics in different areas of the world, to further refine the system so it can provide benefit to all people with CF, and not just those in WA.

7.5 Future directions

This programme of research has demonstrated that telehealth can improve access to care for adults with CF living in rural and remote areas via videoconferencing, and for all adults with CF via an app for reporting respiratory symptoms. The widespread adoption of such technologies in CF care is still in a nascent period, and ongoing evaluation is required to examine their impact on health outcomes, and the cost benefit (i.e. staffing, technology costs, impact on HCU) over longer periods of time. The enthusiasm that can be generated with newer technologies also needs to be met with a sufficient evidence base prior to any widespread adoption. The research presented in this thesis adds to this evidence base with pragmatic solutions to the difficulties experienced with access to care and detecting exacerbations in CF.

One of the major challenges is the difficulty faced in evaluating technologies that are rapidly evolving, as conducting rigorous research using traditional methods (i.e. RCTs) can often take many years and by the time the research is completed the technology may well have been superseded. Despite this, the growing number of technologies and devices available that have the potential to be integrated into CF care warrants enough interest to continue to evaluate their role in the management of this disease. It will be important to not only develop research programs with sufficient numbers of participants and surveillance periods, but to also ensure that the methodologies are appropriate for the technologies being investigated. Considering the role of education and behaviour change as a complimentary mode of treatment to home monitoring technology may also improve the impact of these types of services. Further, utilising similar technologies in other chronic disease groups, such as asthma and chronic obstructive pulmonary disease, will strengthen support for their use in clinical care. This work supports the integration of modern technologies such as videoconferencing and apps with traditional care by CF teams when planning future service delivery.

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Appendix 1

Author attribution statement

Wood, J, Mulrennan, S, Hill, K, Cecins, N, Morey, S, Jenkins, S. Telehealth clinics increase access to care for adults with cystic fibrosis living in rural and remote Western Australia. J Telemed Telecare. 2017;23(7):673–679.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Jamie Wood	✓	✓	✓	✓	✓	40%
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Co-Author 6 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
Total %						**100%**

Wood J, Jenkins S, Mulrennan S, Hill K. The impact of cystic fibrosis on work attendance and performance in adults living in rural and remote Western Australia. J Cyst Fibros. 2017;16(2):e1-e2.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
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Co-Author 4 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
Total %						**100%**

Wood J, Jenkins S, Putrino D, Mulrennan S, Morey S, Cecins N, et al. High usability of a smartphone application for reporting symptoms in adults with cystic fibrosis. J Telemed Telecare. 2017;24(8):547-552.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
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Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
Co-Author 2: Sue Jenkins	✓	✓	✓	✓	✓	15%
Co-Author 2 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
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Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
Co-Author 4: Siobhain Mulrennan	✓			✓	✓	5%
Co-Author 4 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
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Total %						**100%**

Wood J, Jenkins S, Putrino D, Mulrennan S, Morey S, Cecins N, et al. A smartphone application for reporting symptoms in adults with cystic fibrosis: protocol of a randomised controlled trial. BMJ Open. 2018;8(4):e021136.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Jamie Wood	✓		✓	✓	✓	40%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
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Co-Author 3: David Putrino	✓		✓	✓	✓	10%
Co-Author 3 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
Co-Author 4: Siobhain Mulrennan	✓			✓	✓	5%
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Total %						**100%**

Wood J, Jenkins S, Putrino D, Mulrennan S, Morey S, Cecins N, et al. A smartphone application for reporting symptoms in adults with cystic fibrosis improves the detection of exacerbations: Results of a randomised controlled trial. J Cyst Fibros. 2019;S1569-1993(19)30887-2.

Conception and Design	**Acquisition of Data and Method**	**Data Conditioning/ Manipulation**	**Analysis and Statistical Method**	**Interpretation and Discussion**	**Final Approval**	**Total % contribution**
Co-Author 1: Jamie Wood	✓	✓	✓	✓	✓	40%
Co-Author 1 Acknowledgment: I acknowledge that these represent my contribution to the above research output Signed:						
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Total %						**100%**

Appendix 2

Original Article

Telehealth clinics increase access to care for adults with cystic fibrosis living in rural and remote Western Australia

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Abstract

Background: A significant proportion (15%, n=28) of the adults with cystic fibrosis (CF) in Western Australia (WA) live in rural and remote areas and have difficulty accessing specialist care at the state adult CF centre, located in Perth. We aimed to increase access by offering telehealth clinics, and evaluate the impact on health outcomes.

Methods: Telehealth clinics were offered via videoconference over a 12-month period, with uptake and satisfaction measured at the end of the intervention. Participants could still attend in person clinics at the CF centre if requested. Other outcomes comprised healthcare utilisation (HCU), spirometry, weight and health-related quality of life.

Results: In 21 participants, total clinic visits increased from 46 (median [range] per participant 2 [0 to 6]) in the 12-month period preceding the study to 100 (5 [2 to 8] $p<0.001$) during the intervention. Of the 100 clinics in total, 66 were delivered via telehealth. Satisfaction with telehealth was high and most (94%) participants agreed that telehealth is a good way to deliver CF care. An increase in intravenous antibiotic days (incident rate ratio [IRR] 2.3, $p=0.03$) and hospital admission days (IRR 3.7, $p=0.01$) was observed. There was an improvement in the vitality domain of the Cystic Fibrosis Questionnaire – Revised ($p<0.05$).

Conclusion: Telehealth had good uptake and increased clinic attendance in adults with CF living in rural and remote WA, and had high satisfaction amongst participants. The increase in HCU, resulting from increased detection and treatment of exacerbations, may improve long-term outcomes in this population.

Keywords

Telehealth, cystic fibrosis, videoconference, rural and remote, healthcare utilisation.

Introduction

Individuals living in areas of low population density, such as rural and remote areas of Australia, have poorer health outcomes when compared with those living in metropolitan areas.[1] A key contributor to this is reduced access to care, being the inability of an individual to utilise health services that are necessary to improve or maintain their health. This is due in part to the lower numbers of skilled health professionals in these areas, and the large distances needed to travel to specialist healthcare facilities.[2] Of note, earlier work has demonstrated that individuals with cystic fibrosis (CF), who have complex healthcare needs,[3] have poorer health outcomes when not managed in specialist CF centres.[4, 5]

In Western Australia (WA), the state adult specialist CF centre is at Sir Charles Gairdner Hospital (SCGH), in Perth. Of the 190 adults with CF who attend this centre, 28 (15%) live outside Perth, with distances to the centre ranging between 100 and 2,567 km. Due to limited specialist CF resources in these rural and remote areas, adults with CF have previously travelled long distances (via car or plane) to attend their scheduled routine clinics at SCGH. The travel and financial burden for these individuals is a major contributor to their low rates of attendance at clinics. The Australian CF Standards of Care[6] recommend a minimum of four clinic visits per patient per year; however, in the year preceding this study an internal audit revealed that only 22% of adults living in rural and remote WA met this recommendation. Therefore, we sought to explore the use of telehealth in the provision of clinics for adults with CF living in rural and remote WA to improve access to our specialist centre.

Telehealth utilises audio-visual and medical technology to enable remote healthcare, monitoring and rehabilitation of individuals in their home or at a local medical centre. Although previous studies have shown that individuals with CF are willing to utilise telehealth technology,[7] to the best of our knowledge there are no published studies on the feasibility or efficacy of providing clinics via telehealth as part of routine outpatient care in adults with CF living in rural and remote areas. Therefore, the aim of this study was to report on the uptake and participant satisfaction with telehealth clinics for adults with CF living in rural and remote WA, and to evaluate the effect of this service on health outcomes such as healthcare utilisation (HCU), spirometry, weight and health-related quality of life (HRQoL).

Such information is likely to be important because increased clinic attendance at a specialist CF centre by adults with CF who live in rural and remote WA may assist with earlier detection and treatment of respiratory exacerbations, which in turn may slow the rate of decline in spirometry and optimise HRQoL.

Methods

Study design

This was a single group study in which adults with CF who lived in rural and remote WA were invited to utilise telehealth clinics as part of routine care over a 12-month intervention period. Participants were recruited between July 2013 and August 2014. Approval was obtained from the Sir Charles Gairdner Group and Curtin University and all participants provided written informed consent prior to data collection.

Participants

Adults with CF aged 18 years or more and living a minimum of 100km from the specialist CF centre were eligible to participate in this study. Exclusion criteria were pregnancy, previous lung transplantation or current listing for lung transplantation, as individuals meeting these criteria were already required to travel to Perth more frequently for medical care.

Telehealth clinics

We aimed to provide telehealth clinics approximately every three months, or sooner if clinically indicated, for reasons including self-reported acute deterioration in respiratory status or early follow up after a course of intravenous antibiotics (IVAB). Telehealth clinics were scheduled to suit the participants, specialist CF team, regional telehealth coordinators, and a health professional local to the participant (physiotherapist, nurse or general practitioner).

On the day of the telehealth clinic, participants were attended the nearest regional hospital. The participant's height, weight and spirometry were measured by a designated health professional beforehand. Telehealth clinics were held via videoconference using Polycom HDX® series (Polycom, San Jose, USA) equipment at both SCGH and hospitals throughout rural and remote WA. During telehealth clinics, the participant chose whether to be reviewed by each member of the multidisciplinary CF team individually (i.e. consultant physician, nurse practitioner, physiotherapist and dietician) or by the whole team together. A CF pharmacist and social worker were also available to provide input via telephone at a later date if requested by the participant or the team. Following the telehealth clinic, prescriptions were faxed or medications were couriered to the participant's local pharmacy.

Traditional in-person clinics at SCGH were still provided if requested by the participant or if clinically indicated as previously described. We encouraged participants to attend one in-person clinic during the intervention to allow more comprehensive annual review of their clinical status. If a participant required admission to hospital at any time during the study, this was arranged at the specialist CF centre in Perth. Courses of home IVAB were also commenced at the CF centre before the participant returned home. This allowed for intensive medical and allied health input to be provided, as well as access to specialist secondary services such as intravenous access, endocrinology, gastroenterology and immunology.

Outcomes

Uptake of telehealth was measured via the number of telehealth clinic visits. Clinic attendance data, recorded in the participant's medical record, were extracted at the end of the 12-month intervention period and compared with the 12-month period preceding recruitment to the study.

Participant satisfaction with telehealth clinics was measured at the end of the intervention period using two questionnaires; the Telehealth Satisfaction Scale (TeSS)[8] and a purpose developed satisfaction survey. The TeSS is a 10 item questionnaire originally developed to assess patient satisfaction with telehealth in a rural memory clinic.[8] For the purposes of this study, the term 'memory clinic team' was replaced with 'CF team' and the final question "How well the staff answered your questions about the equipment", was omitted as the participants in this study were not required to operate the telehealth equipment. The second survey contained six questions that were answered using a 5-point Likert scale (responses ranging from strongly agree to strongly disagree), and provided the participant with the opportunity to provide further feedback on the telehealth clinics including preference for either telehealth or traditional 'in person' clinics. This survey was piloted in adults with CF (n=5) living in the metropolitan area and minor changes were made to optimise its readability. Both surveys were mailed to participants, and were returned by mail in pre-addressed, postage paid envelopes. The content of the surveys did not allow the researchers to identify the participants.

Healthcare utilisation data (total number of clinics, courses and days of IVAB, courses of inhaled and oral antibiotics [AB], hospital admissions and admission days) were extracted from each participant's medical record at the end of the intervention period and compared with the 12-month period preceding recruitment to the study.

Spirometry (FEV_1 and FVC) was measured according to accepted guidelines[9] using either CPFS/D USB™ (MGC Diagnostics Corporation, St Paul, USA) or Easyone™ (NDD Medical Technologies, Andover, USA) spirometers. Health professionals who performed spirometry had previously received training from a certified respiratory technician. Weight and height were used to calculate body mass index (BMI). Health-related quality of life was collected at each clinic using the Cystic Fibrosis Questionnaire – Revised (CFQ-R).[10]

Analyses

Statistical analyses were conducted using Stata® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All data were checked for normality. Satisfaction data were reported using descriptive statistics. Healthcare utilisation data were compared pre- and during- the 12-month intervention period with Poisson or negative binomial regression. Paired t-tests and Wilcoxon signed rank tests were used to compare spirometry, weight, BMI, and HRQoL data pre- and during- the 12-month intervention period as appropriate. Repeated measures analyses of these secondary outcomes were not undertaken as the study was not powered to detect differences. A p-value of < 0.05 was used to denote statistical significance. As the primary aim of this study was to report the uptake of telehealth clinics amongst all individuals with CF living in rural and remote WA, no sample size calculations were undertaken.

Results

Twenty-three out of a possible 28 (82%) adults with CF living in rural and remote WA were recruited for this study (Table 1). Reasons for not participating were regular travel to Perth for other medical reasons (n=3) and intention to move interstate or overseas within the intervention period (n=2). The distance participants were required to travel to their nearest regional hospital was a median (range) of 5 (1 to 22) km (Table 1). Data from two participants were excluded from the analysis as they moved residence during the intervention period (one to Perth and one internationally). One participant chose to travel to Perth for all clinic visits and did not utilise the telehealth intervention, therefore they were not asked to complete the satisfaction surveys.

Uptake of the telehealth clinics

The 21 participants included in the final analyses attended a total of 100 clinics during the intervention period, of which 66 (66%) were provided via telehealth (Table 2). Four participants (19%) utilised telehealth for all of their clinics, however three of these individuals also had hospital admissions at SCGH during the intervention period, and subsequent in-person contact with CF team at this time. The median (range) number of clinics per participant during the intervention period increased from 2 (0 – 6) to 5 (2 – 8) $p<0.001$ (Table 2). A total of 19 of the 21 participants (90%) attended four or more clinics during the intervention period, compared with 4 (19%) in the previous year. On two occasions, participants did not attend their scheduled telehealth clinic and failed to inform the CF team. Of the 34 in-person clinics where participants attended the specialist CF centre, 19 (56%) were requested by the CF team for clinical indications.

Satisfaction

The TeSS and purpose developed participant satisfaction survey data were available for 17 (81%) participants. The participants' rated all nine items on the TeSS as either 'good' or 'excellent', with the exception of one participant's response to the item relating to the voice quality of the equipment (Table 3).

Results from the purpose developed satisfaction survey (Table 4) showed that 16 (94%) participants strongly agreed or agreed that telehealth clinics were a good way to manage CF care. Ten (59%) participants preferred telehealth clinics for their routine outpatient care.

Healthcare utilisation

During the intervention period, there was an increase in IVAB days, hospital admissions and admission days per participant (Table 2) (all $p<0.05$). The number of courses of IVAB, oral AB and inhaled AB per participant also increased, however this was not significant (Table 4). Of the 25 exacerbations requiring IVAB during the intervention period, 20 (80%) were detected during telehealth clinics.

Spirometry, BMI and HRQoL

No significant changes were seen in spirometry (FEV_1 and FVC) following the intervention. In the 20 participants for whom weight gain was a goal, there was an increase in median (IQR) BMI from 20.9 (4.7) to 21.7 (3.4), however this was not significant (p=0.12). One participant was excluded from the BMI analysis as they were morbidly obese and weight loss was being encouraged. Fourteen (70%) participants gained weight during the intervention, with a mean (SD) increase of 2.2 (2.1) kg, or 3.7 (3.6) %. There was an improvement in the vitality domain (p=0.04) of the CFQ-R, and a trend toward improvement in the weight domain (p=0.06) (Table 5). No changes were observed in other domains of the CFQ-R.

Discussion

This study is the first to evaluate the uptake of telehealth clinics implemented as part of routine outpatient care in individuals with CF living in rural and remote areas. We have demonstrated that telehealth technology increases access to care for these individuals and resulted in 90% of participants meeting the recommended number of clinic visits[6] during the intervention period. Although both telehealth and traditional in-person clinics were offered during the intervention period, participants chose the telehealth option for more than two-thirds of their clinics. One participant did not attend the CF centre (for a clinic or hospital admission) as it was not convenient for them during the intervention period. This is a potential limitation of telehealth, as certain assessments (e.g. bone mineral density, general respiratory function testing and chest computed tomography) are not readily available in all rural and remote areas. While one participant chose not to use the telehealth intervention, the inclusion of their data in measures related to healthcare utilisation provides a more conservative and real world estimate of the effect telehealth had on these outcomes.

The observed increase in antibiotic use and hospital admissions reflects increased surveillance of the participants, and a corresponding increased detection of respiratory exacerbations. Although this short-term increase in HCU was observed, the increased frequency of clinic visits and contact with the clinical team as a result of this telehealth intervention may lead to increased patient adherence and improved longer term health outcomes. Specifically, more frequent contact with the CF team[11] and earlier detection of exacerbations that will allow treatment to be initiated sooner,[12] is likely to slow the rate of decline of FEV_1, and potentially improve nutritional status and HRQoL.

Recruitment for this study was good (over 80%), with only five potential participants not enrolling because they were required to travel to Perth for other medical reasons, or had intentions to move during the intervention period. The most likely explanation for the high recruitment rate is the reduction in travel burden as a result of telehealth, as most of the participants travelled many hours by car or plane to Perth to attend in-person clinics in Perth. It is also likely that our recruitment was influenced by the mean age (31.4 years) of the study sample, as younger adults may be more open to the idea of integrating modern technology into their care. Our study adds support to previous studies reporting that individuals with CF are willing to utilise telehealth technology.[7]

Responses to the TeSS reflected an excellent level of satisfaction with telehealth clinics. The only item given a score less than three (out of four) by a participant was regarding the voice quality of the equipment, which could be attributed to the voice delay occasionally experienced with the system. The TeSS responses demonstrated that participants perceived telehealth clinics to be a highly acceptable method to provide regular healthcare review. However, responses to the purpose developed participant satisfaction survey indicated that some participants (12%) preferred traditional in-person clinics over telehealth clinics and some had no preference (29%). This is understandable given that in-person clinics have been offered for many years and have advantages such as the ability for physical examination, access to on-site specialist secondary services (e.g. intravenous access, endocrinology, immunology and hepatology) and immediate admission to hospital if required.

In keeping with this finding, a meta-analysis of telehealth for Chronic Obstructive Pulmonary Disease found that individuals were largely satisfied with receiving care via telehealth at home, as long as face to face consultations were still available on request.[13] The positive view of telehealth among our participants is consistent with previous telehealth studies in CF,[7] and provides merit to the continuation of its use as part routine CF care. In a home monitoring study measuring feasibility and satisfaction,[14] 80% of participants with CF stated they would opt to continue recording of spirometry, oxygen saturation and symptoms on a daily basis for routine management.

It is difficult to make comparisons between the HCU results of this study and other telehealth studies in CF due to the differences in the interventions and study designs. Weekly videoconferencing with the CF team has previously been utilised by a small number of individuals with CF (n=7) awaiting lung transplantation over a six-month period, and no differences in HCU were found when compared to usual care.[15] Videoconferencing has also been used effectively as a means of assessing functional exercise capacity[16] In 19 individuals with CF from adult and paediatric centres, the monitoring of spirometry and symptoms on a daily basis at home over a six-month resulted in no difference in the number of exacerbations per participant when compared to the same period prior to the study; however an increase in courses of oral AB was noted during the intervention.[17] Another intervention[18] comparing daily monitoring of spirometry and oximetry (n=17) to usual care (n=28) over seven months found no difference in the rate of hospitalisation, but an increase in clinic visits during the intervention period was observed. Despite the differences in study designs across these studies, many share an observed increase in certain measures of HCU.

This study was not powered to detect changes in spirometry (FEV_1 and FVC), and therefore the lack of significant difference in these measures was not unexpected. The increased treatment of exacerbations may explain the improvement in the vitality domain of the CFQ-R, which consists of four questions relating to energy levels. Although the minimal clinically important difference for the vitality domain of the CFQ-R has not been established, the magnitude of change in this domain demonstrated in our study (11 out of 100 points) exceeded the magnitude of change (8 points) reported following 28 days of inhaled Aztreonam Lysine in individuals with CF colonised with Pseudomonas aeruginosa. As the change in HRQoL alongside the improvement in pulmonary function was considered to be clinically meaningful to the participants in this earlier study, it is likely that the improvement seen in our study would also to be perceived as clinically meangingful.[19] The trend towards improvement in the weight domain of the CFQ-R, alongside the weight gain in fourteen (67%) of the participants may reflect an increase in dietetic input delivered during the intervention period, as well as the improved management of respiratory exacerbations. It is well established that in individuals with CF, a loss of appetite and weight are associated with exacerbations[20] and earlier management of such episodes may have minimised weight loss during the intervention period.

This study demonstrated that telehealth clinics are a feasible way to deliver care for individuals with CF living in rural and remote areas, and as a result this service will continue to be offered to adults living in Western Australia. Adults with CF in these areas are willing to utilise this technology and most prefer telehealth clinics over traditional in-person clinics offered at the specialist CF centre at SCGH. There are limitations to our study, such as a small sample and lack of control group, which are also common among many of the published telehealth studies in CF to date.[7] Furthermore, other clinical measures commonly used in CF care such as sputum microbiology, inflammatory and diabetic markers, and chest radiography were not included as outcomes as they were beyond the scope of this study. Given the differences in geography, CF centre resources and government health service provision between states and countries throughout the world, it would be difficult to conduct a multi-centre randomised controlled trial in this area. Therefore, future studies can focus on the evaluation of the longer term implementation of telehealth services as part of routine care, and their impact on a wider range of health outcomes.

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Declaration of Conflicting Interests

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Table 10. Participant (n=23) characteristics at baseline.

Participants, n	23
Female, n (%)	14 (61)
Age, yr	31.4 (10.2)
BMI, kg/m^2	21.1 (18.7 to 58.0) [a]
FEV_1, L	2.08 (0.78)
FEV_1, % predicted	60 (20)
Distance from specialist CF centre, km	417 (100 to 2,567) [a]
Distance from nearest regional hospital, km	5 (1 to 22) [a]
Pseudomonas aeruginosa, n (%)	21 (91)
CF-related diabetes, n (%)	4 (17)
Pancreatic insufficiency, n (%)	21 (91)

Data are presented as mean (SD) unless otherwise stated.

[a] data are presented as median (range).

Table 2. Healthcare utilisation data for participants (n=21) who completed the intervention, comparing the 12-month periods pre- and during telehealth.

	Pre -Telehealth		During Telehealth				
	Nº	per participant	Nº	per participant	IRR	Std. err.	p
Clinics	46	2 (0 to 6)	100	5 (2 to 8)	2.2	0.4	< 0.001
IVAB courses	14	0 (0 to 3)	25	1 (0 to 4)	1.8	0.3	0.08
IVAB days	170	8 (0 to 32)[b]	350	17 (0 to 61)[a]	2.3	0.8	0.03 [a]
Hospital admissions	8	0 (0 to 2)	19	1 (0 to 3)	2.4	1.0	0.04
Admission days	56	3 (0 to 15)[b]	209	10 (0 to 36)[a]	3.7	0.4	0.01 [a]
Oral AB courses	24	1 (0 to 3)[b]	29	1 (0 to 3)[a]	1.2	0.3	0.5
Inhaled AB courses	18	1 (0 to 2)	31	2 (0 to 3)	1.7	0.5	0.07

Data are presented as number (Nº) and median (range). IRR = incidence rate ratio. Std. err. = standard error. Analyses performed using Poisson regression or [a] negative binomial regression.

[b] data are presented as mean (range).

Table 3. Participant (n=17) responses to questions from the TeSS.

Overall, how satisfied were you with:	
The voice quality of the equipment	4 (1 to 4)
The visual quality of the equipment	4 (3 to 4)
Your personal comfort using the telehealth system	4 (3 to 4)
The ease of getting to the telehealth department	4 (3 to 4)
The length of time with the CF team	4 (3 to 4)
The explanation of your treatment by the CF team	4 (3 to 4)
The thoroughness, carefulness and skilfulness of the CF team	4 (3 to 4)
The courtesy, respect, sensitivity, and friendliness of the CF team	4 (3 to 4)
How well your privacy was respected	4 (3 to 4)

Data are presented as median (range). Questions were answered using a 4-point scale: Excellent = 4, Good = 3, Fair = 2, Poor = 1.

Table 4. Participant (n=17) responses to questions from the purpose developed satisfaction survey, with data presented as percentage of participants.

	SA	A	U	D	SD
The organisation of the clinics met my expectations	29	65	6	0	0
The timing of the telehealth clinic appointments were convenient for me	47	53	0	0	0
The healthcare I received during the telehealth clinics met my expectations	35	59	6	0	0
I was able to communicate effectively with the CF team using this technology	35	59	6	0	0
I prefer telehealth clinics over traditional 'face to face' clinics	18	41	29	12	0
Telehealth clinics are a good way to manage my CF care	18	76	6	0	0

Questions were answered using a 5-point Likert scale: SA = Strongly Agree, A = Agree, U = Unsure, D = Disagree, SD = Strongly Disagree.

Table 5. Participant (n=21) responses to the CFQ-R pre - and post - telehealth intervention.

CFQ-R domain	Pre -Telehealth	Post -Telehealth	Difference [c]	p
Physical functioning [a]	71 [33 to 42]	75 [42 to 90]	-	0.64 [b]
Vitality	44 (21)	55 (20)	11 (1 to 22)	0.04
Emotional functioning	69 (23)	71 (19)	2 (-9 to 12)	0.75
Eating [a]	100 [61 to 100]	100 [67 to 100]	-	0.43 [b]
Treatment burden	58 (17)	56 (20)	-2 (-9 to 4)	0.51
Health perceptions	53 (23)	58 (19)	5 (-7 to 17)	0.39
Social	63 (20)	61 (18)	-2 (-8 to 5)	0.56
Body Image	71 (26)	68 (28)	-3 (-14 to 8)	0.56
Role	78 (16)	77 (21)	-1 (-10 to 9)	0.86
Weight [a]	67 [33 to 100]	100 [50 to 100]	-	0.06 [b]
Respiratory symptoms	55 (24)	64 (19)	9 (-3 to 20)	0.13
Digestive symptoms [a]	89 [67 to 100]	89 [67 to 100]	-	0.97 [b]

Data are presented as mean (SD) (normally distributed data) or [a] median [IQR] (non-normally distributed data). An increase in score represents improvement, with a maximum score of 100. Analysis performed using paired t test or [b] Wilcoxon signed rank test.

[c] data are presented as mean (95% CI)

Appendix 3

Letter to the Editor

The impact of cystic fibrosis on work attendance and performance in adults living in rural and remote Western Australia

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Absenteeism; presenteeism; cystic fibrosis; employment; work

Letter to the Editor

The impact of cystic fibrosis on work attendance and performance in adults living in rural and remote Western Australia

Dear Editor,

As the expected age of survival increases, adults with CF will likely stay in the work force for longer. Previous studies have reported that, in adults with CF, employment status is related to age and time spent in hospital [1], lung function and quality of life [2]. While it is known that many (67%) engage in paid employment [3], to our knowledge there is minimal data available regarding the impact that CF has on work attendance (absenteeism) [4] and performance (presenteeism) [5]. At Sir Charles Gairdner Hospital in Perth, we recently evaluated telehealth clinics for adults with CF living in rural and remote Western Australia (WA), and, as part of our study quantified absenteeism and presenteeism.

During outpatient clinic visits (telehealth and in-person) throughout a 12-month period, participants completed the absenteeism and presenteeism questions of the World Health Organisation's Health and Work Performance Questionnaire [6]. This self-reported 11 item questionnaire collects information regarding; (i) expected and actual hours worked during the previous 7 and 28 days, (ii) part or entire days of work missed (for health or holiday), (iii) overtime worked and (iv) perceived work performance (rated out of 10) for the participant and colleagues undertaking similar work. Responses are used to calculate relative absenteeism and relative presenteeism. Relative absenteeism is the percentage of time absent from work. A maximum score of 1 indicates 100% absenteeism; a score of 0 indicates no absenteeism. Negative scores indicate the hours worked exceeded employer's expectations. Relative presenteeism is work performance compared to others in similar employment. A score of 1 represents equal performance, 0 represents worst performance, and a maximum score of 2 represents performance at least twice as good as colleagues.

Twenty-three adults with CF (14 female, aged mean±SD 31±10 years, forced expiratory volume in one second 60±20%predicted, living median [range] 417 [100 to 2567] km from Perth) completed the study. Data were collected during a total of 91 clinic visits. Participants were engaged in paid work on 61 (67%) of these occasions. Twenty two (96%) participants were employed on at least one occasion, and 11 (48%) were employed on all occasions throughout the entire 12 months. Only one participant, a fulltime carer, had no paid work in this time.

For those employed, the median (range) number of hours worked per week was 38 (10 to 80). The mean (range) number of entire work days missed in the previous 28 days because of problems with physical or mental health was 2 (0 to 21) days, while the number of part work days missed in this period for the same reason was to 1 (0 to 11) days. Participants worked longer hours than expected on 2 (0 to 28) days during the previous 28 days. Overall, relative absenteeism (mean [range]) in those employed was 0.1 (-1.2 to 0.9).

Participants' reported that their work performance over the past one to two years was median (range) 8 (5 to 10) out of 10, which was similar to how they rated the performance of colleagues in similar employment, also being 8 (5 to 10). However when asked to rate their work performance over the past 28 days, the participants' responses were more variable (8 [0 to 10]). Overall, relative presenteeism in those employed was 1.0 (0.0 to 1.8).

These data provide further evidence of the potential impact of cystic fibrosis on an individual's ability to work. Despite having a chronic disease that is associated with a significant treatment burden, most adults with CF living in rural and remote WA engaged in paid work during the 12-month study period. Absenteeism scores were variable, and demonstrated that CF affected the work attendance of many, but not all participants. Presenteeism scores, while also variable, demonstrated that on average participants felt they performed as well as their colleagues at work. However with many reporting that CF does have has a large impact on their work performance, further work is required in larger samples to understand the full impact of CF on presenteeism. Measuring absenteeism and presenteeism provides a useful insight into the disease-related impact on work attendance and performance in adults with CF, and this outcome measure can be considered for use in future studies in this population.

Acknowledgements

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Appendix 4

SIR CHARLES GAIRNDER HOSPITAL TELEHEALTH CF CLINICS:
PARTICIPANT SATISFACTION SURVEY & TELEHEALTH SATISFACTION SCALE

These 2 short surveys are designed to gather and evaluate your feedback on the new telehealth CF clinics that have been implemented as part of your outpatient care.

Please provide your feedback on the following items:

1) The organisation of the telehealth clinics met my expectations

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

2) The timing of telehealth clinic appointments were convenient for me

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

3) The healthcare I received during the telehealth clinics met my expectations

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

4) I was able to communicate effectively with the CF team using this technology

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

5) I prefer telehealth clinics over traditional 'face to face' clinics

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

6) Telehealth clinics are a good way to manage my CF care

Strongly Agree Agree Unsure Disagree Strongly Disagree

Comments: _____
_____

7) Would you like to add any other comments about your experience with CF telehealth clinics?
_____
_____

The Telehealth Satisfaction Scale - overall, how satisfied were you with:

1) The voice quality of the equipment

Excellent Good Poor/Fair

Comments: _____

2) The visual quality of the equipment

Excellent Good Poor/Fair

Comments: _____

3) Your personal comfort using the telehealth system

Excellent Good Poor/Fair

Comments: _____

4) The ease of getting to the telehealth department

Excellent Good Poor/Fair

Comments: _____

5) The length of time with the CF team

Excellent Good Poor/Fair

Comments: _____

6) The explanation of your treatment by the CF team

Excellent Good Poor/Fair

Comments: _____

7) The thoroughness, carefulness and skilfulness of the CF team

Excellent Good Poor/Fair

Comments: _____

8) The courtesy, respect, sensitivity, and friendliness of the CF team

Excellent Good Poor/Fair

Comments: _____

9) How well your privacy was respected

Excellent Good Poor/Fair

Comments: _____

Appendix 5

Original article

High usability of a smartphone application for reporting symptoms in adults with cystic fibrosis

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Abstract

Introduction/Aim: In cystic fibrosis (CF), exacerbations impair lung function and health-related quality of life, increase healthcare costs and reduce survival. Delayed reporting of worsening symptoms can result in more severe exacerbations and worse clinical outcomes; therefore there is a need for a novel approach to facilitate the early identification and treatment of exacerbations in this population. This study investigated the usability of a smartphone application to report symptoms in adults with CF, and the observer agreement in clinical decision making between senior clinicians interpreting smartphone application responses.

Methods: Adults with CF used the smartphone application weekly for four weeks. The application comprised 10 yes/no questions regarding respiratory symptoms and two regarding emotional well-being. Usability was measured with the System Usability Scale (SUS); Observer agreement was tested by providing a CF physician and a nurse practitioner with 45 clinical scenarios. For each scenario the clinicians, who were blinded to each other's responses, were asked to indicate whether or not they would: (i) initiate telephone contact, and/or (ii) request a clinic visit for the individual.

Results: Ten participants (5 female), aged mean (SD) 33 (11) years, FEV_1 49 (27)% predicted completed the study. The mean (SD) SUS score was 94 (6). There was perfect agreement between clinicians for initiating contact with the participant (κ=1.0, $p<0.001$), and near-perfect for requesting a clinic visit (κ=0.86, $p<0.001$).

Conclusion: The use of a smartphone application for reporting symptoms in adults with CF has excellent usability and near-perfect agreement between senior clinicians when interpreting the application responses.

Introduction

Cystic fibrosis (CF) is the most common lethal genetic disease affecting Caucasians, occurring in approximately one in 3,600 live births[1]. Although it is a multi-system disease, respiratory failure in those with poor lung function is the most common cause of mortality[2]. Exacerbations are an important contributor to the decline in lung function[3, 4] with approximately 25% of individuals who require intravenous antibiotics (IVAB) for an exacerbation failing to return to their pre-exacerbation (i.e. baseline) level of lung function following initial treatment[5, 6]. Of note, more than half (58%) of these patients still do not reach their previous baseline level of lung function after 12 months[5]. Earlier work has demonstrated that recovery of lung function following an exacerbation is dependent, at least in part, on the time between exacerbation onset and the initiation of treatment. Specifically, the number of days elapsed prior to commencing IVAB after the diagnosis of an exacerbation is a predictor of lung function outcomes after treatment cessation[5, 7]. These studies reveal that early detection and treatment of exacerbations are of critical importance in the clinical care in this population. Nevertheless, it is well-established that the identification of exacerbations can be delayed in individuals with CF as they may not attend a CF clinic or seek medical advice as soon as they develop worsening symptoms. The cause of this delayed presentation is multi-factorial and includes competing issues such as study, work or family commitments, the travel and financial burden involved in attending a CF clinic, a lack of understanding of the disease process, or feelings of anxiety and depression[8, 9].

There is a need for a novel approach to facilitate the early identification and treatment of exacerbations in this population. For this reason, we have developed a smartphone application that can be used by adults with CF to immediately report symptoms suggestive of an exacerbation to the CF team.

The aim of this study was to determine the: (i) usability and satisfaction of this smartphone application to report symptoms suggestive of an exacerbation in adults with CF and, (ii) observer agreement between two senior clinicians in clinical decision making based on the symptom responses obtained using this technology.

Methods

Study design

This was a single group usability study of four weeks duration, conducted at the adult CF centre at Sir Charles Gairdner Hospital. Adults with CF who owned a smartphone with iOS or Android operating systems were invited to participate at routine outpatient clinic appointments, with recruitment targeted to ensure equal numbers of male and female participants. In total, 190 adults with CF attend the centre, and at the time of recruitment 183 (96%) owned a smartphone. Approval was obtained from the Human Research Ethics Committees for Sir Charles Gairdner Group and Curtin University.

Smartphone application

Experienced CF clinicians who were investigators in this study formulated the twelve questions used in the smartphone application. Members of the research team reviewed the questions for face validity. Ten of the respiratory symptom questions were derived from exacerbation scales previously used in CF research[10, 11] (Table 1) and two questions (i.e. those pertaining to wheeze and chest tightness) were added as these symptoms have been identified by adults with CF as indicators of an exacerbation[12]. Finally, two questions pertaining to emotional wellbeing were included, because in individuals with CF, greater feelings of anxiety and depression have been associated with the greater respiratory symptoms, as well as poorer lung function, HRQoL and physical functioning[13]. All smartphone application questions were answered yes or no, and each time an answer was selected the application automatically moved to the next question. The font size of the text in the application was set at a minimum of 18 to ensure all users could read the questions.

A prototype of the application was designed by a smartphone application engineer, and internal testing was then undertaken by several members of the research team to ensure the application was functioning as intended. The final version of the application was then made available free of charge on iTunes and the Google Play Store, allowing participants to install it on their smartphone after enrolment in the study.

Following enrolment in the study and installation of the application, participants were required to answer the questions once a week over four consecutive weeks. Four occasions of use was considered sufficient by the research team, given another study that explored the usability of a telehealth system in CF based their conclusion on a single use[14]. Participants in the current study were asked to set a recurring alert on their smartphone, which prompted them to answer the questions on a pre-specified day and time each week of their choosing. To login securely, each participant had a unique four digit user code. Once all questions were answered, the responses and user code were emailed in binary code (1 = yes, 0 = no), along with the login used to generate each set of responses, to an account established for the purpose of the study. To maintain data security, only the principal investigator could identify each participant based on their user code. Participants were informed that for the purpose of this study, symptom responses were not being used by the CF team to detect exacerbations and were instructed to contact the CF clinic by phone if they required an appointment. Participants were not reviewed in the CF clinic during the four-week period, and therefore no comparison was undertaken regarding the smartphone application answers and clinical status.

Outcomes

System usability

Usability was measured at the end of the intervention period with the System Usability Scale (SUS)[15]. This scale comprises 10 items that ask about the usability aspects of the new technology, such as its complexity and functionality, and the participant's confidence in using it. Each item was answered using a 5 point Likert scale with responses that ranged from 5 (strongly agree) to 1 (strongly disagree). Scores from each of the 10 items were scaled to provide a score out of four, then combined and multiplied by 2.5 to provide a total score out of 100. Scores from the SUS were also grouped into two subscales: usability (8 items) and learnability (two items), both of which were also scored out of 100. The SUS has been widely used in the information technology industry, and more recently in studies evaluating the usability of telehealth technologies used in CF[14] and chronic obstructive pulmonary disease[16].

Participant satisfaction

Participant satisfaction was assessed at the end of the intervention period using a purpose-developed survey which comprised seven items relating to the design and use of the smartphone application. Items alternated between positive and negative wording, and were answered with a 5-point Likert scale with responses that ranged from 5 (strongly agree) to 1 (strongly disagree).

Observer agreement

A physician and nurse practitioner who specialise in CF were presented with an identical set of 45 clinical scenarios. A nurse practitioner was included to reflect the growing utilisation of this role as a first point of contact in CF centres internationally. These scenarios were created by pairing one of three case studies, with one of 15 different combinations of smartphone application responses. The three case studies described clinical presentations of an adult with mild, moderate or severe CF and were reviewed for authenticity by a respiratory physician with extensive experience in CF, who was not otherwise involved in the study. For each scenario, the two clinicians were asked to indicate whether or not they would; (i) initiate telephone contact to discuss symptoms further, and/or (ii) request the individual attend an outpatient clinic for further assessment. The clinicians were blinded to each other's responses.

Data analysis

Statistical analyses were conducted using SPSS® (Statistical Package for Social Sciences, version 22.0, IBM corp., New York, USA). System Usability Scale data were reported using descriptive statistics. Observer agreement between clinicians was assessed using a Cohen's kappa statistic. A sample size of 45 responses was adequate to detect a difference in proportion between chance and anticipated agreement of 0.5, assuming a relative error of 30%.

Results

Ten participants with CF completed the study (Table 2). Each participant used the smartphone application once per week over the four-week period. Seven (70%) participants used iPhones, and three (30%) used phones with Android operating systems.

System usability

The mean (SD) raw SUS score was 94 (6) (Table 3). When summed as subscales, participants scored the smartphone application as 92 (7) and 100 (0) for usability and learnability, respectively.

Participant satisfaction

Nine (90%) participants responded that the smartphone application was a good method for reporting symptoms to the CF team. All participants (100%) found the instructions in the application easy to follow (Table 4).

Observer agreement

Observer agreement between clinicians was perfect for the question regarding whether or not to initiate contact with the patient to further discuss symptoms (κ=1.0, $p<0.001$). Specifically, both clinicians indicated that they would initiate contact for 42 (93%) scenarios, but not for three (7%) scenarios. There was near-perfect agreement for whether or not the patient should visit the outpatient clinic (κ=0.86, $p<0.001$). Specifically, both clinicians indicated that they would request the patient visit the outpatient clinic for 24 (53%) scenarios, but not for 18 (40%) scenarios. Clinicians disagreed on three (7%) scenarios, which was for the same scenario across all three case studies. This asked "in the past week have you had increased cough or new pain on coughing?"

Discussion

This study has shown that a smartphone application that can be used to report symptoms that may be suggestive of an exacerbation has excellent usability in adults with CF. Furthermore the symptom responses from the application were interpreted in a similar way by different experienced CF clinicians in the process of clinical decision making.

The integration of telehealth with usual care in CF is an expanding area of research. To date, feasibility has been demonstrated in interventions such as using Skype and WhatsApp to communicate with patients[17], videoconferencing to deliver routine outpatient clinics[18], monitoring of lung function and symptoms at home[19-21], and assessing exercise capacity within the patient's home[14]. While the evidence supporting the role of telehealth in CF is relatively limited, the aim of such interventions in the longer term will be to improve health outcomes via increased treatment adherence and the earlier detection of exacerbations. Strategies similar to those used in CF have also been employed in chronic diseases such as type 1 diabetes[22], with demonstrated improvements in access to routine care. A recent systematic review[23] into mobile health interventions in diabetes mellitus and other cardiovascular and respiratory diseases found mixed evidence supporting the effectiveness of these interventions on treatment adherence and health outcomes.

The use of out-of-hospital monitoring systems to detect changes in symptoms and physiological parameters suggestive of an exacerbation is a growing area of interest[19-21]. One shortcoming of these previous studies was poor adherence to the monitoring system, which resulted, at least in part, from the equipment being large and bulky. The smartphone application described in this study overcame this limitation, as it was small and portable, and integrated easily with the lifestyle of adults with CF. Further, in contrast with earlier work which required daily use of the monitoring system by all participants, those in the current study were asked to use the system less frequently (i.e. once a week); a factor which may also have contributed to the excellent adherence. While the optimal frequency of reporting in order to detect an exacerbation is unknown, daily reporting in other studies likely contributed to the observed poor adherence. Therefore weekly reporting appears to be a pragmatic alternative which was well tolerated. In clinical practice, to minimise the possibility of missing the onset of an exacerbation that occurred between weekly use of the smartphone application, patients could be instructed to use the smartphone application anytime between scheduled uses if they felt their symptoms had worsened.

The high SUS scores indicate that the smartphone application achieved an 'A' rating for usability. This rating is at the top of the "acceptable" usability range, and is described on the SUS adjective rating scale as "best imaginable" usability[24]. In addition, raw scores of over 90 on the SUS indicate that a system is in the 99th percentile of usability for the tested demographic[24]. Finally, this score also indicates that users would be more likely to recommend this technology to a friend[24].

The SUS scores observed in this study are similar to those reported for interventions in adults with CF investigating the feasibility of an internet based tool to promote physical activity[25], and using a videoconference system to assess exercise capacity[14]. This was not surprising given the uncomplicated design and functionality of the smartphone application, including asking for yes/no responses to questions and requiring minimal time to answer the questions (less than two minutes). Similarly, participant satisfaction, as measured using the purpose developed survey was very high. All of the participants owned smartphones prior to the study, and therefore the high level of usability and satisfaction observed may be a function of their pre-existing comfort with technology. This was expected, as 74% of adults in Australia owned a smartphone in 2015[26].

We observed near-perfect agreement in clinical decision making between experienced CF clinicians. This suggests that others will be able to use this application to arrive at similar clinical decisions regarding whether the patient requires further assessment for a potential exacerbation, however having only two clinicians participating in the observer agreement study is a limitation. It is possible that for the question with poor agreement, the ambiguity related to asking the clinician to interpret responses regarding two different symptoms (increased cough and new pain on coughing). This ambiguity might be overcome by dividing this into two separate questions: one regarding increased cough and a second regarding chest pain. This will allow patients to report chest pain irrespective of whether it is related to coughing.

This system, while designed to detect exacerbations, did not include spirometry. This is a potential limitation as FEV_1 is regarded as one of the key measures of clinical status in CF[27]. However the provision of a spirometer would have greatly increased cost and reduced the portability of the reporting system. We aimed to develop a system that required no additional equipment to the participant's own smartphone, allowing us to achieve high usability. This system, which was based entirely on patient reported symptoms, will allow the CF team to determine whether spirometry is required. We do acknowledge however, that the inclusion of home spirometry as part of our system may provide more accurate diagnosis of an exacerbation before the patient needed to attend the CF clinic."

Although the sample size for this study was modest, participants were recruited across a broad range of ages and severity of lung function, and there was equal representation from both genders. Participants living in rural and remote areas (n=2) also participated in the study. Seven (70%) had treatment for an exacerbation in the 12 months prior to commencing the study. Participants were employed in a wide variety of occupations, including administration, retail, information technology and healthcare, and one was a fulltime university student. This allowed the investigators to gather usability data from people who were representative of the broader adult CF population.

The results of this study have demonstrated that amongst adults with CF, a smartphone application used to report symptoms suggestive of an exacerbation has excellent usability, and provides symptom responses that can be interpreted consistently between clinicians who are experienced in the management of this clinical population. A randomised controlled trial is now warranted to investigate whether this system can reduce the delay in time taken by a patient to report symptoms to a CF clinic, and measure the impact on health-related outcomes in adults with CF.

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Declaration of conflicting interests

Mr. Wood reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study; grants from Technipro Pulmomed, non-financial support from Novartis, non-financial support from Pharmaxis, outside the submitted work. A/Prof Jenkins reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study. A/Prof Putrino has nothing to disclose. Clin A/Prof Mulrennan reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study; personal fees from Vertex, non-financial support from Novartis, outside the submitted work. Mrs. Morey has nothing to disclose. Mrs. Cecins has nothing to disclose. A/Prof Hill has nothing to disclose.

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Table 1

Smartphone application questions.

In the past week, have you had:
An increase in or sputum volume or change in colour?
New or increased blood in your sputum?
Increased cough, or new pain on coughing?
New or increased wheeze?
New or increased chest tightness?
Increased shortness of breath or difficulty breathing?
Increased fatigue or lethargy?
Fever?
Loss of appetite or weight?
Sinus pain or tenderness?
In the past week, have you felt:
Low in mood?
Worried?

Table 2

Participant (n = 10) characteristics.

Male, n (%)	5 (50)
Age, yr	32 (11)
BMI, kg/m^2	23 (5)
FEV_1, % predicted	49 (27)
Location, n (%)	
Metropolitan	8 (80)
Rural or remote	2 (20)

Data are presented as number (%) or mean (SD). BMI = body mass index; FEV_1 = forced expiratory volume in one second.

Table 3

Participant (n=10) responses to items of the System Usability Scale.

Item	SD				SA
I think that I would like to use this system frequently	0	0	10	40	50
I found the system unnecessarily complex	90	10	0	0	0
I thought the system was easy to use	0	0	0	10	90
I think that I would need the support of a technical person to be able to use this system	100	0	0	0	0
I found the various functions in this system were well integrated	0	0	30	30	40
I thought there was too much inconsistency in this system	70	20	0	10	0
I would imagine that most people would learn to use this system very quickly	0	0	0	0	100
I found the system very cumbersome to use	80	20	0	0	0
I felt very confident using the system	0	0	10	0	90
I needed to learn a lot of things before I could get going with this system	100	0	0	0	0

Data are presented as percentage of participants. Each item is answered using a 5-point Likert scale from strongly disagree (SD) to strongly agree (SA).

Table 4

Participant (n = 10) responses to the purpose developed satisfaction survey.

Item	SA	A	U	D	SD
I liked the graphic design (layout, colours etc.) of the app	0	80	20	0	0
It was easy to follow the instructions on the app	80	20	0	0	0
It was difficult to know what the app was asking me to do next	0	0	0	60	40
The questions I was asked about my symptoms were easy to understand	50	30	0	20	0
The questions I was asked about how I felt were difficult to understand	0	10	0	50	40
Using the app was a good way for me to report my symptoms to the CF team	40	50	10	0	0
Using the app to report my symptoms was an inconvenience or intrusion into my daily life	0	0	0	30	70

Data are presented as percentage of participants. SA = Strongly Agree, A = Agree, U = Unsure, D = Disagree,

SD = Strongly Disagree

Appendix 6

Case Study 3

- 29 year old female with CF
- Lives in Bunbury, married, works part time, one daughter
- Best FEV_1 in past 12 months = 1.9L (61% predicted)
- Sputum: Pseudomonas aeruginosa
- Pancreatic insufficient, osteopenia
- Meds: Creon, Pulmozyme, HTS, VitABDECK
- Last course of IVABs = 7 months ago

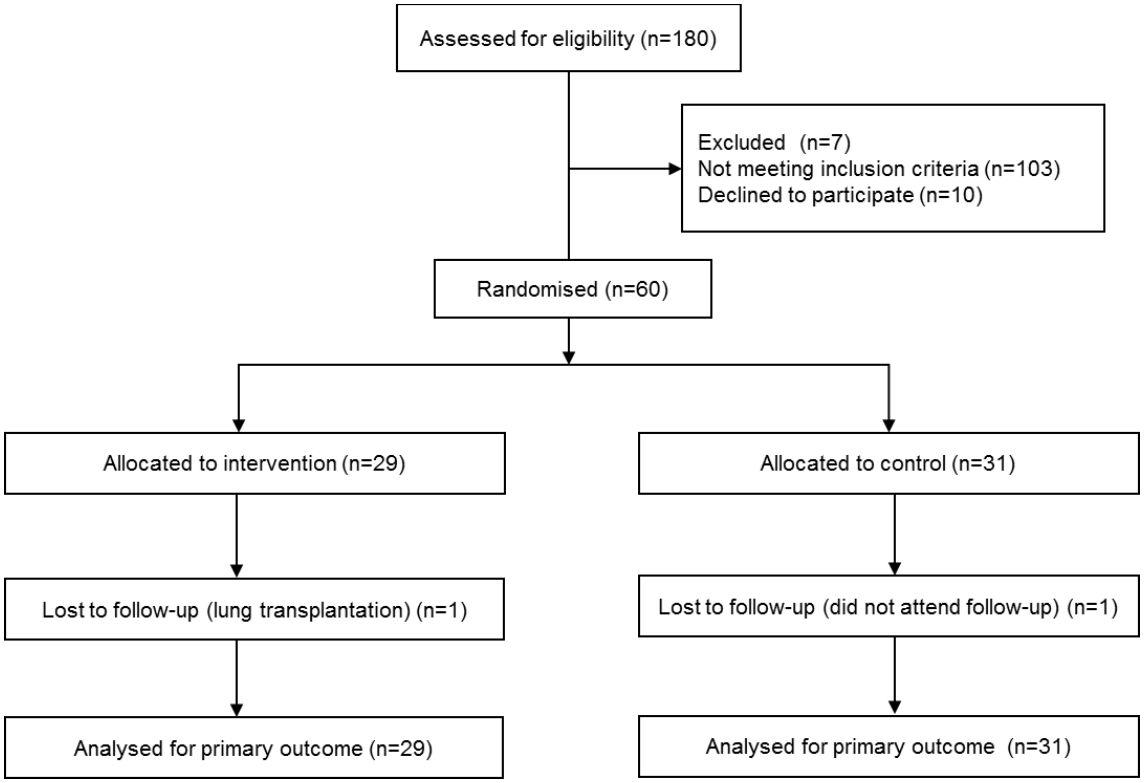
Scenario 3

In the past week have you had:	
An increase in sputum volume or change in colour	No
New or increased blood in your sputum	No
Increased cough, or new pain on coughing	No
New or increased wheeze	**Yes**
New or increased chest tightness	No
Increased shortness of breath or difficulty breathing	No
Increased fatigue or lethargy	No
Fever	No
Loss of appetite or weight	No
Sinus pain or tenderness	**Yes**
In the past week have you:	
Felt low in mood	No
Felt worried	No

Would you initiate phone contact with this person? **YES** **NO**

Appendix 7

CONSORT diagram



Appendix 8

Protocol

A smartphone application for reporting symptoms in adults with cystic fibrosis: protocol of a randomised controlled trial

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ABSTRACT

Introduction: In people with cystic fibrosis (CF), exacerbations have been shown to have profound and prolonged negative effects such as reducing physical activity and health-related quality of life, increasing the rate of decline of lung function and healthcare costs, and ultimately increasing the risk of mortality. Delayed initiation of treatment following the signs of an exacerbation has been shown to be associated with failure to recover to baseline. Therefore, the late identification and treatment of an exacerbation due to delayed presentation will potentially worsen short and long-term outcomes. We have developed a smartphone application, containing questions which require yes or no responses relating to symptoms suggestive of a respiratory exacerbation. Its use is intended to facilitate the early identification of symptoms suggestive of a respiratory exacerbation, and allow the CF team to initiate treatment sooner, thereby potentially reducing the risk of severe exacerbations which require intravenous antibiotics (IVAB) and often a hospital admission.

Methods: We will undertake a randomised controlled trial (RCT). Sixty adults with CF will be recruited and randomised to either the intervention or control group. The intervention group will use the smartphone application weekly for 12 months, or earlier than the next weekly reporting time if they feel their symptoms have worsened. The control group will continue to receive usual care, involving regular (approximately 3-monthly) CF outpatient clinic appointments. The primary outcome measure will be courses and days of IVAB.

Ethics and dissemination: Approval was obtained from the Sir Charles Gairdner Group Human Research Ethics Committee for WA Health (2015 - 030), and Curtin University Human Research Ethics Committee (HR212/2015), and has been registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615000599572). Results of this study will be presented at international conferences and published in peer-reviewed journals in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement.

Strengths and limitations of this study

This is the first long term randomised controlled trial investigating a smartphone application for reporting symptoms in adults with cystic fibrosis.

The pharmacist collecting primary outcome data, and the physicians prescribing intravenous antibiotics, are blinded to the participants' group allocation.

Selecting questions to include in the smartphone application was difficult due to a lack of consensus of what defines an exacerbation in cystic fibrosis.

It was not feasible to include spirometry in the intervention in this study which may improve clinical interpretation of reported symptoms.

INTRODUCTION

Cystic fibrosis (CF) is a disease characterised by periods of clinical stability, interspersed with periods of acute deterioration, known as exacerbations. Respiratory exacerbations have been shown to have profound and prolonged negative effects on people with CF, such as reducing physical activity[1] and health-related quality of life (HRQoL),[2] increasing the rate of decline of lung function[3] and healthcare costs,[4] and ultimately increasing the risk of mortality.[5] The decline in lung function may also contribute to increased feelings of depression.[6] In people with CF, an exacerbation has been defined as a change in four or more disease-specific criteria comprising cough, sputum, haemoptysis, dyspnoea, fatigue, sinus pain and discharge, fever, worsening airflow obstruction (i.e. reduced forced expiratory volume in one second [FEV_1]), anorexia or weight loss, and changes in physical examination of the chest or chest radiography.[7]

Of concern, of those individuals who experience an exacerbation requiring intravenous antibiotics (IVAB), approximately 25% have a persistent reduction in FEV_1 at the end of their treatment,[8] and more than half (58%) of these individuals do not regain their pre-exacerbation level of FEV_1 after 12 months.[8] Delayed initiation of treatment has been shown to be associated with this failure to recover to baseline.[8] Therefore, the late identification and treatment of an exacerbation due to delayed presentation will potentially worsen short and long-term outcomes. People with CF may delay their presentation to a CF clinic for management of an exacerbation due to study, work or family commitments, the travel and financial burden involved in attending a CF clinic, a lack of understanding of the disease process, or if affected by anxiety and depression.[9]

Telehealth has been evaluated in studies in people with CF using interventions such as monitoring of spirometry,[10-12] oxygen saturation[10 13] and symptoms from home,[10-12] using videoconferencing to measure exercise capacity[14] and provide health assessment in the home,[15] and to provide routine outpatient clinics.[16] Although telehealth, in the form of home monitoring, appears to be feasible and readily accepted by people with CF,[17] to date, studies have not demonstrated a significant impact of telehealth on health outcomes such as exacerbation rates, lung function, HRQoL and healthcare utilisation (HCU). One reason for this may relate to the burden associated with the telehealth interventions. That is, earlier work often required participants to record measurements as often as daily and did not offer the opportunity to complete these measures outside the home (i.e. there was no use of mobile technology), which compromised participant adherence to the telehealth intervention.

We aim to overcome this shortcoming by investigating the effects of using of an application for reporting symptoms that is completely mobile and stored on the participant's own smartphone. This novel approach is intended to facilitate the early identification of symptoms suggestive of a respiratory exacerbation, and allow the CF team to initiate treatment sooner in the form of oral and inhaled antibiotics, and increased mucolytic therapy and airway clearance. This may potentially reduce the risk of severe exacerbations which require IVAB and often a hospital admission.

METHODS AND ANALYSIS

This will be a prospective 12-month, single blinded randomised controlled trial (RCT).

Participant screening and selection

Eligible participants will be identified by the principal investigator and recruited from routine outpatient clinic appointments at the adult CF centre at Sir Charles Gairdner Hospital (SCGH), Perth. The Patient Information and Consent Form will be provided to potential participants, who will then be contacted by the principal investigator approximately 48 hours later to discuss their willingness to participate.

Inclusion criteria

Adults who meet the following criteria will be eligible to participate: diagnosis of CF; aged ≥ 18 years; under the care of the SCGH CF team; respiratory exacerbation requiring treatment with IVAB in the preceding 12 months; currently in a period of clinical stability, defined as no signs of an exacerbation for the previous 2 weeks; and able to understand written and spoken English.

Exclusion criteria

Criteria to exclude individuals from participating will be: previous lung transplantation or current listing for lung transplantation; inability to undertake a prescribed treatment regimen, or inability to use or not being in possession of a smartphone.

Randomisation and allocation concealment

Participants will be randomly allocated to the intervention or control group using the University of Sydney National Health Medical Research Council Clinical Trials Centre randomisation service. Recruitment will be stratified according to gender, location (metropolitan versus rural and remote) and whether the participant is prescribed Ivacaftor or Lumicaftor/Ivacaftor, as these medications can reduce the rate of exacerbations and improve lung function, weight and HRQoL.[18 19]

Study measurements

Participants will have assessments performed at baseline (prior to randomisation), and at 6 and 12 months, unless otherwise stated. Assessments will be performed when the participant is in a period of clinical stability, defined as no signs of an exacerbation for the previous 2 weeks. If the participant has signs of an exacerbation at their scheduled follow up time, the assessments will be completed at the subsequent visit when they are clinically stable. The principal investigator will perform all assessments during follow up visits at SCGH. For telehealth assessments, spirometry and weight will be assessed by a health professional local to the participant, with the remainder of the assessments completed by the principal investigator.

Primary Outcome

Number of courses of IVAB and IVAB days

Information regarding the use of IVAB will be obtained from the medical records of the participants by a pharmacist blinded to the study groups and verified against SCGH pharmacy dispensing records. This will be collected at the final assessment only.

Secondary Outcomes

Lung function (FEV_1)

Lung function will be measured using a Medgraphics USB spirometer (MGC Diagnostics, Minnesota, USA), or Easyone spirometer (ndd Medical Technologies, Massachusetts, USA). Each participant will perform up to eight maximal forced expiratory manoeuvres to ensure the two best attempts meet published standards.[20]

HRQoL – Cystic Fibrosis Questionnaire – Revised (CFQ-R)

This self-complete questionnaire comprises 50 questions answered on a 4 point Likert scale, and covers 12 domains comprising physical, vitality, emotion, treatment burden, health, social, body, role, weight, respiratory, digestion and eating.[21] The CFQ-R requires the user to recall information from the previous 2 weeks.

Feelings of anxiety and depression – Hospital Anxiety and Depression Scale (HADS)

The HADS[22] contains 14 self-report questions, evenly divided into anxiety and depression scales (7 each). A 4-point Likert scale (0 to 3) is used to answer questions based on a recall period of 7 days.

Nutritional status - Body Mass Index (BMI)

Participants will have their height and weight measured, and BMI will be calculated.

Measures of HCU including time to first exacerbation requiring IVABs, oral and inhaled antibiotic use and cost, hospital admissions and cost, and number of CF clinic visits

At the final assessment only, the participant's medical record will be reviewed to extract information pertaining to HCU. This includes: time (in days) from randomisation to the first exacerbation requiring IVAB; number of hospital admissions and days; number of courses and days of oral and inhaled antibiotics; number of CF clinic visits; estimated cost of IVAB and other antibiotic treatment; and, estimated cost of hospital admissions. Costs related to HCU will be estimated using information provided from the SCGH Pharmacy and Finance departments. All potential participants receive their care at the SCGH CF Centre or via shared care with an external respiratory physician (and not from a general practitioner). Prescribed antibiotic use will be well documented in the medical record, and participants will not be required to keep a diary of antibiotic use. Non-clinical costs relating to participants' travel, parking, time off work and telephone calls will not be recorded.

Medication adherence – Treatment Adherence Questionnaire – CF (TAQ-CF)

Adherence to routine CF treatments will be assessed using the TAQ-CF.[23] This measure has 12 treatment items and asks the user to report on the frequency of each treatment on a 7 point Likert scale (ranging from "not at all" to "3 or more times per day"), and the duration of treatment on a 6 point Likert scale ("0" to "25+" minutes). The TAQ-CF also asks the participant to report on the barriers to individual treatments.

Absenteeism/Presenteeism – World Health Organisation's Heath and Work Performance Questionnaire (HPQ)

Absenteeism is defined as being absent from work or study due to illness whereas presenteeism is defined as the loss of productivity associated with attending work or study when unwell.[24] This questionnaire uses the absenteeism and presenteeism questions of the HPQ.[25]

System usability – System Usability Scale (SUS)

The SUS[26] is a validated assessment tool comprising 10 questions regarding the usability of technological systems, and is answered on a 5 point Likert scale. Other measures of system usability will include the time of day the smartphone application is used and how many times the questions were not completed.

Intervention

A smartphone application has been developed for use by participants to report symptoms on their own smartphones. The application contains 14 questions (Table 1) that are required to be answered 'yes' or 'no'. Twelve questions relate to respiratory symptoms; 10 questions are derived from the Fuchs exacerbation scale,[7] with the addition of two symptoms (wheeze and chest tightness) commonly identified by adults with CF as indicators of an exacerbation[27] and considered important by the research team. The application also asks the participant to answer two questions relating to their feelings of anxiety and depression. The data will then be transmitted securely via password protected email to members of the research team. This smartphone application has demonstrated high system usability in people with CF, as well as good observer agreement between CF clinicians interpreting the data.[28]

Experimental group

Participants will be asked to use the smartphone application once per week on a set day and time of their choosing, for a period of 12 months. A smartphone calendar alert will remind the participant to answer the symptom questions. Participants can also use the application earlier than the next weekly reporting time if they feel their symptoms have worsened. If the participant misses one of their weekly reporting times, they will be prompted to answer the application questions via text message. If the participant responds 'yes' to any of the symptom questions, the principal investigator will alert the CF nurse practitioner, who will then phone the participant to discuss their symptoms and whether treatment (i.e. oral or inhaled antibiotics) is required, in consultation with a CF physician blinded to the participant's study group. The CF nurse practitioner will also determine if a formal review in the

CF clinic is required. If the participant's respiratory disease has been stable for 3 months, they will attend a routine CF clinic appointment.

Control group

Participants in this group will continue to receive usual care, involving routine CF clinic appointments (approximately 3 monthly). Participants can contact the CF Nurse Practitioner via telephone sooner if there is a change in their clinical status.

Statistical analysis

Statistical analyses will be undertaken with Stata ® (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) in accordance with the intention-to-treat principle. The distribution of data will be assessed for normality. A p value of < 0.05 will be considered statistically significant. Negative binomial regression, and independent t-tests or Mann Whitney U tests will be used to determine differences between the two groups. Further analyses will include general linear models to adjust for possible covariates.

Number of courses of IVAB and number of IV antibiotic days

Summary statistics and frequencies will be provided for continuous and categorical variables. Descriptive plots will also be produced for all variables. Independent t-tests will be used to determine whether the number of courses of IVAB, and number of IVAB days, differs between the two groups. Further analyses will include general linear models to adjust for possible covariates including age, gender, BMI, Pseudomonas aeruginosa, pancreatic insufficiency and CF-related diabetes. Appropriate transformations will be conducted if the data is not normally distributed.

Other measurements

For all variables, a between-group analysis of these outcome measures will be performed using an independent t-test (parametric data) or Mann Whitney U test (non-parametric data). Within group

changes in outcome measures collected at each visit will be assessed using one-way repeated measures analysis of variance (parametric data) or Friedman's test (non-parametric data).

Sample size calculations

This is a study comparing participants who will use a smartphone application and those who will not. To investigate the difference in the number of IVAB courses between the two groups, assuming a within group standard deviation of 1.21 (based on IVAB usage at the SCGH CF centre during the two years prior to the study), a sample size of 23 in each group will be required to detect a difference of one exacerbation requiring IVAB per participant, with 80% power and a significance level of $p < 0.05$. To account for any loss to follow up or drop out, we will recruit an additional seven individuals per group for a total sample size of 60. No additional individuals are required to detect the same difference under non-parametric settings.

Patient and public involvement statement

The intervention used in this study was designed with input from participants in a pilot study conducted by the research team.[28] There was no further involvement in the development of this RCT by patients or the public.

DATA COLLECTION AND MANAGEMENT

Participant data will not contain any information that allows the person's identity to be known. All data stored electronically at SCGH will be kept on a password-protected computer or locked in a filing cabinet in the Department of Respiratory Medicine. Any printed information including signed consent forms will be kept in locked filing cabinets. Data will be kept for a minimum of 15 years. After this time, data collection forms will be shredded and electronic files will be deleted.

Data transmitted from the smartphone application will be transmitted securely via password-protected email to members of the research team at SCGH, and not kept in 'cloud' storage at any stage. After transmission from the participant's phone or tablet, the data will be automatically deleted, preventing any potential breach of privacy if the device is lost or stolen. The application will also request the user to enter a unique, 4-digit passcode before being able to access the application questions.

ETHICS

Approval was obtained from the Sir Charles Gairdner Group Human Research Ethics Committee for WA Health (2015 - 030), and Curtin University Human Research Ethics Committee (HR212/2015). This trial has been registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615000599572). Results of this study will be presented at international conferences and published in peer-reviewed journals in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement (Figure 1).[29]

DISCUSSION

This will be the first RCT investigating the impact of a smartphone application used by people with CF to report symptoms suggestive of a respiratory exacerbation directly to the CF team. By reducing the delay often seen in the reporting of symptoms, and therefore facilitating the earlier provision of treatment, the severity of exacerbations and the need for IVAB and hospital admissions may be reduced.

Contributor ship statement

J Wood, S Jenkins, D Putrino, S Mulrennan, S Morey, N Cecins and K Hill assisted in the design of the study protocol. J Wood drafted the manuscript, which was also contributed to by S Jenkins, D Putrino, S Mulrennan, S Morey, N Cecins and K Hill. All authors read and approved the final version of the manuscript.

Competing interests

Mr. Wood reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study; grants from Technipro Pulmomed, non-financial support from Novartis, non-financial support from Pharmaxis, outside the submitted work. A/Prof Jenkins reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study. A/Prof Putrino has nothing to disclose. Clin A/Prof Mulrennan reports grants from Sir Charles Gairdner Group Research Advisory Council, during the conduct of the study; personal fees from Vertex, non-financial support from Novartis, outside the submitted work. Mrs. Morey has nothing to disclose. Mrs. Cecins has nothing to disclose. A/Prof Hill has nothing to disclose.

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Data sharing statement

There are currently no additional data available relating to this protocol.

Acknowledgements

N/A

Figure 1 legend

'Study Design'

References

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Table 1

Smartphone application questions (participants answer yes or no).

In the past week, have you had:
Worsening sputum volume or colour?
New or increased blood in your sputum?
Increased cough?
New or increased chest pain?
New or increased wheeze?
New or increased chest tightness?
Increased shortness of breath or difficulty breathing?
Increased fatigue or lethargy?
Fever?
Loss of appetite or weight?
Sinus pain or tenderness?
In the past week do you feel that your health has worsened?
In the past week, have you felt:
Low in mood?
Worried?

Appendix 9

Original article

A smartphone application for reporting symptoms in adults with cystic fibrosis improves the detection of exacerbations: results of a randomised controlled trial

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Abstract

Background: Respiratory exacerbations impair lung function and health-related quality of life in people with CF, with delayed identification of exacerbations often resulting in worse outcomes. We developed a smartphone application (app) for adults with CF to report symptoms to the CF team, and investigated its impact on antibiotic use and other outcomes.

Methods: Participants were randomised to intervention (use of the app weekly or sooner if symptoms had worsened) or control (usual care). The app comprised questions relating to symptoms suggestive of an exacerbation. If worsening symptoms were reported, the participant was contacted by the nurse practitioner. The primary outcome measure was the number of courses and days of intravenous antibiotics.

Results: Sixty participants (31 male, aged [mean±SD] 31±9 years, FEV_1 60±18% predicted) were recruited, with 29 (48%) allocated to the intervention group. Over the 12-month follow-up, there was no clear effect of the app on the number of courses of intravenous antibiotics (incidence rate ratio [IRR] 1; 95% confidence interval [CI] 0.6 to 1.7), however number of courses of oral antibiotics increased (IRR 1.5; 95% CI 1.0 to 2.2). The median [IQR] time to detection of exacerbation requiring oral or intravenous antibiotics was shorter in the intervention group compared with the control group (70 [123] vs.141 [140] days; p=0.02). No between-group differences were observed in other outcomes.

Conclusion: The use of an app reduced time to detect respiratory exacerbations that required antibiotics, however did not demonstrate a clear effect on the number of courses of intravenous antibiotics.

Introduction

In cystic fibrosis (CF), a respiratory exacerbation has been defined as having a change in four or more disease-specific criteria comprising cough, sputum, haemoptysis, dyspnoea, fatigue, sinus pain and discharge, fever, reduced forced expiratory volume in 1 second (FEV_1), anorexia or weight loss, and changes in physical examination of the chest or chest radiography (1). Exacerbations can have a severe and long-lasting impact on people with CF, by accelerating the rate of decline in lung function (2), increasing the time spent in hospital (3), reducing health-related quality of life (HRQoL) (4, 5) and physical activity (6), increasing feelings of depression (7), and ultimately increasing the risk of mortality (8).

The early detection of exacerbations is an integral component of CF care. Delayed initiation of treatment (i.e. antibiotics) has been associated with failure of lung function to recover to pre-exacerbation levels (9). Furthermore, up to 25% of people with CF who have an exacerbation fail to have their lung function recover following treatment (9). Therefore, strategies that are targeted at the early identification of exacerbations may be a vital step in optimising long-term outcomes in people with CF.

In people with CF who develop an exacerbation, delayed identification of exacerbations is often due to delayed presentation to a CF clinic. The reasons for this delay are multifactorial, and include commitments such as work, study and family, as well as the barriers to attending a CF clinic such as travel and financial burden, a lack of education and understanding around the need to report symptoms sooner, and feelings of anxiety and depression associated with attending a CF clinic (10). The use of telehealth is becoming an increasingly popular way of reducing the barriers associated with accessing CF care.

The impact of telehealth technology in CF has been evaluated in interventions aimed at identifying exacerbations (11-15), providing outpatient clinics (16), and providing exercise assessment and training (17, 18). Although adults with CF are likely to be comfortable with the use of mobile technologies, the effectiveness of telehealth at detecting exacerbations (11-15) has previously been compromised by suboptimal adherence (i.e. 10% to 67%). This is likely due to the high reporting burden experienced by participants, such as daily reporting of symptoms and/or regular spirometry. Minimising this burden in order to optimise adherence is an important consideration when designing telehealth technology.

We have previously developed a simple, intuitive, and novel smartphone application (app) (19) that allows the user to report changes in their symptoms directly to the CF team. The aim was to explore the effects of this app on overcoming the delay in presentation to a CF clinic by facilitating the earlier detection of exacerbations, which in turn may provide an opportunity to initiate treatment sooner. To optimise adherence, the app was designed to exclusively utlilise smartphone technology that was mobile and already owned by the majority of young adults in society. We hypothesised that by improving symptom reporting and reducing the time to detect exacerbations, the risk of more severe exacerbations requiring treatment with intravenous (IV) antibiotics may be reduced.

Methods

This study was a prospective, single centre randomised controlled trial (RCT) which was undertaken according to a published protocol (19).

Participants

People with a diagnosis of CF were eligible if they were; (i) aged ≥ 18 years, (ii) attended the adult CF centre at Sir Charles Gairdner Hospital in Perth, Western Australia, (iii) had at least one exacerbation requiring IV antibiotics in the preceding 12 months, (iv) exacerbation free for a minimum of 2 weeks prior to recruitment, (v) in possession of a smartphone, (vi) able to understand

written and spoken English. People who had previous lung transplantation or were currently listed for lung transplantation were excluded.

Participants were recruited during routine outpatient clinic visits during the period from January 2016 to February 2017. The participant information and consent form was provided by the Principal Investigator, and potential participants were contacted at least 48 hours later to discuss their willingness to participate. This study was approved by The Sir Charles Gairdner Group Human Research Ethics Committee for Western Australia Health (2015-030) and Curtin University Human Research Ethics Committee (HR212/2015). It was registered prospectively with the Australian New Zealand Clinical Trials Registry (ACTRN12615000599572).

Study design and intervention

Following informed consent, all participants completed measures prior to randomisation. Thereafter, participants were allocated to the intervention or control group using an independent computer-generated phone randomisation service (Figure 1). The randomisation sequence was stratified according to factors known to influence exacerbation rates, such as sex, location (metropolitan vs. rural/remote) and whether or not the participant had been prescribed either ivacaftor or lumacaftor/ivacaftor.

Participants in the intervention group downloaded the app on their smartphone. The app comprised 12 questions regarding changes in respiratory symptoms that were adapted from Fuchs exacerbation scale (1) and 2 questions regarding emotional well-being. Each question required a ‘yes’ or ‘no’ response. The app was previously tested in a usability study and demonstrated high usability amongst people with CF and near-perfect agreement between CF clinicians interpreting the data (19).

Participants were asked to answer the 14 questions via the app once a week or sooner if they felt their symptoms had worsened. If a participant failed to report their symptoms during a week, a text message was sent to remind them to complete the questions the following week. The symptom data was securely transmitted via password-protected email to the research team. If the participant reported that any symptoms had worsened, the CF nurse practitioner contacted them by phone to discuss their symptoms and whether they required a formal review in the CF clinic, or whether treatment (i.e. oral or inhaled antibiotics) was to be initiated immediately. Antibiotics were prescribed by, or in consultation with the CF physicians. Although clinical judgment rather than standardised criteria were used to define an exacerbation, the physicians prescribing the antibiotics were blinded to group allocation. Participants were asked to attend the CF clinic every 3 months if they had not presented sooner.

Participants in the control group continued with usual care, which involved attending the CF clinic appointments every 3 months. They were also able to contact the CF nurse practitioner via phone at any time to report a change in their clinical status.

Measurements

The primary outcome measure was the number of courses and days of IV antibiotics over the 12-month intervention period. These data were extracted from the medical records for each participant on study completion. Antibiotic use was verified by a pharmacist who was blinded to group allocation. Secondary healthcare utilisation (HCU) outcomes extracted for each participant on study completion comprised the time (days) to detection of exacerbation requiring IV antibiotics, time to detection of exacerbation requiring oral or IV antibiotics, number of courses and days of oral and inhaled antibiotics, number of hospital admissions and days, and number of CF clinic visits. Adherence to the weekly use of the app and the symptom data were collated upon study completion.

Other secondary outcomes, were collected prior to, and at 6 and 12 months following randomisation. These comprised spirometry (Medgraphics USB spirometer [MGC Diagnostics, Minnesota, USA] or Easyone spirometer [ndd Medical Technologies, Massachusets, USA]), nutritional status (body mass index [BMI]), HRQoL (Cystic Fibrosis Questionnaire – Revised [CFQ-R]), feelings of anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), medication adherence (Treatment Adherence Questionnaire-CF [TAQ-CF]), and absenteeism and presenteeism (Health and Work Performance Questionnaire). System usability of the app was measured at 6 and 12 months following randomisation with the System Usability Scale (20), scored out of 100.

Statistical analyses

Statistical analyses were undertaken with Stata (StataCorp, Stata Statistical Software Release: V.14) in accordance with the intention-to-treat principle. Categorical data is presented as frequencies and proportions. Continuous data and count is presented as medians and ranges due to skewed distributions. General linear mixed models were used to examine continuous outcomes with suitable distributions. Health care utilisation data presented as count data with skewed distributions. Negative binomial regression was used to examine difference between groups for HCU, with this model chosen over Poisson as the data was over dispersed. Models were adjusted for adjusted for corresponding baseline variables, sex, FEV_1, and courses of IV antibiotics in the preceding 12 months. Kaplan-Meier and Cox regression were used to compare time to detection of exacerbation.

Sample size calculations

To detect a between-group difference ($\alpha = 0.05$, $1 - \beta = 0.8$) in the number of IV antibiotic courses of one per participant, assuming a standard deviation of 1.21 (based on IV antibiotic usage at the SCGH CF centre during 2013 and 2014), a sample size of 23 in each group was required. To account for any loss to follow up or drop out, we aimed to recruit an additional seven participants to each group for a total sample size of 60.

Results

Participant characteristics

Of the 180 patients attending the CF centre, 70 (39%) met the inclusion criteria and were invited to participate in the study. Sixty participants were enrolled in the study (Table 1), with 29 (48%) allocated to the intervention group. One (3%) participant in the control group did not attend the 6 or 12 month study visits, and one participant in the intervention group received lung transplantation prior to the 12 month assessment.

Number of courses and days of IV antibiotics

Following adjustment for the courses of IV antibiotics in the preceding 12 months, sex, and forced expiratory volume in 1 second, over the 12 month intervention period there was no important effect of the intervention on the number of courses and days of IV antibiotics per participant (Table 2).

Secondary HCU outcomes

Over the 12 month intervention period, there was no clear effect of the intervention on the time to detection of exacerbation requiring IV antibiotics, being a median (interquartile range) of 186 (298) vs. 273 (184) days in the control group ($p = 0.20$; Figure 2). The time to detection of exacerbation requiring oral or IV antibiotics was shorter in the intervention group compared to the control group with a median (interquartile range) of 70 (123) vs. 141 (140) days, respectively ($p = 0.02$; Figure 2). There was evidence to support an increase in the prescription of oral antibiotics in the intervention group, but not in the prescription of inhaled antibiotics (Table 2). There was no clear effect on the number of hospital admissions and admission days and number of CF clinic visits. Participants in the intervention group communicated via phone with the nurse practitioner median (IQR) 7 (8) times during the study, compared to 3 (4) times ($p = 0.01$) for participants in the control group.

Adherence to the weekly use of the app was a mean (range) of 77 (25 to 100)%, with 1,136 of a possible 1,483 reporting occasions completed. Subgroup analysis demonstrated an increase in oral antibiotic prescription, and reduction in IV antibiotic prescription, compared with the 12 months preceding the study in participants in the intervention group with adherence ≥ 80% (n = 15) (Figure 3).

Of the completed reporting occasions, participants reported an increase in at least one symptom 399 (35%) times, (median [range] 10 [1 to 44]) per participant). Oral or IV antibiotics were subsequently prescribed on 113 (28%) of these occasions. The most commonly reported symptoms were increased cough, increased fatigue or lethargy, and worsening sputum volume or colour (Table 3).

Other secondary outcomes

The mean (SD) system usability score for the app at 6 and 12 months was 87 (13) and 89 (13), respectively. There was no clear evidence of effect on spirometry (Table S1), nutritional status (Table S1), HRQoL (Table S2), feelings of anxiety and depression (Table S3), medication adherence, or absenteeism and presenteeism.

Discussion

For adults with CF, we developed a novel app for reporting changes in symptoms suggestive of an exacerbation and investigated its effect on the number of exacerbations requiring IV antibiotics and other health outcomes. Adherence to the weekly use of the app was much greater than reported in previous telehealth studies in people with CF, and system usability was maintained above 85% at both 6 and 12 months. The 95% CI for between-group differences in the number of exacerbations requiring IV antibiotics suggest there was no important effect of the intervention. However, exacerbations requiring oral or IV antibiotics were detected earlier, and there was an increased prescription of oral antibiotics in the intervention group. There was no important effect on spirometry, nutritional status, HRQoL or feelings of anxiety and depression, medication adherence, or absenteeism and presenteeism.

The level of adherence (77%) to the use of our app was somewhat better than earlier work that has investigated home monitoring interventions, in which adherence has ranged from 10% to 67% (11-15). Any intervention that is inconvenient and time consuming will likely have poorer adherence, given it is in addition to the already large treatment burden that people with CF experience (21). Adherence in our study did vary though, with 14 (48%) participants using the app less than 80% of the required weeks. It is also difficult to determine whether adherence to the app reflects real world medication adherence, given the TAQ-CF likely contains self-report bias and complete data relating to pharmacy medication collection were not able to be obtained. Sub-group analyses suggest that those participants in the intervention group who were more adherent (≥ 80%) to the weekly use of the app experienced an increase in oral antibiotic use and a subsequent reduction in IV antibiotic use. Further investigation is needed to determine the characteristics of participants likely to have better adherence to apps and other monitoring interventions so that prospective studies can determine the effectiveness in this sub-group.

The high usability of our app is further supported by the low attrition from the intervention group (3%). This is considerably less than earlier studies of telehealth interventions in a CF population, in which attrition ranged from 24% to 63% (11-14). The level of adherence and low attrition in our study is likely attributed to the use of smartphones, a small and portable technology already incorporated into the lifestyle of the participants, and the once weekly reporting requirement which took only two minutes to complete. The usability scores at both 6 and 12 months reflected those reported in the previous usability study for this app (19). High usability was maintained through to 12 months, indicating that the app is a potential longer term solution within routine clinical care.

The earlier detection of exacerbations and increased provision of oral antibiotics in the intervention group did not translate into results compatible with an important reduction in the number of courses of IV antibiotics. The greater number of courses of IV antibiotics prescribed in the intervention group was consistent with the number of courses seen in the preceding 12 months, and was adjusted for in the analysis. This does raise the question as to whether the early provision of oral antibiotic treatment alone can translate into a reduction in the need for IV antibiotics, and highlights the limited options available for clinicians when treating exacerbations. Likewise, as noted for the difference in IV antibiotics, our data are compatible with no important differences in secondary outcomes such as spirometry, nutritional status, HRQoL, feelings of anxiety and depression, absenteeism and presenteeism and treatment adherence. Despite this finding, it is encouraging that the app provided a means of earlier detection of exacerbations, and if implemented over a longer surveillance period (e.g. 3 years), this may provide clearer answers regarding the potential longer term benefits such as slowing the rate of decline in lung function.".

We were surprised to see that when compared with the 12 months preceding enrolment, there was an important reduction in the number of courses of IV antibiotics in both groups during the 12 month intervention period. While this may simply reflect a spurious finding, it is likely that participating in a study of this kind led to increased contact with the CF centre and potentially offered greater opportunity for people to collect prescriptions from the hospital pharmacy. Participants in both groups attended a higher number of CF clinic visits than are currently recommended (i.e. 4 per year) (22); therefore involvement in the study seems to have improved access to care for all participants. The single centre design of this study is a limitation in the ability to generalise the results to other CF centres, and a larger multicenter study is now warranted.

The most common symptoms reported in our study were cough, sputum, fatigue, shortness of breath and chest tightness, mirroring those previously reported as being triggers for seeking treatment for an exacerbation by children and adults with CF (23). Most of the symptoms included in the app questions were adapted from Fuchs exacerbation scale (1), but of note the symptom 'chest tightness' was included as it has been previously reported by people with CF as being commonly associated with exacerbations (23). As there is no universal agreement on how to diagnose an exacerbation in this population, (24), we made the pragmatic decision to mirror clinical practice and relied on symptom reporting alone as the first line of detection.

We chose not to include monitoring with smartphone spirometry because of the increased burden on the participant, which is likely to have compromised adherence. Future studies planning to add additional technology to supplement data obtained from the app must carefully consider the benefit versus the risk to adherence. The use of other readily available smartphone technologies, such as measurements of daily steps may be a useful addition as physical activity may decline during exacerbations, and this data can be collected with minimal additional burden.

It is also possible that once weekly reporting of symptoms was insufficient and that increased frequency may be helpful. That is, with more frequent reporting of symptoms, exacerbations may be detected earlier than in the present study. Given the high level of adherence observed with weekly reporting, there is scope to increase this to two or three times per week; however the impact of increasing the frequency of reporting on adherence will need careful evaluation, especially given that the results of this study have not demonstrated that using an app is more effective than simply calling or emailing the CF team.

Conclusion

This is the first app used by adults with CF to report changes in their symptoms directly to the CF team. The high level of adherence is attributed to the low reporting burden and use of technology already owned by participants. Provision of the app facilitated the earlier detection of respiratory exacerbations and treatment in the form of oral antibiotics. While our data did not demonstrate an

important effect on the number of courses of IV antibiotics for the participants over a 12 month period, this study supports the continued development and investigation of similar apps and technologies used to identify exacerbations, with the aim of improving long term health outcomes.

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Authorship

JW, SJ, DP, SAM, SM, NC, SJ contributed to the conception and design of the study; JW, DP, SM contributed to the acquisition of data; JW, SJ, DP, SAM, SM, NC, NB, SJ contributed to the analysis and interpretation of data; JW, SJ, DP, SAM, SM, NC, NB, SJ drafted the article and gave final approval of the version to be submitted.

Declaration of conflicting interests

Mr. Wood reports grants from Sir Charles Gairdner Osborne Park Healthcare Group during the conduct of the study; A/Prof Jenkins reports grants from Sir Charles Gairdner Osborne Park Healthcare Group during the conduct of the study. A/Prof Putrino has nothing to disclose. Clin A/Prof Mulrennan reports grants from Sir Charles Gairdner Osborne Park Healthcare Group, during the conduct of the study; Principal Investigator in Vertex clinical trials, non-financial support from Novartis, outside the submitted work; non-financial support from Novartis, outside the submitted work. Mrs. Morey has nothing to disclose. Mrs. Cecins has nothing to disclose. Mrs. Bear has nothing to disclose. A/Prof Hill has nothing to disclose.

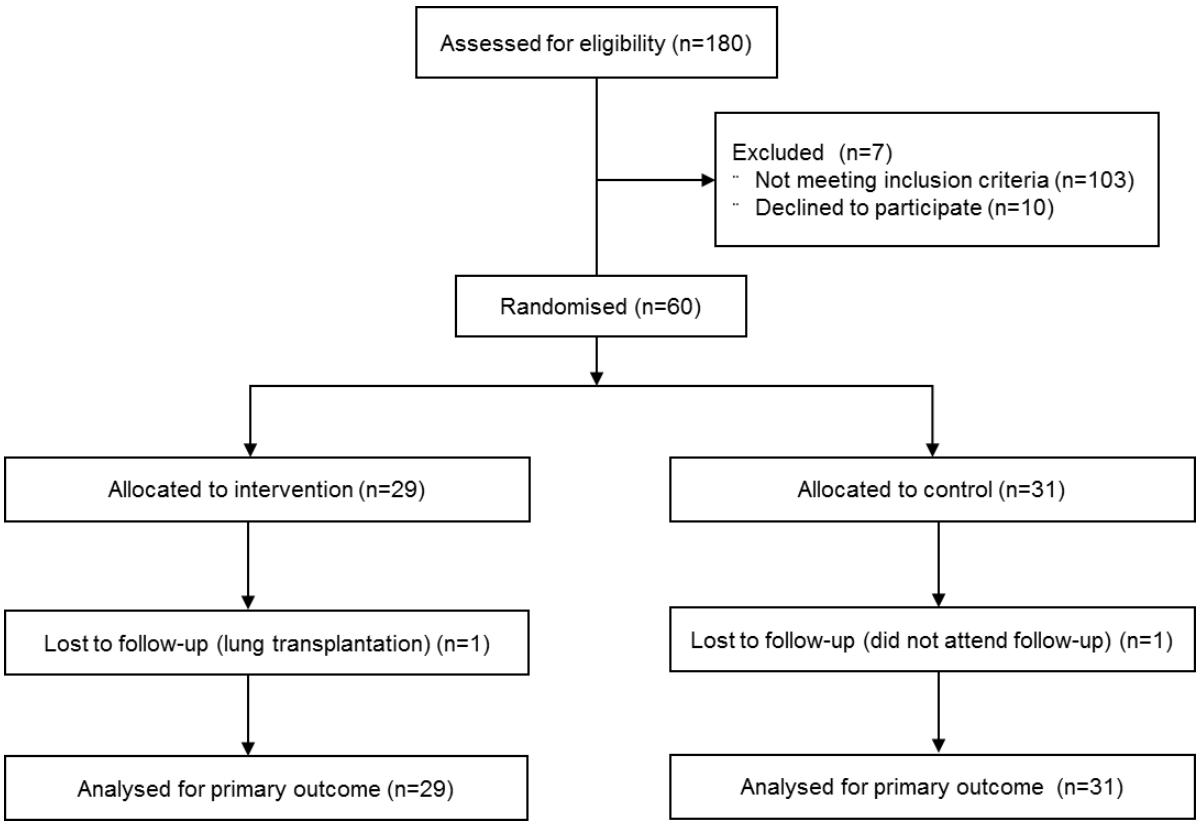

Figure 1. CONSORT flow diagram.

Table 1. Participant characteristics at baseline (n = 60)

	Intervention	Control
Participants, n (%)	29 (48)	31 (52)
Female, n (%)	17 (59)	12 (39)
Age, yr	31 (10)	31 (8)
FEV_1, % predicted	58 (18)	61 (17)
FVC, % predicted	71 (16)	78 (14)
BMI, kg/m^2	21 (5)	23 (3)
CFQ-R respiratory domain	67 (17)	71 (16)
IV antibiotics courses in past 12 months, n	60	45
Living in a rural / remote region, n (%)	4 (14)	6 (19)
Pseudomonas aeruginosa, n (%)	29 (100)	30 (97)
CF-related diabetes, n (%)	5 (17)	13 (42)
Pancreatic insufficiency, n (%)	23 (79)	29 (93)
ivacaftor or lumacaftor/ivacaftor, n (%)	8 (28)	9 (29)

Data are presented as mean (SD) unless otherwise stated. FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, BMI = body mass index, CFQ-R = Cystic Fibrosis Questionnaire – Revised, IV = intravenous.

Table 2. Participant healthcare utilisation data

	Intervention (n = 29)		Control (n = 31)			
	Nº	per participant	Nº	per participant	IRR	95% CI
IV antibiotic courses	42	1 (0 to 4)	30	1 (0 to 6)	1	0.6 to 1.7
IV antibiotic days	609	14 (0 to 64)	468	14 (0 to 105)	1.1	0.5 to 2.6
Oral antibiotic courses	71	2 (0 to 8)	46	1 (0 to 5)	1.5	1.0 to 2.2
Inhaled antibiotic courses	24	0 (0 to 4)	18	0 (0 to 4)	1	0.7 to 1.4
Hospital admissions	27	1 (0 to 4)	21	0 (0 to 5)	1	0.5 to 2.0
Admission days	244	4 (0 to 44)	214	0 (0 to 57)	0.9	0.5 to 2.0
CF clinic visits	249	9 (1 to 21)	216	6 (1 to 22)	1.1	0.8 to 1.4

Data are presented as number (Nº) and median (range) per participant. Analyses performed using Negative Binomial regression, adjusted for sex, forced expiratory volume in 1 second, and courses of IV antibiotics in the preceding 12 months, measured prior to randomisation.

IRR = incidence rate ratio. CI = confidence interval. IV = intravenous.

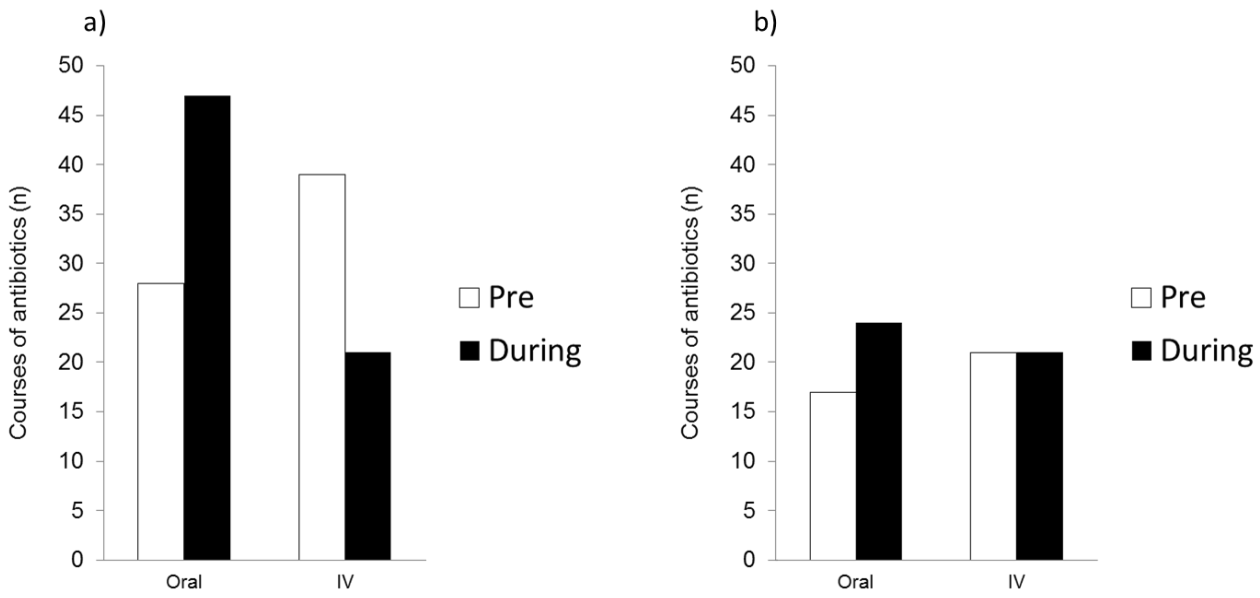

Figure 2. Intravenous and oral antibiotic use in the 12 months pre and during the study for a) participants in the intervention group who were ≥ 80% (n = 15); and b) < 80% adherent (n=14) to the weekly use of the app.

Data are presented as the total number of courses. Analyses performed using negative binomial regression. IV = intravenous.

a) An increase in oral antibiotic prescription (p = 0.02) and reduction in IV antibiotic prescription (p = 0.03) was observed during the intervention;

b) No change in oral or IV antibiotic prescription during the intervention.

Table 3. Smartphone application questions and response data for participants in the intervention group (n = 29). Questions required a 'yes/no' response

In the past week, have you had:	Nº	per participant
Worsening sputum volume or change in colour?	144	3 (0 to 22)
New or increased blood in your sputum?	50	0 (0 to 10)
Increased cough?	184	5 (1 to 28)
New or increased chest pain?	53	1 (0 to 20)
New or increased wheeze?	101	2 (0 to 25)
New or increased chest tightness?	124	2 (0 to 20)
Increased shortness of breath or difficulty breathing?	124	3 (0 to 19)
Increased fatigue or lethargy?	171	4 (0 to 28)
A fever?	39	0 (0 to 18)
Loss of appetite or weight?	52	1 (0 to 7)
Sinus pain or tenderness?	75	1 (0 to 19)
In the past week do you feel that your health has worsened?	143	4 (0 to 22)
In the past week, have you felt:		
Low in mood?	78	1 (0 to 19)
Worried?	79	1 (0 to 24)

Data are presented as the total number (Nº) of times each question had a 'yes' response, and the median (range) per participant.

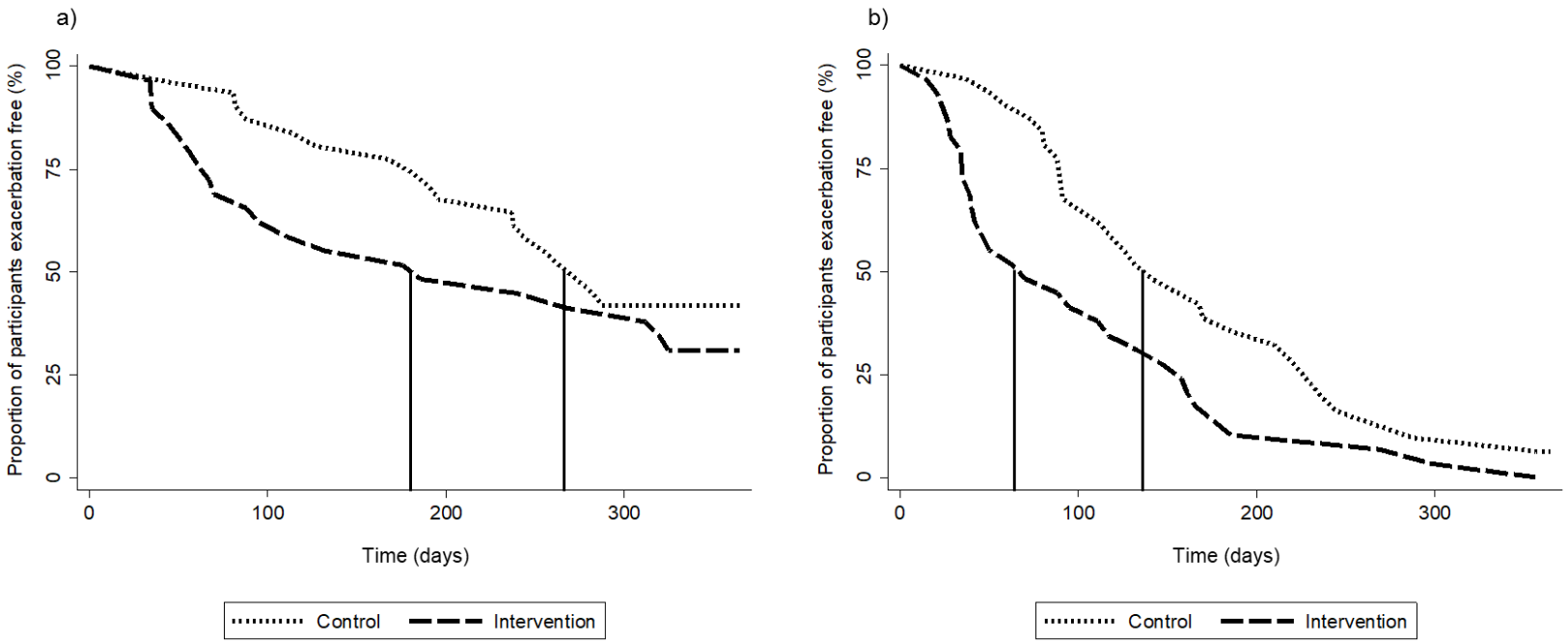

Figure 3. Time to detection of exacerbation requiring a) intravenous (IV) antibiotics; and b) oral or IV antibiotics plotted against time (days).

Data are presented as the proportion (%) of participants. Analyses performed using Kaplan-Meier, Cox regression. IV = intravenous.

a) No difference between the intervention and control groups (median ([IQR] of 186 [298] vs. 273 [184] days, respectively), p = 0.20; b) Shorter time to detection of exacerbation requiring oral or IV antibiotics in the intervention group compared to the control group (median [IQR] of 70 [123] vs. 141 [140] days, respectively), p = 0.02.

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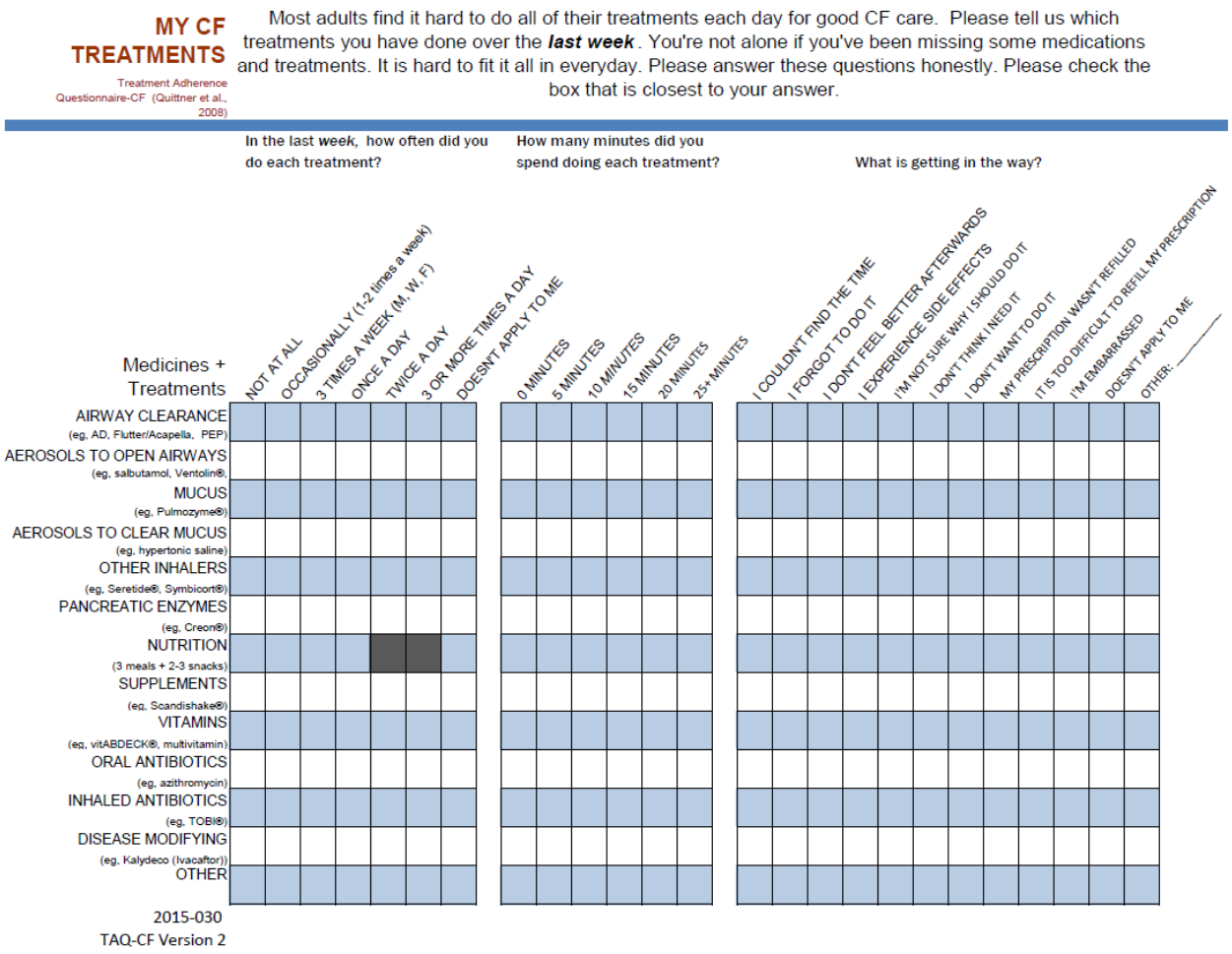
Appendix 10


MY CF TREATMENTS
Treatment Adherence Questionnaire-CF (Quittner et al., 2008)
Most adults find it hard to do all of their treatments each day for good CF care. Please tell us which treatments you have done over the last week. You're not alone if you've been missing some medications and treatments. It is hard to fit it all in everyday. Please answer these questions honestly. Please check the box that is closest to your answer.
In the last week, how often did you do each treatment?
How many minutes did you spend doing each treatment?
What is getting in the way?
Medicines + Treatments
NOT AT ALL
OCCASIONALLY (1-2 times a week)
3 TIMES A WEEK (M, W, F)
ONCE A DAY
TWICE A DAY
3 OR MORE TIMES A DAY
DOESN'T APPLY TO ME
0 MINUTES
5 MINUTES
10 MINUTES
15 MINUTES
20 MINUTES
25+ MINUTES
I COULDN'T FIND THE TIME
I FORGOT TO DO IT
I DON'T FEEL BETTER AFTERWARDS
I EXPERIENCE SIDE EFFECTS
I'M NOT SURE WHY I SHOULD DO IT
I DON'T THINK I NEED IT
I DON'T WANT TO DO IT
MY PRESCRIPTION WASN'T REFILLED
IT IS TOO DIFFICULT TO REFILL MY PRESCRIPTION
I'M EMBARRASSED
DOESN'T APPLY TO ME
OTHER: _____
AIRWAY CLEARANCE (eg, AD, Flutter/Acapella, PEP)
AEROSOLS TO OPEN AIRWAYS (eg, salbutamol, Ventolin®,
MUCUS (eg, Pulmozyme®)
AEROSOLS TO CLEAR MUCUS (eg, hypertonic saline)
OTHER INHALERS (eg, Seretide®, Symbicort®)
PANCREATIC ENZYMES (eg, Creon®)
NUTRITION (3 meals + 2-3 snacks)
SUPPLEMENTS (eg, Scandishake®)
VITAMINS (eg, vitABDECK®, multivitamin)
ORAL ANTIBIOTICS (eg, azithromycin)
INHALED ANTIBIOTICS (eg, TOBI®)
DISEASE MODIFYING (eg, Kalydeco (Ivacaftor))
OTHER
2015-030
TAQ-CF Version 2