PROTOCOL

Acceptability, feasibility and impacts of remote symptom monitoring and automated treatment plans in children with Cystic Fibrosis (CF) on highly effective modulators: a pilot randomised controlled trial.

HREC #: 91117

Protocol Version and date:
Version 2 28/10/2022

Document history:

Version Number and Date	Summary of changes
Version 1 26.10.2022	**Initial submission**
Version 2 28.10.2022	**Re-submission 1 to address ethics queries**

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

PROTOCOL SYNOPSIS

TITLE	Acceptability, feasibility and impacts of remote symptom monitoring and automated treatment plans in children with Cystic Fibrosis (CF) on highly effective modulators: a pilot randomised controlled trial.
STUDY DESCRIPTION	This is a pilot randomised controlled trial with participants randomly allocated to remote symptom monitoring and automated treatment plan care model (intervention group) versus usual hospital CF care (control group). The two models of care will be compared and the feasibility and acceptability of the new model of care will be assessed.
OBJECTIVES	Primary: 1. To assess the **uptake and feasibility** of the remote monitoring and automated treatment plans 2. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **family experience** 3. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **CF multidisciplinary team (MDT) experience** Secondary: 1. To understand **changes in outcome measures** over time between the two groups in children on highly effective modulators 2. To assess the **cost-effectiveness** of the remote monitoring and automated treatment plans compared to usual care by undertaking a health economic evaluation from healthcare and societal (family) perspectives.
OUTCOMES AND OUTCOME MEASURES	1. To assess the **uptake and feasibility** of the remote monitoring and automated treatment plans a. Number of symptom surveys completed (retention of participants and survey completion rate) b. Number of tasks completed c. Number of contacts between CF team and family (staff workload) 2. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **family experience** a. Semi structured interviews with participants investigating beliefs, acceptability and feasibility of the remote symptom monitoring and automated treatment plan care model b. Overall service satisfaction 3. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **CF MDT experience** a. Semi structured interviews with staff investigating beliefs, acceptability and feasibility of the remote symptom monitoring and automated treatment plan care model 4. To understand **changes in outcome measures** over time between the two groups in children on highly effective modulators a. Change in child lung function (Forced Expiratory Volume in 1 Second, FEV_1) b. Number of detected pulmonary exacerbations c. Antibiotic usage d. Child Quality of Life (measured with the CF Questionnaire Revised, CFQ-R and EQ-5D-Y)

	5. To assess the **cost-effectiveness** of the remote monitoring and automated treatment plans compared to usual care by undertaking a health economic evaluation from healthcare and societal (family) perspectives. a. Number of detected pulmonary exacerbations b. Antibiotic usage c. Number of hospital admissions and ED presentations d. Hospital length of stay e. Travel time and costs for appointments and admissions f. Caregiver time off work & patient time off school to attend appointments/admissions g. Number of contacts between CF team and family
TRIAL POPULATION	Children with cystic fibrosis on highly effective modulator therapy (either ivacaftor or elexacaftor–tezacaftor–ivacaftor (ETI)) under the care of the Royal Children's Hospital. Members of the RCH CF MDT
DESCRIPTION OF SITES	The Royal Children's Hospital (single site)
DESCRIPTION OF INTERVENTIONS	Intervention group participants will be asked to complete a symptom survey twice a week. Over the course of ensuing 12-months, if the system detects a pulmonary exacerbation is present, families will be asked to complete the symptom survey on a daily basis and will receive an automated treatment plan sent via the electronic medical record informing them of changes to their child's treatment plan. Control group participants will receive usual care for their child's CF at RCH which typically involves 4 outpatient clinics per year.
TRIAL DURATION	It is estimated that the trial will be completed in 18 months.
PARTICIPANT DURATION	Participants will be involved in the study for approximately 14 months, including the intervention period of 12 months and baseline and final semi-structured interviews.

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
CF	Cystic Fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
FEV1	Forced expiration in the first minute
CFQ-R	Cystic fibrosis questionnaire revised
ETI	Elexacaftor/tezacaftor/ivacaftor
RCH	Royal Children's Hospital
EMR	Electronic medical record
TGA	Therapeutic goods association
MDT	Multidisciplinary team
QOL	Quality of life
LOS	Length of stay
SPSS	Statistical Package for the Social Sciences

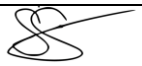
INVESTIGATOR AGREEMENT

I have read the protocol entitled “Remote symptom monitoring and automated treatment plans in children with Cystic Fibrosis”.

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki and the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.

I will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.

Name	**Role**	**Signature and date**
Jen Corda	Principal investigator	 17.10.2022
Shivanthan Shanthikumar	Associate Investigator	 22.10.22

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

This trial will be registered with the relevant clinical trial registries upon ethical approval and before the start of the trial intervention.

1.2. Sponsor

Trial Sponsor	MCRI
Contact name	Shivanthan Shanthikumar
Address	48 Flemington Road Parkville, 3052, Victoria
Sponsor-Investigator	Shivanthan Shanthikumar

1.3. Expected duration of study

Recruitment: 2 months

Intervention and follow period for participants: 12 months

1.4. Contributorship

Name	**Summary of contribution**
Jen Corda	Principal investigator, study design, data extraction and analysis, complete and analyse interviews, draft manuscripts
Dr Shivanthan Shanthikumar	Provide advice on study design and supervision throughout project
Professor Harriet Hiscock	Provide advice on study design and supervision throughout project
Dr Joanna Lawrence	Provide advice on study design and supervision throughout project
Diana Truong	Assist with data extraction
Andrew Dao	Assist with data extraction
Li Huang	Health economic evaluation

1.5. Stakeholder involvement

The Royal Children's Hospital (RCH) Cystic Fibrosis (CF) team have worked alongside the following stakeholders in the creation of the following protocol:

- RCH Virtual Care team
- RCH electronic medical record (EMR) team
- Five parents of children with CF, currently being cared for at RCH
- Melbourne Academic Centre for Health
- RCH Health Services Research Unit

Collaboration on prototypes of the remote monitoring system have been trialled and improved upon by the above teams over the past 18 months prior to the ethics application being submitted. Consumers were also involved in guiding the pilot protocol and plans for intervention.

2. INTRODUCTION AND BACKGROUND

2.1. Trial rationale and aim

The aim of this study is to assess the feasibility, acceptability, and potential effectiveness of a new model of care involving remote symptom monitoring and automated treatment plans in children with Cystic Fibrosis who are on highly effective modulators.

2.2. Background

Cystic Fibrosis (CF) is the most common genetically inherited life limiting disease caused by a defect on chromosome seven affecting the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene[1]. The *CFTR* gene encodes for an ion channel (also called CFTR) which helps regulate the movement of salt and water across the cell surface. The defect in the CFTR channel leads to dehydration of the cell surface liquid and the stagnation of movement of mucus which lines the cell surface. CF is a multisystem disease but primary manifestation is in the lungs, with decreased movement of mucus in the lungs leading to a recurrent cycle of infection and inflammation resulting in irreversible damage with respiratory failure being the most common cause of death[1]. Pulmonary exacerbations result in loss of lung function and in turn decreased life expectancy[2]. It is known that in approximately 25% of exacerbations people with CF do not return to their baseline lung function[3, 4]. It is proposed that delayed identification and treatment of pulmonary exacerbations may contribute to worse outcomes for people with CF. Several studies have found that those CF centres who review their patients more frequently and treat exacerbations more aggressively have better outcomes[5, 6].

Recently there have been advancements in the medical management of people with CF, with the introduction of new drugs targeting the effectiveness of CFTR channel. Collectively these drugs are called CFTR modulators, and they increase the cell surface liquid to varying effects improving outcomes for people with CF[7]. Two drugs have been deemed “highly effective modulators” in the CF literature, due to the significant improvements in outcomes seen in their associated trials. elexacaftor/tezacaftor/ivacaftor (ETI) and ivacaftor are the two highly effective modulators known to improve forced expiration volume in the first second (FEV_1), a measure of lung function, by over 10% and decreased pulmonary exacerbations by 35-63%[8-13]. These two drugs are available to approximately 90% of the CF population, with ivacaftor being approved by the Therapeutic Goods Association in 2014[14] and ETI being approved in March of 2022[15]. Currently much is unknown about both the short and long term impacts of highly effective modulators on symptoms exhibited during a pulmonary exacerbation. It is unclear how the improved health of people treated with highly effective modulators will impact on pulmonary exacerbation detection. For example, if modulator treatment result in milder symptoms during a pulmonary exacerbation, they may go undetected in the current care model which relies on patients and families recognising the symptoms.

Alongside these medical advancements in the care of people with CF, the COVID 19 pandemic led to a significant expansion in the utilisation of remote monitoring and virtual clinics. Prior to 2020 there

was limited literature relating to the use of remote monitoring or telehealth clinics in people with CF[16-25]. A multi-centre RCT from the United States, reported an increase in the number of pulmonary exacerbations detected in a home monitoring group compared to usual care, however this did not impact clinical outcomes in the trial period[18]. A more recent study demonstrated good participant engagement in their remote monitoring trial, however exhibited a large drop off rates in participant interaction with the remote symptom monitoring model as the study progressed [26]. Studies assessing symptoms remotely all required interactions between the participants and CF teams to implement treatments to any pulmonary exacerbations detected by the remote monitoring. Since this time, there have been vast technological enhancements to virtual platforms, app integration, remote monitoring through wearables and other devices, however integration into everyday care in CF remains limited.

The RCH CF service is limited by our current model of care which affords four clinics visits per patient per year. This means most children with CF get their symptoms monitored four times a year in clinic, leaving large gaps of time without assessment which may lead to unidentified and untreated exacerbations affecting their long-term outcomes. The current model of care also places a large burden on parents and carers of children with CF to monitor their child's symptoms between clinic appointments. The RCH CF team has worked hard to sign up 80% of its population to the RCH Patient portal and has gained access to home spirometers for most children over the age of 5 years, setting up the service to implement more remote monitoring.

Evidence gap

Currently there is no literature relating to remote symptom monitoring in the era of highly effective modulators in people with CF. It is unknown whether or not the significant improvements in clinical outcomes translate to changes in symptom presentations associated with pulmonary exacerbations. It is unknown whether remote monitoring will have the required sensitivity to detect pulmonary exacerbations in this new era.

Whilst remote monitoring and telehealth models of care have shown varying rates of feasibility and effectiveness, all previous studies have required the CF multidisciplinary teams (MDT) input to prescribe patients with treatment plans in the face of a pulmonary exacerbation. There is no known literature relating to implementation of automated treatment plans in people with CF.

This study will generate new evidence relating to the use of remote symptom monitoring and automated treatment plans in children with CF on highly effective modulators. To do so we will compare this new model of care to usual care in a pilot randomised controlled trial.

3 TRIAL OBJECTIVES AND OUTCOMES

3.1 Aims

In a sample of children with CF attending the RCH CF service and on a highly effective modulator, we aim to:

- evaluate the feasibility and acceptability of a remote symptom monitoring and automated treatment plan care model (intervention only)
- understand changes in outcome measures over time between the two groups in children on highly effective modulators; and

- determine the costs to the healthcare system and to families of the remote symptom monitoring and automated treatment plan care model versus usual care.

Hypothesis:
We hypothesise that compared with usual care, the remote symptom monitoring and automated treatment plan care model will:

1. Be an acceptable method of monitoring for families and the CF MDT;
2. Be a feasible method of monitoring for families and CF MDT;
3. Detect more pulmonary exacerbations earlier and enable earlier treatment than usual care; and
4. Be cost neutral compared to usual care.

Objectives:
Primary:

1. To assess the **uptake and feasibility** of the remote monitoring and automated treatment plans (measured as number of symptom surveys completed, and tasks completed);
2. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **family experience** (measured as experience of the program; acceptability of the program);
3. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **CF MDT experience** (measured as experience of the program; acceptability of the program) compared to usual care.

Secondary:

4. To understand **changes in outcome measures** over time between the two groups in children on highly effective modulators
5. To assess the **cost-effectiveness** of the remote monitoring and automated treatment plans compared to usual care by undertaking a health economic evaluation from healthcare and societal (family) perspectives.

Primary and Secondary Objectives	Outcome of Interest	Data Sources	Methods of collection	Period of Data Collection		
				3/12	6/12	12/12
ACEPTABILITY & FEASIBILITY						
1. What is the **feasibility** of the remote monitoring system for **families and CF MDT**?	What is the **uptake** of the remote monitoring and automated treatment plans (number of surveys completed, number of tasks completed, number of contacts between CF MDT and patients)	EPIC EMR	EPIC pre-made reports specific to the trial.	●	●	●
2. What is the **CF MDT's** experience of the remote monitoring system?	Confidence in system detecting exacerbation, appropriateness treatment initiated, confidence in navigating system and data in EPIC, feasibility/acceptability of the model	MDT semi structured interviews	Qualitative interviews completed via MS Teams	●		●
3. What is the **families** experience of the remote monitoring system?	Confidence in system detecting exacerbation, appropriateness treatment initiated, confidence in navigating the portal, feasibility/acceptability of the model	Family semi structured interviews	Qualitative interviews completed via MS Teams	●		●
CLINICAL EFFECTIVENESS						
4. What is the impact of remote monitoring on **changes in outcome measures** over time?	Number of pulmonary exacerbations detected, change in lung function, outpatient clinic visits, hospital admissions and length of stay, antibiotic usage and QOL scores	Trial data from EPIC Family Survey CFQ-R EQ-5D-Y	Chart review and EPIC reports, exacerbation survey & QOL surveys via REDCap	●	●	●
HEALTH ECONOMIC EVALUATION						
5. What is the **cost** of implementing the model of care? What is the **cost effectiveness**?	Costs of conducting the model of care compared to usual care; costs/savings of change in OP/admissions encounters; costs/savings to families compared with accessing usual care.	Trial data and supplementary unit costings	Trial data on the model of care, health service costs, health service use and patient costs and outcomes will be combined with relevant unit costs to produce a cost-effectiveness analysis.	●	●	●

TRIAL DESIGNOverall design

Design:

This will be a pilot randomised, non-blinded, single center trial in children with CF attending the RCH on highly effective modulators. The study will compare usual care to an intervention arm, with the intervention being the new remote symptom monitoring and automated treatment plan model of care.

Participants:

Participants will be children with a confirmed diagnosis of Cystic Fibrosis under the care of RCH, on a highly effective modulator (ETI or ivacaftor) and their caregiver. Participants will be included in the study only if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

- Diagnosis of Cystic Fibrosis
- On ETI or ivacaftor for a minimum of 2 weeks
- Clinically stable without antibiotic treatment for a pulmonary exacerbation in 2 weeks prior to consent
- Attending RCH CF clinic
- Able to complete home spirometry (standard of care for all children with CF >5 years at RCH CF clinic)
- Sufficient English to complete a survey
- Access to a smart phone to access remote symptom monitoring surveys

Exclusion criteria:

- Participants not signed up or not willing to sign up to the RCH Portal (note that 80% of RCH CF patients are already signed up to the portal)
- Participants who do not have access to a smartphone or computer on a daily basis
- Participants who do not have access to a home spirometer for lung function purposes
- Participants will be excluded from the study for technological access reasons such as lack of access to the RCH Portal and IT equipment as this is the basis of the intervention.

Sample:

Although this is a randomised controlled trial it is a pilot and currently there is no known sample size in the literature relating to a pilot trial. However, we will aim to include a minimum of 30 participants in the study in line with other pilot trials conducted by CI Hiscock [27]. We believe this will give us sufficient data on the feasibility and acceptability of the new model of care and potential effectiveness. If the intervention is feasible and acceptable the outcome data, which can be collected with minimal burden on participants and resources, will be crucial to inform sample size calculations for fully powered RCTs.

Recruitment:

Potential participants will be recruited through the following multi-pronged approach:

Patients

- *Self-enrolment:*

Participants will be sent information regarding the study, including study overview and contact details for the study team, in a letter signed by the CF centre director via the RCH Portal (Appendix 1). The letter will include a QR code taking interested families directly to a screening questionnaire for study eligibility (Appendix 2). If meeting eligibility criteria the participant will be linked to the PICF (Appendix 3) where they can read in more detail about the study. There will also be a child information sheet regarding the study. Families will indicate consent by checking a box at the start of the online survey and will subsequently be recruited into the study. Families will then complete the baseline demographic survey (Appendix 4). The initial demographic survey will include an item seeking their permission to contact them to potentially participate in a qualitative interview via MS Teams if allocated to the intervention arm. These families will be invited to include a preferred contact mode (either email or telephone) and a member of the research team will contact parents or carers via their preferred contact mode to invite them to participate in the interview.

- *Phone call enrolment:*

For those who do not self-enrol from the initial letter, a follow up phone call will be made by the principal investigator (an RCH CF physiotherapist) one week after letter has been sent out, to ascertain interest in the study. The principal investigator will explain the study to the potential participant. Interested families will complete the screening survey (Appendix 2) over the phone with the PI and will be sent links to the: 1) PICF (Appendix 3), 2) Online consent, and 3) Baseline demographic survey (Appendix 4) by the RCH portal.

- *Clinic enrolment (face to face or via telehealth):*

Potential participants attending their routine CF clinic may be approached by the principal investigator to ascertain their interest in the study. The principal investigator will explain the study to the potential participant. Interested families will complete the: 1) screening survey (Appendix 2) 2) PICF (Appendix 3), 3) consent, and 4) Baseline demographic survey (Appendix 4) in person or if time does not permit will be sent links by the RCH portal.

Recruitment will begin in December of 2022 and continue until February 2023 or until minimum sample size is achieved.

There are currently 100 children on either ETI or ivacaftor who are signed up to the RCH patient portal, showing that recruitment to this study is feasible.

CF MDT

All members of the CF MDT will be invited to participate in semi structured interviews (Appendix 6) via email as part of the acceptability and feasibility evaluation.

Consent:

Parents

In the initial explanatory letter sent to participants a link a brief inclusion/exclusion survey will be included. If participants meet these criteria, they will be directed to the Participant Information and Consent Form (PICF) (Appendix 3). This document will describe the purpose of the trial, the procedures to be followed, and the risks and benefits of participation – as per the initial letter sent to them. It will be made clear that all participants will be free to withdraw from the study at any time without jeopardizing their medical care. Informed consent will be obtained from the parent/caregiver prior to baseline demographic survey commencement.

Children with CF

For all consent approaches age appropriate written and/or oral information will be provided to the child/adolescent in accordance with their level of maturity (where appropriate). The investigator will provide the Parent/Guardian Information and Consent Form to the parent/legal guardian and, the Participant Information and Consent Form to the child/adolescent. Both of these documents are listed in Appendix 5 This document will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The parent/legal guardian will be invited to provide written consent. Where deemed competent and mature to provide consent, the child/adolescent will also be invited to provide written consent. The level of maturity will be determined by the Investigator in accordance with local process. Consent will be voluntary and free from coercion.

CF MDT staff

CF MDT will be sent a PICF (Appendix 6) describing the purpose of the trial and inviting them to participate in semi-structured interviews. Once consent has been gained, the PI will contact them to make a time for the semi-structured interview.

Randomisation:

Randomisation will occur after consent in signed and will be performed by a person independent to the study. A stratified randomization will be employed with the goal of ensuring balance between study arms by risk category employed by the RCH CF team. The randomisation schedule will be created by computer-generated random numbers, before the first participant has been recruited. The participant cohort will be stratified by child risk category (2 levels of category: 1 Very high risk & high risk and 2 Medium risk & low risk). Within each strata, permuted block randomisation will be used to ensure balance between the intervention and control group. A randomly generated sequence of block sizes containing 2, 4, or 6 participants will be used. This will help ensure balance in numbers between intervention and control groups, prevent potential confounders of risk category type impacting the measurement of outcomes, and prevent any predictability in intervention allocation[28]. The schedule will be held by an independent person, and allocation will not be

revealed prematurely to CI. Because of these procedures, the research team will be unable to predict which group the participant will be allocated to.

4 STUDY VISITS AND PROCEDURES

Study timeline:

Information relating to study sent via letter		
Opportunity for self-enrolment, clinic enrolment, phone enrolment	A	
Consent	B	
Randomisation	Intervention	Control
Baseline data collection	C D E	C D E
3 months	F G H	F G
6 months	F G	F G
12 months	D E F G H	D E F G

A	Survey screening for inclusion/exclusion criteria sent to all potential participants
B	Children meeting inclusion criteria and interested in study referred to PICF and consent form
C	Demographic information (as part of the baseline questionnaire)
D	Spirometry
E	CFQ-R & EQ-5D-Y (as part of the baseline questionnaire)
F	Data download from EPIC (admissions, LOS, contacts with CF team)
G	Online follow up questionnaire
H	Semi structured interviews

Description of intervention

Remote symptom monitoring and automated treatment plans:

Participants randomised to the intervention arm will receive onboarding material (Appendix 7) detailing instructions of how to access and use the remote monitoring system via the RCH portal.

Participants will be asked to complete two surveys:

1. Baseline symptom survey (Appendix 8)

Participants will be prompted to complete survey by a push notification sent to their mobile phone and built into EPIC at the:

- Commencement of the trial;
- Each month post commencement of the trial; and
- After each exacerbation is detected.

2. Twice weekly symptom survey (Appendix 8)

Participants will be prompted to complete a survey by a push notification sent to their mobile phone and built into EPIC twice a week

The survey is a validated tool for detecting pulmonary exacerbations in people with CF[29].

A score is assigned to each survey field. Every symptom-monitoring questionnaire completed by the patient or patient's family is compared to their last known baseline questionnaire.

If the frequency or severity of **two or more symptoms** have worsened compared to baseline, the **Exacerbation Pathway** is triggered (Appendix 9 for exacerbation calculations).

If the system detects an exacerbation, it will send an automated treatment plan out to the patient and their caregiver including:

- Directions to commence a specific antibiotic
- Directions to change/or increase airway clearance and inhalation therapy.

Information regarding antibiotic, airway clearance and inhalation therapy prescription will be extracted from the participant's EPIC file.

At this time participants will be asked to complete their **symptom survey on a daily basis.**

A message will be sent to the CF team alerting them of the exacerbation and the results of the symptoms survey. The RCH respiratory lab will book a telehealth appointment to perform home lung function to provide further detail of the exacerbation. Lung function will be performed at the start of the exacerbation and at 10-14 days later.

10-14 days after the exacerbation pathway is triggered, the program will assess if symptoms reported in the daily symptom survey have returned to baseline or not.

If the patient symptoms return to (or are better than baseline) on day 10-14:

1. The program re-assigns the non-exacerbation tasks:
    a. Monthly baseline questionnaire
    b. Symptom-monitoring questionnaire (twice a week).
2. An automated In Basket message will be sent to the CF team notifying them that the exacerbation has ceased.
3. An automated message is sent to notify the participant that symptoms have improved and the exacerbation has ceased, instructing them to cease antibiotics (if not already), return to baseline airway clearance and inhalation therapy and complete their normal twice weekly symptom surveys.

If the patient symptoms do not improve on day 10-14 (Extended Exacerbation):

1. An In Basket Message will be sent to the CF team prompting for a clinical review via telehealth.
2. A notification will be sent to the participant via the portal notifying them that their symptoms have not become better and expect contact from the treatment in 24 hours.

The RCH EMR team have designed a workflow for the pilot to help assist in ensuring all aspects of care are completed.
Participants randomised to the intervention group will also receive all aspects of usual care in

addition to the above information, including quarterly visits to the CF clinic.

Usual Care:
Participants in the control arm will receive usual which consists of quarterly CF clinic visits and more urgent visits triggered by telephone calls from families concerned about their child's clinical status. This model of care relies on the participant/caregiver contacting the CF team if they notice a change in their symptoms.

Questionnaires
All online questionnaire links will be sent to participants via the portal.

Screening questionnaire:
A once off screening questionnaire will be linked to the initial study letter for participants to fill out prior to accessing the PICF and consent forms (Appendix 2).

Baseline:
Demographic questionnaire and data collection
A baseline demographic survey will be sent to all participants after online consent is gained (Appendix 4). Patient demographic and baseline data will also be collected via the EMR (Appendix 11)

Cystic Fibrosis Questionnaire- R (CFQ-R)
The CFQ-R (Appendix 12) is a validated questionnaire used to assess the health-related quality of life of people with CF of all ages [30]. It contains five generic domains, four specific domains, three

symptom scales and an overall health perception scale. It takes approximately 10 minutes to complete and can be self-administered.

EQ-5D-Y
The EQ-5D-Y (Appendix 13) is a validated survey assessing quality of life in a range of populations including CF [31]. It is a five-dimension survey encompassing mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. It takes approximately 3 minutes to complete

3, 6 & 12 month follow up survey
A follow up survey will be sent to both the intervention and control group at 3, 6 and 12 months and will ask about number of pulmonary exacerbations, and data for health economics evaluation (e.g. time off work, travel costs) and information relating to burden of trial (Appendix 10)

At 12 months the *CFQ-R and EQ-5D-Y* will be completed also.

Procedures:
Spirometry

Spirometry will be performed either in person or via telehealth as is usual care for children with CF. Spirometry and lung volumes will be measured in accordance with international standards, utilising Jaeger Masterscreen body or Pneumo respiratory function equipment [32]. All pulmonary function testing will be carried out by experienced paediatric physiologists. If spirometry is performed at RCH, height will be measured to the nearest 0.1cm utilising a stadiometer (Seca) and weight will be measured with minimal clothing the nearest 0.1kg (Tanita). In keeping with current clinical practice, for spirometry performed via telehealth, anthropometric data will either be reported from measurements taken at home or the most recent in hospital measurements will be used.

Interviews:

Semi structured interviews (caregivers)

The initial demographic survey will include an item seeking caregiver permission to contact them to participate in a qualitative interview via MS Teams if in the intervention arm. These families will be invited to include a preferred contact mode and a member of the research team will contact caregivers via their preferred contact mode to invite them to participate in the interview. The PICF (Appendix 3 & 5) will outline that any interviews as a part of the study are purely voluntary.
Semi-structured interviews will be scheduled based on feasibility and preference. At the initial time of consent, the researcher will describe to the participants the reason for conducing the interview by providing a copy of the PICF (Appendix 3 & 5). The researcher will invite and respond to any questions or concerns from participants and invite participants to sign a consent form.
Participants will be informed of confidentiality procedures and that the interview will be audio recorded on MS Teams for research purposes. The participant will be advised that they can turn off their camera if they do not wish for a visual image to be recorded. If participants decline to be recorded, the interview will proceed with the PI taking notes of discussion. Prior to commencing the interview, the researcher will inform participants that they are able to stop the interview at any time

and revoke their consent to participate during or after the interview. In this event, interview recordings and transcripts will be removed from the study and destroyed. The withdrawal of participants at any part of the study will not affect their care in any way.

We aim to conduct interviews with up to 15 parents. The interviews aim to understand caregiver's experiences of the new model of care, including potential benefits, risks, ease of use and future improvements. Interview guide for parent semi structured interviews can be found in Appendix 14.

Semi structured interviews (CF MDT)

Members of the CF MDT will be approached by the principal investigator via email to ascertain their interest in participating in a semi-structured interview. Interviews will be scheduled based on feasibility and preference.

At the initial time of consent, the researcher will describe to the participants the reason for conducing the interview by providing a copy of the PICF (Appendix 6). The researcher will invite and respond to any questions or concerns from participants and invite participants to sign a consent form.

Participants will be informed of confidentiality procedures and that the interview will be audio recorded on MS Teams for research purposes. The participant will be advised that they can turn off their camera if they do not wish for a visual image to be recorded. If participants decline to be recorded, the interview will not proceed. Prior to commencing the interview, the researcher will inform participants that they are able to stop the interview at any time and revoke their consent to participate during or after the interview. In this event interview recordings and transcripts will be removed from the study and destroyed.

We will aim to perform interviews with as many members of the CF MDT as possible, aiming a minimum of 5 staff members. The interview guide for CF MDT semi-structured interviews can be found in Appendix 15 and aims to explore experiences of the new model of care, including potential benefits, risks, ease of use and future improvements.

EPIC reports

Pre-made reports have been created in EPIC associated with the remote symptom monitoring and automated treatment plan model of care. The report collates the following information for intervention group participants only:

- Number of baseline surveys completed
- Number of symptom surveys completed
- Number of exacerbations
- Length of exacerbation
- Symptoms experienced with exacerbation
- Number of airway clearance tasks completed.

This will assist with monitoring of intervention uptake and feasibility.

Other data to be collected from EPIC across the intervention and control groups include:

- Number of hospital admissions due to pulmonary exacerbation
- Hospital length of stay
- Number of CF specific outpatient appointments (face to face and telehealth)

- Number of contacts made with participants (portal messages, phone, email)

These data will inform the health economic analysis.

Discontinuation of intervention
Participants are free to withdraw from the trial at any time upon their request or the request of their legally acceptable representative. Withdrawing from the trial will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals.

If a participant chooses to discontinue with the intervention the principal investigator will phone the participant to understand reason for withdrawal.

Non-adherence to the trial will not be grounds for discontinuation as this is a feasibility trial, it is important to understand reasons for non-adherence.

Losses to follow-up

A participant will be considered lost to follow-up if he or she fails to partake in follow up surveys and is unable to be contacted by the principal investigator. The following actions must be taken if a participant fails to complete scheduled assessment:

- The principal investigator will attempt to contact the participant and reschedule the surveys and ascertain if the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

5 SAFETY MONITORING AND REPORTING

Adverse events (non-serious and serious) will be captured from the time of first administration of the intervention until conclusion of the intervention and all events will be followed until resolution or stabilisation.

Risks:

Risk/Benefit assessment

Known potential risks

- Increased burden of care to families by having to fill out the symptom surveys twice a week
    - Survey will take approximately 3 minutes to fill out each time
- Participants not filling out the survey and therefore not gathering enough data to assess feasibility/effectiveness
- Increased workload for CF team without extra funding
    - The pilot allows patients and families to directly contact the CF team which may increase contacts

    - The pilot may identify more pulmonary exacerbations compared to usual care which may increase contacts with CF team
- Underestimating/overestimating pulmonary exacerbations in patients leading to changes in treatment
    - Underestimating: the system may miss small exacerbations where families would normally self-initiate antibiotics and increase airway clearance, thereby undertreating
    - Overestimating: the system may over detect small exacerbations where families would normally not initiate antibiotics and increase physiotherapy, thereby leading to increased utilisation of antibiotics, however increased airway clearance may benefit the patient without clinical harm.

Known potential benefits

- It is well known that earlier detection and aggressive treatment of pulmonary exacerbations leads to better outcomes in people with CF
- Increased and clearer pathways of communication with CF team
- Continuous rather than episodic care
- Increased participant understanding of what an exacerbation entails
- Symptom monitoring storage in EPIC to help inform traditional CF clinic reviews and improving in-clinic efficiency
- Ongoing symptom monitoring helping to guide ongoing treatment decisions

Assessment of potential risks and benefits

- Underestimating/overestimating pulmonary exacerbations in patients leading to changes in treatment
    - Utilisation of a survey based on a validated survey
- Increased burden of care to families by having to fill out the symptom surveys twice a week
    - Patient choice to fill out survey
- Increased workload for CF team without extra funding
    - Mostly automated system, relieving large burden on CF team
    - CF team involved in design of the intervention

6 Analysis:

STATISTICAL METHODS

Methods of analysis

Quantitative analysis:

Statistical analysis will be performed utilizing Statistical Package for the Social Sciences (SPSS). Descriptive statistics will be presented as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables will be reported descriptively using frequency (n) and proportion (%).

Primary analysis:

1. To assess the **uptake and feasibility** of the remote monitoring and automated treatment plans
    a. Total number of symptom surveys completed will be compared to total number of surveys expected and presented as a percentage.
    b. Total number of tasks completed will be compared to expected number of tasks completed and presented as a percentage.
    c. Number of contacts between CF team and family will be collated and compared between the intervention and control group using paired t tests or the non-parametric equivalents.

Secondary:

1. To understand **changes in outcome measures** over time between the two groups in children on highly effective modulators
    - Number of exacerbations detected
        - Total number of exacerbations per year will be calculated in each arm and presented descriptively. Comparison between groups will occur using t-tests or Chi squared test (or non-parametric alternatives as required)
    - Change in FEV_1
        - Data will be expressed as litres and percentage predicted. For each individual the FEV_1 at study entry will be compared to the FEV_1 at study completion, to determine the change in FEV_1. The average change in FEV_1 between the intervention and control group will then be compared using t-tests or Chi squared test (or non-parametric alternatives as required).
    - Number of admissions
        - Total number of admissions per year will be calculated in each arm and presented descriptively. Comparison between groups will occur using t-tests or Chi squared test (or non-parametric alternatives as required)
    - Hospital length of stay
        - Total number of hospital days per year will be calculated in each arm and presented descriptively. Comparison between groups will occur using t-tests or Chi squared test (or non-parametric alternatives as required)
    - CFQ-R
        - Total score (mean and standard deviation) will be presented descriptively and comparison between groups will occur using t-tests or Chi squared test (or non-parametric alternatives as required)
    - EQ-5D-Y
        - Total score (mean and standard deviation) will be presented descriptively and comparison between groups will occur using t-tests or Chi squared test (or non-parametric alternatives as required)

2. To assess the **cost-effectiveness** of the remote monitoring and automated treatment plans compared to usual care by undertaking a health economic evaluation from both the perspective of the healthcare system and caregivers.
    a. The cost of the new model will be estimated from the study protocol and budgets.
    b. Difference in the patient's quality of life (EQ-5D-Y and CFQ-R) will be measured within the trial period for each arm and calculated using an area under the curve method.
    c. Health service cost from hospital linked data along with patient costs will also be incorporated
    d. Cost-effectiveness estimates of a cost per exacerbation avoided and cost per QALY for the new model compared with standard care will be generated for the trial period to justify the value of the new model of health monitoring.
    e. Sensitivity analyses will be used to explore the variation in data. Wide cost confidence intervals are expected with a pilot study. The data collection will however inform acceptability and feasibility of economic data and contribute to the case or otherwise for a full trial.

Qualitative analysis:

Primary analysis:

1. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **family experience** (measured as experience of the program; acceptability of the program) compared to usual care;
2. To assess the **impact and acceptability** of the remote system monitoring and automated treatment plans on **CF MDT experience** (measured as experience of the program; acceptability of the program) compared to usual care.

Semi structured interview transcripts will be imported into NViVo for analysis. Inductive thematic analysis will be used, where initially text will be coded relating to factors influencing family and CF MDT perceptions and attitudes to the new model of care. Themes will be developed relating to codes, emerging inductively from the data. An audit trail will be produced to keep a record of coding decisions. De-identified quotations will be used from the transcripts to illustrate important aspects of parent's and the MDT staff attitudes to the new model of care versus usual care.

7 DATA AND INFORMATION MANAGEMENT

Overview

The Principal Investigator is responsible for storing essential trial documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

Data storage:

Quantitative data:

Will be captured from the patients' medical record and inputted into REDCap. Access to REDCap is an MCRI user account, REDCap has functionality that makes adding and removing users and managing user permissions straightforward. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users that are granted permission to view it. Data will be exported from REDCap for the purpose of analysis, as REDCap does not have the functionality to do data analysis. Once exported, the data will be stored in a restricted access folder on the RCH network drive on a password protected computer and will be made available for importing into the project secure research environment. Only designated study team members will have access to the data. Regular back-ups of this data will be made in accordance with RCH IT processes.

All surveys will be completed via REDCap and stored here.

Qualitative:

Interviews: Data will be collected in the form of audio recording and will be transcribed by a member of the research team and then uploaded into NVivo for analysis. All transcriptions and data analysis will be stored on the RCH network drive in a password-protected folder.

Confidentiality:

Participant confidentiality is strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents.

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

- The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.
- Participant identifiers will be stored securely in REDCap which has permission control functionality.
- Participant data will be identified through use of a unique participant study number/code assigned to the study participant and these will be securely stored on REDCap using its permission control functionality
- Separation of the roles responsible for management of identifiers and those responsible for analysing content. Data will be stored securely in REDCap which has the functionality to provide users with different levels of access. Only the level of access required to complete their role will be provided to the research team members. For example, data analysts will only be provided access to variables not labelled as 'identifiers'.

Disposal of data:

Audio recordings from semi structured interviews will be destroyed once transcribed. All other study information will be kept until five years after the end of the study as per guidelines. All electronic data stored will be managed by Project Team. The data will be used for research directly related to this study.

8 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

There are no financial and other competing interests for investigators for the overall study.

Dissemination of results:

At the end of the project the investigators will send a letter to participants detailing the results of the study. Final results of the study may be presented as a conference abstract and prepared as a manuscript for submission to a peer-reviewed journal.

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