CFHealthHub Data Observatory

A Quality Improvement project and Trials within Cohort platform for Cystic Fibrosis

RESEARCH PROTOCOL
Version 9.0   19 March 2020

IRAS: 216782
STH: 19387

Authorised by: Martin Wildman

Funding

Roles and responsibilities

Names, affiliations, and roles of protocol contributors

The following all contributed to drafting elements throughout the protocol: Martin Wildman, Consultant Respiratory Medicine (Sheffield Teaching Hospitals NHS Foundation Trust); Pauline Whelan, mHealth Applications Manager (University of Manchester); Kimberley Horspool, Carla Girling Study Manager, Daniel Hind, Assistant Director, Mike Bradburn, medical statistician, Amanda Loban, data manager (Sheffield Clinical Trials Research Unit, University of Sheffield).

MW is the guarantor of the study design; MB is the guarantor of the statistical design and analysis plan

Sponsor

Sheffield Teaching Hospitals NHS Foundation Trust
D Floor
Clinical Research Office
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF
Tel: (0114) 2256424
Fax: (0114) 2265937

Role of study sponsor and funders

Neither the funder nor the sponsor have had any role in study design, data collection and analysis, decision to publish, or preparation of manuscripts.

Key Contacts

Study Manager

Carla Girling
Clinical Trials Research Unit
The University of Sheffield
School of Health and Related Research
30 Regent Street
Sheffield
S1 4DA
Tel: (0114) 222 4027
Fax: (0114) 222 0870
e-mail: c.girling@sheffield.ac.uk

Chief Investigator

Dr Martin Wildman
Adult CF Centre
Northern General Hospital
Herries Road
Sheffield
S5 7AU

Tel: (0114) 2715212
Fax: (0114) 222 0870
e-mail: Martin.Wildman@sth.nhs.uk

Composition, roles, and responsibilities

Project Management Group

Name	Role	Institution
Dr Martin Wildman	Chief Investigator	Sheffield Teaching Hospitals NHS Foundation Trust
Professor Cindy Cooper	CTRU Director	School of Health and Related Research, University of Sheffield
Carla Girling	Study Manager	School of Health and Related Research, University of Sheffield
Emma Young	Research Assistant	School of Health and Related Research, University of Sheffield
India Davids	Research Assistant	School of Health and Related Research, University of Sheffield
Dr Pauline Whelan	m-Health Applications Manager	Farr Institute, University of Manchester
Prof Madelynne Arden	Behavioural Psychologist	Sheffield Hallam University
Marlene Hutchings	Lead CF physiotherapist	Sheffield Teaching Hospital NHS Foundation Trust
Amanda Bevan	National CFHH lead Pharmacist	University Hospital Southampton NHS Trust
Charlotte Carolan	National CFHH Quality Improvement Lead	Sheffield Teaching Hospitals NHS Foundation Trust
Sophie Dawson	National CFHH Quality Improvement Lead	Nottingham University Hospital NHS Foundation Trust

Contents

Tables

Figures

Protocol amendments since version 1

Version number	Changes made
2	Section 7.3.3. Correction to describe roles under the CIC will be contracted, not sub-contracted. Table 2. Consent statement removed.
3	Expansion of Project Management group to include Professor of Health Psychology and Research Physiotherapist, removal of team member no longer supporting PMG. Date of site opening amended in Lay Summary, clarified informed consent process, including sending letter to patients' GP to inform of participation and make follow up recruitment call optional (Section 5.5). Updated Table 2 to reflect new consent statement. Update to Uncontactable participants (Section 5.6) to reflect optional telephone call. Additional section on re-screening (Section 5.7), screening new patients (Section 5.8) and patient stories (Section 5.10). Removed unnecessary detail training for CF team (Section 6.1). Patient data collection; additional patient reported questions on effort and automaticity at baseline (Section 6.2), Table 3 updated to be consistent and additional clarity on time points for data collection including the removal of prospective data collection for exacerbations (updated also in 7.4) and inclusion of chipped nebuliser data from existing devices, patient report effort and automaticity of nebuliser use at baseline and review, patient reported involvement in other research studies at baseline and review, additional criteria used for screening (pseudomonas status, diabetes status, deprivation index, lung transplant status) and removal of 2 year time window for adding retrospective data to CFHealthHub. A period of 4 weeks between consent and ongoing support for adherence (Section 6.3). Quality Improvement baseline adherence questionnaire will be administered to each CF centre prior to undertaking QI work (Section 6.5). Acronym 'TWiCs' updated throughout. Anonymised Screening data to be encrypted and sent to Sheffield CTRU(Section 7.2).
3.1	Recruitment of patients for studies supported in the Data Observatory can be performed by a member of the local CF team
4	Change of Project Management group membership to remove Kim Horspool as Study Manager and include Anna Packham as Research Assistant. Exclusion criteria updated (Section 5.2.2) to exclude patients post lung transplant. Behaviour change intervention to be offered two months post consent visit (Section 6.3). Research requesting use of the Data Observatory platform requirements updated to include approval from recognised ethics committees outside of the NHS (Section 6.7.2). New section added (Section 7) to detail the Process Evaluation sub-study. Appendix 1 added to document the Data Observatory Logic Model.
5	Kimberely Horspool removed as Study manager throughout document. New section 5.9 added to detail the phased approach for existing CFHealthHub RCT participants. Section 5.10 withdrawal option updated to remove option to use CFHealthHub without participating in the study. New section (5.11) added to detail request and linkage of HES data. Table 3, section 9 updated to include HES data, section 9.2 data handling and recording keeping updated to include details for HES data, removal of 1998 DP act. Section 9.3.3 updated to 2019 (removing 2017) as the year of transition into the CIC. Sponsor named as data controller.
6	Additional information in section 5.11 to detail video recordings of participants for conferences and training/educational purposes.
7	Project management group updated. Spelling and grammar corrections throughout. Clarity of the aims of the project by specifying the aim to study implementation. The process for recruitment of new participants into Data Observatory and full transition of RCT sites

	described in section 5.9. Sampling wording updated. Section 4.4.2 updated to explain end of the use of the Binebs, and the inclusion of ineb devices. Clarity in section 4.6 that CFHealthHub also collects metrics on usage by the clinical team, and that usage data will be shared. Ongoing support for patients section (section 6.3) updated to explain new participants in 2019 will not require a two month gap between consent and CFHealthHub access/support.
8	Inclusion of additional study objective required by the funder for 2019-2020. Confirmation of ineb device entry, and explanation of bineb devices being removed from the study. Removal of lung transplant exclusion criteria. New section (6.8) to describe the inclusion of three work packages for medicines optimisation for completion during 2019-2020 funding. Updates to section 7, Process Evaluation, to give details of data collected from the revised logic model and the inclusion of a questionnaire for healthcare professionals at participating CF centres to complete to measure barriers to implementation. Sampling of health care professionals in phase 4 sites clarified. Logic model revised (see appendix 1). Inclusion of implementation strategy (appendix 2).
9	Addition of new/changed project management members under the 2019-2020 CF self-care CQUIN funding. All further changes made to adapt CFHH to changing healthcare system during the COVID-19 pandemic. For pwCF, CFHH must continue to be available and accurate, to support participants with adherence to their preventative inhaled medications. Section 5.5 new information about using telephone consent appointments to reduce unnecessary patient contact. Section 6.3 amended so that CFHH central team can perform local CFHH researcher functions during the pandemic, allowing patient continuity on CFHH during potential NHS staff shortages. Footnote added to specify who these members would be. Appendix 3. New appendix added detailing COVID19 adaption protocol for adherence support, ensuring that CFHH remains available for participants during the pandemic.

Lay Summary

Cystic Fibrosis (CF) is an inherited disease affecting 10000 people in the UK with an average age at death of 28 years in 2012. The lungs of people with CF (PWCF) are prone to infections. Daily physiotherapy and inhaled medications are needed to stay healthy. Around £30 million is spent annually on inhaled therapy but average adherence has been shown to be only 36%. Data suggest that adherence is better in younger children (71% in under 12s, falling to 50% in teenagers) but of the 10000 UK PWCF almost 6000 are now adults. PWCF who collect <50% of their medication cost the healthcare system significantly more than PWCF who collect more than 80% and most of the additional cost results from unscheduled emergency care and hospital admission. This unscheduled emergency care is distressing for PWCF and their families.

Current research investigating whether adult PWCF can build successful, self-management, treatment habits using dose-counting nebulisers to collect adherence data, displaying this data on a website (CFHealthHub) and using a behaviour change toolkit, supported by a health professional, is ongoing. (ACtiF study funded by the National Institute for Health Research, Programme Grants for Applied Research programme RP-PG-1212-20015).

The current study aims to develop CFHealthHub as a Data Observatory or cohort. There are two purposes; first, adherence data from PWCF using dose-counting nebulisers will be shared with health professionals to explore how adherence data can be used within routine care encounters and within Quality Improvement (QI) projects to deliver improved care locally and nationally. Second, collecting data from a large number of PWCF may support future CF research studies, focussing moreover on behaviour change. This approach, called 'Trials within Cohorts' (TwiCs) will help CF researchers to overcome the difficulties associated with conducting research in rare conditions such as high costs and poor recruitment.

Over the next 4 years we will recruit as many as possible of the 6000 adults with CF in the UK. Recruitment will begin from early 2017 when we will start to recruit up to 140 participants in Sheffield who will use chipped nebulisers as part of routine care. In 2017 35 patients in Nottingham, and 35 Southampton and Poole (Southampton and Poole is a single CF unit across two hospitals) who had been using chipped nebulisers as part of a pilot study will complete the pilot and be invited to join the Data Observatory and continue using the chipped nebulisers as part of standard care. From September2017 a further 100 patients in Nottingham and a further 100 in Southampton and Pool will be invited to join the Data Observatory. With appropriate consent, adherence data and patient data from CF registry and patient notes will be stored within CFHealthHub. CFHealthHub will capture information related to their prescription, treatment habits, motivation and barriers for self-management and behaviour change, identified by patient's personal details (name, DOB, contact details and NHS number).

CF is an archetypal long-term condition in which adherence to life saving therapy is an important indicator of the effectiveness of the support and empowerment provided by the local CF clinical team. Local QI projects, facilitated by a trained Microsystems Coach will explore how feedback of adherence data can support tests of change in which clinical teams attempt to make the care offered by the CF team more effective in supporting PWCF to succeed with the challenge of daily self-management. Two metrics are particularly important, the overall adherence measured at centre level (which uses anonymised aggregate data) and the proportion of patients who are willing to share individual identifiable data with the clinical team. The willingness of PWCF to share identifiable data is an indicator of the quality of relationship between PWCF and the clinical team. QI projects related to adherence data might for example test of change whereby teams change their working patterns to be available to support PWCF when PWCF get home from work. An increase in overall centre adherence would support this change in practice as an improvement in the quality of care provided by the CF team. The two metrics of adherence rate and the proportion of patients within a centre willing to share identifiable data with the clinical team will be made available as aggregate quality indicators of unit

performance. These aggregate data will not contain patient identifiers and will allow CF centres to be compared.

The Data Observatory establishes a cohort of patients providing a continuous stream of data about the metric of adherence behaviour and the metric of willingness to share individual data with the MDT and this data rich cohort provides a platform for learning. Data from PWCF may be used for future research which results in no changes to patient care but might for example provide data about the relative speed at which different nebulisers might allow treatment to be delivered. PWCF may also consent to being included in selection for future research which may result changes in care, for example, testing new treatments or testing new patterns of care delivery. Data Observatory participants can consent to be involved or not in any of the possible combination of QI projects and pragmatic trials that the platform will support. Consent to 'selection' does not pre-determine nor mitigate the need for informed consent for future studies. Participants will of course be able to decline participation in future research with no impact on their inclusion in the Data Observatory, and consent for the Data Observatory can be changed or withdrawn at any time without reason.

Adherence data and QI data will be explored to investigate the importance of this data to measure the quality of care delivered by CF sites. As the Data Observatory includes more of the patients in Southampton, Poole, Nottingham and Sheffield the data capture and feedback platform will be assessed and iterated so that it will be sufficiently robust the recruit more of the 6000 adults with CF in the UK when the 20 centre RCT which is being carried out in parallel with the Data Observatory is complete. It is important to emphasise that the justification of the Data Observatory does not depend on the success of the RCT. It is recognised that an adequate assessment of a PWCF involves measurement of lung function, weight and adherence to effective lifesaving therapy. The most basic but transformative function of the Data Observatory is to deliver the IT infrastructure that ensures that adherence is available at every consultation. If the behaviour change intervention delivered within the RCT fails to support an increase in adherence, that will not be a reason not to measure adherence, but will instead provide even more reason to continue to measure adherence in a new trial with an improved behaviour change intervention.

1 Introduction

1.1 Background

Cystic Fibrosis (CF) is a long term condition (LTC) in which poor adherence to high cost drugs shortens lives and increases NHS costs. CF is a LTC affecting 10,000 people in the UK with PWCF typically dying from lung damage at a median age of 28 years [1]. Randomised controlled trials show that preventative medications reduce exacerbations and/or preserve lung function,[2–8] however adherence is poor. A recent review of objective measures of adherence using medicine possession ratios (MPR: prescriptions collected over prescriptions issued) and instrumented medication monitors showed adherence ranging from 67% for oral antibiotics, 31-53% for inhaled antibiotics, 53-79% for mucolytics agents and 41-72% for hypertonic saline [9]. Accumulating evidence suggests poor adherence is associated with poor outcomes. PWCF collecting four or more courses of alternate month nebulised tobramycin per year were 60% less likely to be admitted to hospital than PWCF collecting one or less [10]. Lower composite MPR predicted exacerbations requiring intravenous antibiotics (IVAB)[8] and over a 12 month period PWCF with an MPR of 80% had significantly lower total healthcare costs than PWCF with an MPR <50% with a cost difference $14,211 per patient and most excess costs related to hospital care [11]. Rescue therapy with IVAB can cause renal failure [12]. The total 2012 UK spend for CF was estimated to be £100 million of which £30 million was spent on inhaled antibiotics and mucolytics [13]. Although patient self-reported adherence to inhaled therapy was 80%, objective measurement showed median adherence was only 36% and the clinicians were unable to predict which PWCF were able to successfully adhere [14] making adherence support difficult. In 2012, the UK CF population received 171,907 days of IVAB with the 93,455 of these that occurred in hospital costing an estimated £27 million [15]. It is recommended that adherence interventions should be targeted where adherence really matters [16] and targeting support towards the high cost inhaled preventative drugs in CF (median adherence 36%) has the potential to impact on the 171,907 days of IVAB a proportion of which will represent rescue therapy necessitated by failed prevention.

1.2 Rationale

Understanding patient adherence and supporting PWCF who find adherence to treatment regime difficult may lead to improvements in the quality of CF care delivered to individuals and across CF units nationally. The opportunity to explore the use of a 'process' metric (adherence data) in routine care and it's utility as a measure of the quality of care is novel in the management of a chronic long term condition. Furthermore, understanding adherence data from CF centres across the UK, will enable researchers to benchmark and thus promote greater examination of the processes and service organisation which supports greater adherence with CF patients. Making adherence data visible to MDT's at CF centres has the potential to influence regular routine encounters and deliver greater person- centred care. Quality improvement projects which also examine how adherence behaviours are developed and supported through care contacts may also influence service delivery and design to maximise opportunities to develop adherence behaviours. Sharing data and QI best practice, within a theoretical and reproducible QI programme may also be an important driver of care quality nationally.

Whilst pragmatically understanding and influencing CF care, the data collected via CFHealthHub will support the Trials within Cohorts (TwiCs) functionality. As the number of patient records within CFHealthHub increases the platform can be utilised to support research into CF, predominantly focussing on behaviour change research. The use of such cohorts as platforms for trials is now becoming common and is especially valuable for rare disease populations [17].

2 Aims and Objectives

The aim of CFHealthHub Data Observatory is to explore the use of adherence data for quality improvement and as behavioural data within a cohort for future CF studies.

Specifically, we will
1) Develop a clinician facing software platform (CFHealthHub) which maximises the salience of adherence data and other important indicators of patient health which can be utilised in routine care.
2) Develop and implement change ideas for quality improvement work initially with CF teams (n=3) which aim to support adherence behaviours (it is anticipated that collaborative QI work will be offered across all 26 adult CF units from 2020).
3) Explore the consistent reporting of quality improvement projects with CF sites.
4) Statistically explore the variation in adherence data/patient data as an indicator of change in CF units and the representativeness of PWCF in the Data Observatory compared to the CF population.
5) Pilot the use of the Data Observatory as a cohort for future research.
6) Develop a set of resources and procedures which are reproducible and scalable to widen participation in the Data Observatory (n=20 CF centres) in the Data Observatory across the UK.
7) Develop procedures for the receipt of requests to access the CFHealthHub data in future research.
8) Explore the implementation of adherence data from CFHealthHub into routine clinical practice
9) Use objective adherence data to understand medication waste for system optimisation
10) Explore the potential for CFHealthHub adherence data to improve local protocols for drug escalation

3 Design

A pragmatic, development study which consists of;

1) an observational cohort study.

2) a platform for quality improvement projects across the NHS.

4 Existing Interventions

4.1 Overview

The CFHealthHub Data Observatory will support quality improvement projects and Trial within Cohorts (TwiC's) methodology studies utilising existing interventions, which can be defined as; a) a microchipped device (nebuliser) for delivering inhaled medications (b) information technology infrastructure to capture and store adherence data from the nebulisers and display it to PWCF and the CF team, and (c) the CFHealthHub software as a behaviour change intervention. Details about these three existing interventions can be found below and the interaction of these interventions and the CF patient are outlined in figure 1;
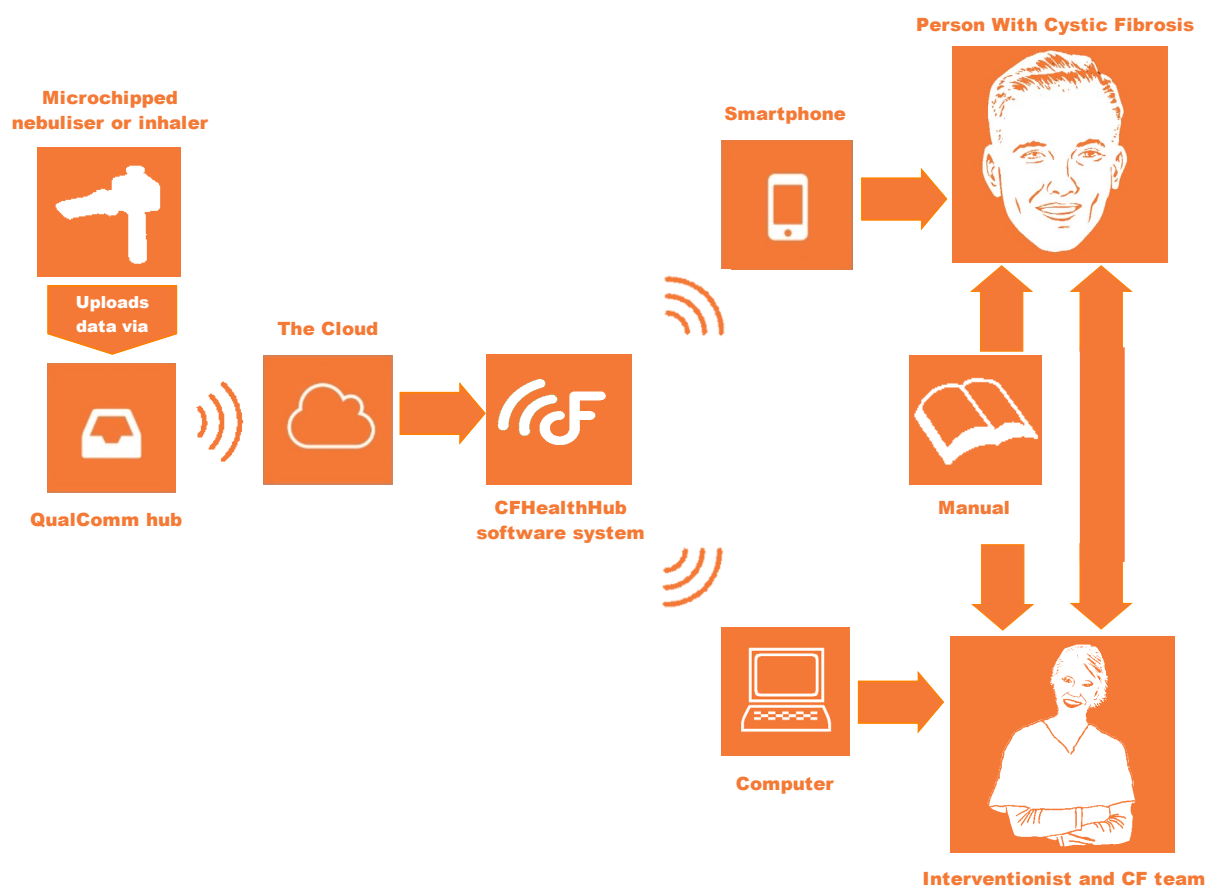
Figure 1: Interaction of existing intervention and the CF patient

4.2 Chipped nebuliser devices

Nebuliser adherence data will be automatically uploaded from a participant's nebulisers in their own home. This will be collected via two different microchipped nebulisers, the eTrack nebuliser system and the Bi-neb AAD System. The device use will be determined by the different treatment strategies at the CF site.

4.2.1 The eTrack nebuliser system (Pari GmbH)

The eTrack controller is a modified version of the eBase controller and can be used to operate both the eFlow rapid nebulizer or Altera nebulizer. Compared to the eBase controller the eTrack is equipped with a Bluetooth chip and has a monitoring function to allow the capture of inhalation adherence data. The eFlow rapid nebuliser with eTrack controller is a CE marked medical device to be used for inhalation therapy. The device allows medications (approved for inhalation) to be transported deep into the lungs.

4.2.2 The Bi-neb/i-neb AAD System from (Philips Healthcare)

The I-neb AAD system is a CE marked medical device which is intended for use to deliver aerosolised liquid medications for participants with cystic fibrosis. The drug delivery device is small and battery powered designed to deliver a precise dose of drug into patient's lungs. The Bi-neb AAD system is designed to deliver liquid medications that are specifically approved for use with the Bi-neb AAD System.

In 2019 the Bineb system will be replaced with interim ineb upload capability in CFHealthHub. The ineb upload facility will not deliver automatic adherence data, instead requiring a member of staff to upload a data file from the ineb into CFHealthHub, via a docking station provided by Phillips. However, future generation inebs may have automatic real time upload functionality.

4.3 Information technology infrastructure

The information technology infrastructure for the Data Observatory comprises;

a) The Bi-Neb/i-neb data transfer system
b) The Qualcomm hub
c) CFHealthHub

4.4 The Bi-Neb/i-neb data transfer system

The Bi-Neb Bluetooth data transfer system is intended to automatically extract breathing device use (adherence data) from the device (Bi-Neb) via a smartphone hub and a secure data server onto CFHealthHub. Providing the Bi-Neb is within the Bluetooth range within the patient's house, the system can retrieve this data once a day. The Bi-neb system will be phased out within 2019 and replaced with the i-neb system. Data from i-neb devices is uploaded to CFHealthHub at site during clinic visits via a docking station provided by Phillips.

4.5 The Qualcomm hub

The Qualcomm hub (Qualcomm; Cambridge, UK) is a wireless device which acquires data from the chipped device and transmits it to a cloud-based data centre. It is a Class I MDD and CE registered in Europe. It is designed, developed and manufactured in accordance with a quality system compliant with ISO13485 standards, meaning it aligns with the quality requirements of international regulatory agencies in the health care industry.

4.6 CFHealthHub

CFHealthHub is an online portal which displays adherence data and provides behaviour change resources and tools for PWCF, these tools used alongside trained CF health professionals support changes in patient self-management (nebuliser adherence). It is available on-line via computers, tablets or mobile phones. Previous research has focussed on the development of an adherence intervention for PWCF (CFHealthHub) and is subject to ongoing evaluation. These work packages have been supported by an NIHR applied programme grants (Reference RP-PG-1212-20015).

The CFHealthHub modules which support behaviour change and habit formation for self-management are mapped to the COM-B theoretical framework are summarised in fig 2 and table 1. Yet, it is important to emphasise that the functionality CFHealthHub provides within the RCT is distinct from the functionality provided in the Data Observatory. In the RCT the patient facing platform provides structured behaviour change to support adherence. Within the Data Observatory CFHealthHub is providing a clinician facing data display of metrics which help clinicians understand the performance of the local unit in delivering high quality support for patients to self-manage their CF. Within the Data Observatory the key metrics include a real time

understanding of adherence across the unit and how this is changing and the proportion of patients in the centre willing to share identifiable data with the clinical team. CFHealthHub will also allow clinicians to look at all patients within a centre ranked by adherence rate and lung function decline to help identify the patients needing support. CFHealthHub also monitors clinician use. These metrics are fed back to clinicians and the research team as measures of engagement. This distinction is important as the utility of the Data Observatory is not dependent on the success of the patient facing modules within the RCT. If the patient facing modules happened to be ineffective in supporting adherence the Data Observatory would then provide a platform within which refined behaviour change modules might be tested in the future. In this way the utility of the Data Observatory is independent of the results of the RCT.

A= Automatic, R= Reflective, C= Capability, O=Opportunity
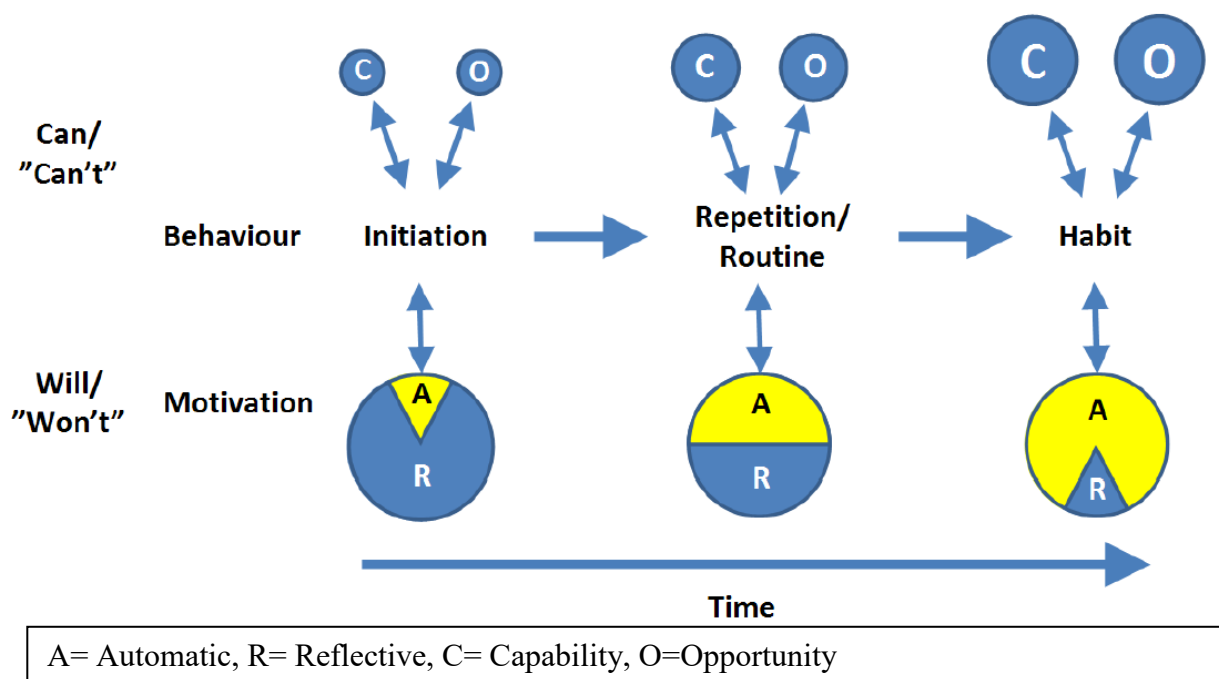
Figure 2: Interplay between COM-B components during habit formation

Table 1: CFHealthHub modules, theoretical behaviour change (COM-B) and theoretical domains framework

Module	COM-B	Intervention functions	Behaviour Change Techniques	Mode of Delivery
Universal parts of the CFHealthHub				
Self-monitoring	Psychological capability Reflective Motivation	Education Environmental restructuring Enablement	• Self-monitoring of behaviour • Adding objects to the environment (CFHealthHub)	• Charts of objective adherence data presented within CFHealthHub
Goal setting & review	Psychological capability Automatic motivation	Enablement Incentivisation	• Goal setting (behaviour) • Feedback on behaviour • Discrepancy between current behaviour and goal • Review behavioural goals • Graded tasks • Social reward	• Discussion and agreement of goal with interventionist • Review of goal • Feedback on progress (through CFHealthHub and interventionist) • Visual reward if goal met on CFHealthHub
Treatment plan	Psychological capability Physical Opportunity Social Opportunity Automatic motivation	Training Environmental restructuring Enablement	• Action planning • Habit formation • Prompts/cues (tailored)	• Action planning tool within CFHealthHub • Option to set reminders
Confidence building	Reflective Motivation	Persuasion	• Focus on past success	• Interventionist encouraging focus on periods of higher adherence on charts

Module	COM-B	Intervention functions	Behaviour Change Techniques	Mode of Delivery
Tailored parts of CFHealthHub (based on baseline COM beliefs and barriers questionnaire (COM-BMQ)[1] *and consultation with CFHealthHub researcher*				
My treatment	Reflective Motivation Psychological capability	Education Persuasion Modelling	• Information about health consequences • Credible source • Salience of consequences • Demonstration of the behaviour • Vicarious consequences • Self-talk	• Q&A linked to information within CFHealthHub (tailored by baseline beliefs and prescription data) • Presentation though text, patient stories, 'talking heads' and animation • Credible sources including clinicians, PWCF and interventionist • Interventionist eliciting self-talk through focus on why motivation is not lower than rating given on pre-screening questionnaire
Confidence building	Reflective Motivation	Modelling Persuasion	• Demonstration of behaviour	• 'Talking heads' videos of coping stories within CFHealthHub
Problem-solving (including skills training)	Physical capability Psychological capability Physical opportunity Social opportunity	Training Environmental restructuring Enablement	• Instruction on how to perform the behaviour • Demonstration of the behaviour • Behavioural practice/rehearsal • Problem solving • Restructure the physical environment • self-talk • social support (practical)	• Tailored problem solving guided by interventionist • Solution bank within CFHealthHub. • Construction of if-then coping plans • Videos demonstrating correct use of nebulisers within CFHealthHub

---

[1]

Incorporating the Beliefs about Medicines Questionnaire (BMQ-specific nebuliser treatment) Horne, 2010

5 Participants and Study Setting

5.1 Locations

UK specialist CF units will be offered the NHS CQUIN funding which supports the CFHealthHub Data Observatory in Nottingham, Sheffield, Southampton and Poole and the CQUIN also supports an RCT evaluating the patient facing behaviour change component of CFHealthHub in up to 20 additional centres in the UK. The RCT is the subject of a distinct protocol and ethics application also submitted to the London Brent Research ethics committee. It is anticipated that when centres complete the RCT in 2019 they will be offered the opportunity to join Nottingham, Sheffield, Southampton and Poole in the Data Observatory.

5.2 Participant Eligibility Criteria

5.2.1 Inclusion criteria for participants

1. Diagnosed with CF and with data within the CF registry
2. Aged 16 years and above
3. Taking inhaled mucolytics or antibiotics via a chipped nebuliser (e.g. eTrack or I-Neb) or able and willing to take via eTrack or I-Neb.

5.2.2 Exclusion criteria for participants

1. Lacking in capacity to give informed consent

5.3 Sampling

All CF centres will have the opportunity to accept the NHS CQUIN funding which will support the project activities.

In the first phase of the Data Observatory patients in Nottingham, Sheffield, Southampton and Poole will be invited to take part. Currently it is anticipated that the CQUIN will fund 132 chipped e-Track devices in Nottingham, 132 in Sheffield and 132 in Southampton/Poole. It is possible that additional patients may be included in the observatory in these centres using the Bi-neb.

When the RCT is completed in 2019 the 20 RCT centres will be invited to join the Data Observatory. All patients using chipped nebulisers may join the Data Observatory, resulting in a potential sample of up to 6000 adults with CF.

5.4 Recruitment and Screening

PWCF from CF units will be identified through the local site CF registry. The CF registry will apply the eligibility criteria to participants held on the unit registry data set and provide a pseudo-anonymised participant list to the site. The local CFHealthHub researcher or a member of the direct clinical team researcher will use this list to check the inclusion and exclusion criteria against information held in patient notes and where eligible will post an information sheet and consent form to invite the patient to participate in the study

5.5 Informed Consent

The informed consent appointment will be conducted face to face with the local CFHealthHub Researcher, at the CF centre or at the patients' home. An optional telephone call to the patient, from the local CFHealthHub researcher or a member of the CF clinical team, may be conducted to arrange the consent appointment after the postal invitation has been sent. Due to the COVID-19 pandemic, consent appointments may be conducted

over the telephone to reduce the risk of unnecessary patient contact. The CFHealthHub researchers will use the audio consent form provided (which includes a telephone script).

Informed consent will be taken by the local CFHealthHub researcher or CF team member, in accordance with Good Clinical Practice, who will have received training on the consent procedures for the project and whom have been delegated informed consent duties on the local delegation log. A copy of the consent form will be posted back to the research team at the University of Sheffield, and the patient's GP will be informed on their participation in the Data Observatory by letter. Where telephone consent has been conducted, a copy of the audio consent form will be posted to the participant.

Participants will be presented with a variety of options for consent to the study (table 2), and will be in control of their consent options throughout the study. These can be amended via a submission of a participant withdrawal form (see section 5.7) by the local CFHealthHub researcher. Throughout participation in the Data Observatory, participants maintain their ability to turn on/off sharing identifiable data with their clinical team

Table 2: Consent requirements for the study

Activity supported	Consent statement	Consent required	Consent optional
Quality Improvement 'and' Trial within cohorts (TWiCs)	Share data from my existing nebuliser, patient notes	*	
	CF team to contact me via mobile phone (calls and texts), emails, and Skype to discuss the study and my adherence.	*	
	Share their CF registry data and conversely allow for CFHealthHub data to be shared with CF registry	*	
	Contribute existing data stored within CFHealthHub to be added to the CFHealthHub Data Observatory project	*	
Quality Improvement	Allow CFHealthHub to record personal details, adherence data, CFHealthHub usage data, and other data stored within CFHealthHub such as behaviour change data	*	
	Contribute pseudo-anonymised data to centre level aggregated data	*	
	Allow the local CF clinical team to view patient identifiable data on CFHealthHub to be used for routine care		* (modifiable within CFHealthHub)
TwiCs	Contribute pseudonymised data for future non-randomised research studies related to CF		*
	Consent to be included in randomisation for future research studies		*

5.6 Uncontactable participants

Where the local CFHealthHub researcher opts to call participants to discuss participation in the project and book consent appointments, approximately three attempts to contact the patient via telephone will be made. This can include a call outside of normal working hours and also permits the use of confidential voicemail message to a personal mobile number. Individuals who remain uncontactable will be offered a final opportunity to participate in the study when attending the CF centre for routine care.

5.7 Re-approaching patients who decline or withdraw

Patients who are eligible to participate in the Data Observatory may initially decline to participate, yet during routine care for CF the clinical team may decide to re-approach the patient where adherence support is required. These patients will be screened against the most recent local CF registry data and provided with an invitation letter, PIS and consent form, prior to taking informed consent (*see section 5.5*).

5.8 Screening new patients

New patients who transition or are transferred to sites participating in the Data Observatory will be screened on transition/transfer. In the absence of local CF registry data, the CFHealthHub researcher will contact the CF team responsible for previous care to obtain their most recent annual review data to complete screening. These patients will then be sent an invitation letter and follow consent procedures *(see section 5.5).*

5.9 Participants from the CFHealthHub RCT

There will be a two phased approach for participants from the CFHealthHub RCT (IRAS 218519, REC reference 17/LO/0035).

Part 1: Consent of RCT intervention and control arm participants
CFHealthHub RCT intervention group participants will be screened and sent the study information (section 5.4) prior to a scheduled RCT study visit. The interventionist, who is already employed at each participating CF centre, will call the participant in advance to confirm their willingness to discuss participating in the Data Observatory. At the scheduled RCT study appointment, the interventionist and patient will complete the tasks detailed in the Data Observatory consent appointment (section 5.5). However, the participant will not receive a new device or any change to their CFHealthHub account. There will be no further action relating to the Data Observatory for these participants until their involvement in the trial ends in June 2019.

At the end of their involvement in the trial, RCT intervention group participants will have their CFHealthHub accounts transferred from a 'CFHealthHub RCT' account to a 'CFHealthHub MDT' account. All existing data will be transferred automatically into the new account. The participant will keep the same account details (username and password) and continue to use their chipped nebuliser as normal; however they may notice some new features in CFHealthHub.

RCT control participants
Prior to the final RCT study visit (estimated around June 2019), the RCT control group will be screened and sent the study information as per section 5.4 of this protocol. If interested in participating in the Data Observatory, their current CF centre interventionist will arrange to complete the consent appointment at the end of the final RCT study visit. It is important that this consent takes place after the final RCT data collection, so as to not bias the outcomes of the RCT. At the appointment the control group participant will be given access to CFHealthHub and offered adherence support as required. This group will continue to use their chipped device as normal.

Part 2: recruitment of new study participants (June 2019 – onwards)
 From June 2019 (after RCT data collection is complete), new patients from transitioning RCT sites can be recruited into the study. Patients may use etrack or ineb devices. CF Centres will be able to purchase new etrack devices if their Trust is part of the national PSS CF Self-Care CQUIN funding, or self-funding. Specific project milestones for CQUIN centres are detailed in the PSS CF CQUIN document. The process for recruiting new patients is as detailed in this protocol (section 5).
Some Trusts may be unable to take up the CQUIN funding. In this situation will we endeavour to secure excess treatment costs to cover the interventionist salary and data transfer fees for etrack devices already in use at the centre. Trusts may also self-fund if they are able to cover the minimum costs.

5.10 Participant withdrawal

Participants who choose to withdraw consent to any of the minimum consent requirements (see table 2) are considered as withdrawals from the study. Participants are not required to provide a reason. Site staff will complete a withdrawal form with the participant, over the telephone or in person. The withdrawal form will be uploaded onto the study database. Any data already collected in the Data Observatory will be used in any analysis unless the participant explicitly states their data should be destroyed.

5.11 Patient Stories

Pseudonymised participant data from the Data Observatory will be used in CFHealthHub training packages, quality improvement work and dissemination to maximise the effectiveness of these activities. Participants will be purposely sampled and approached by a member of the CFHealthHub research team to contribute their data as a 'Patient Story'. A participant information sheet will be provided face to face and informed consent obtained. Once consented, the participant's data will be obtained by the CTRU research team at Sheffield CTRU and Farr Institute, and pseudonymised. Patient stories will be uploaded to the CFHealthHub development server by the research team at the Farr Institute. The development server maintains the security features of the live serve but is used for technical development, training and demonstrative purposes.

As an additional option on the Patient stories consent form, participants will be asked if they consent to having an interview video recorded. These videos will ask participants about their experiences of using CFHealthHub, to be used for example for educational purposes, at conferences, or for quality improvement work. Information about these videos is included in the 'Patient Stories' participant information sheet, the 'Patient Stories' consent form, and there is an additional copyright agreement for participants to sign if they are participating in this. These forms detail the possible uses of the video recorded interviews. In addition to the optional items on the consent form, if taking part in a video recorded interview, there is also a copyright agreement for the patient to sign. By signing this copyright agreement, participants are agreeing to sign over the copyright of the material to the University of Sheffield.

Participants can withdraw their data at any time and this will not affect their participation in the Data Observatory or the care they receive from their CF centre. Participants are made aware when signing the copyright agreement, that if they decide to withdraw their video recorded interview, whilst any copies in possession will be removed, it may not be possible to remove all copies that may be in circulation.

5.12 Health Episode Statistics Data Linkage

Attempts to reliably collect participant attendance at hospital by site staff has been unfeasible due to the numbers of patients involved in the study and the frequency of hospital appointments and admissions in CF. Therefore, the central study team will obtain data on hospital attendance and admissions through Health Episode Statistics (HES), from the NHS information centre (NHS Digital). The purpose of this additional data collection is:

1) To provide a metric of the 'engagement' of the clinical team for quality improvement projects and process evaluation. HES data will provide attendance at clinic of study participants, and be linked with 'click analytic' data collected automatically by CFHealthHub. The data will be linked to understand whether CFHealthHub is being delivered in routine clinical encounters.

2) To reliably identify periods of admission to hospital for study participants. This will replace the collection of exacerbation data by the clinical team and allow future health economic analysis for the cost effectiveness of CFHealthHub use for the clinical team.

For new participants, an information sheet and consent form for HES data linkage will be provided alongside the study participant information sheet and consent form. Consent to HES data linkage is optional and does not impact the participant's involvement in the study. Existing participants from phase 2 and 3,

Southampton, Nottingham and Sheffield (see legacy diagram) will be sent the information by letter, along with the standard wording updates relating to the General Data Protection Regulation (GDPR). At a follow up clinical or intervention visit participants will be invited to complete the optional consent form.

Access to HES data will be through an application to the relevant NHS information centre. The purpose of obtaining participant consent is to demonstrate the acceptability of HES data linkage, without requiring a further application to the Confidential Advisory Committee (CAG). Future trials that use the Data Observatory platform will be required to submit additional requests to NHS digital.

6 CFHealthHub Data Observatory

6.1 Training for local CFHealthHub researchers and the CF team

The Local CFHealthHub researcher(s)[2] will receive training related to CF care, CFHealthHub, Behaviour change methodology and Quality Improvement (section 6.5) to support the activities of the study and importantly support participants to self- manage their CF using the CFHealthHub software. We anticipate the training requirements will vary, depending on the background and previous experience of the individual undertaking the CFHealthHub researcher role. We will develop a bespoke training package to researchers at the first three sites, with a view to developing standardised training strategies as the project develops.

For a CF centre to provide greater adherence support to patients, it is necessary to cascade the CFHealthHub training across the wider team. This will be developed as part of the quality improvement paradigm but will be led by the local CFHealthHub researcher at each participating site and the central researchers.

6.2 Participant 'set up' in the Data Observatory

Once consent has been provided, the CFHealthHub researcher provides the equipment and access to for the participant to engage with CFHealthHub. This can occur at the consent appointment, or at a separate time, and set up occur in person, over the telephone and supported via written documentation (e.g. standard instructions provided by device manufacturer). Set up arrangements will be tailored to patient need and convenience.

Key activities within set up include 1) Physically providing equipment and supporting the patient to use it and 2) Support the patient to use CFHealthHub and personalising the content which is related to 3) Completing a behaviour change questionnaire (COM-BMQ with the patient) to populate the 'My toolkit' and 'My treatment' sections of CFHealthHub with tailored behaviour change information relevant to their motivational status and beliefs, and 4) Check pseudomonas status and enter current prescription.

Participants who replace I-neb devices (Phillips) with the Bi-Neb (compatible with CFHealthHub) will receive a visit from a clinical trainer who will convert the participant's I-neb to a compatible Bi-neb device. This appointment can be a home visit or at the local CF centre and can occur during the consent visit or arranged as a separate appointment. The CFHealthHub researcher will deliver the remaining set up procedures. For participants using inebs, there is no set up required.

All patients will be asked to complete the COM-BMQ, a single item on the automaticity of their adherence behaviour from the Self Report Behavioural Automaticity Index (SBRAI) and rate their effort to take their nebulisers on a 7-point Likert scale. This data will be added to CFHealthHub and allow a targeted adherence behaviour change information. Other data to add to personalise the adherence data views and content include, and prescription and pseudomonas status.

6.3 Ongoing support/contact for Participants

Two months after participant set up the local CFHealthHub researcher, members of the CF team, or member of the CFHH central team trained to deliver CFHealthHub behaviour change support may work with the participant to support adherence. For new participants joining in 2019 there will be no period between set up

---

[2] During the COVID-19 pandemic, members of the CFHealthHub central team, that are NHS employed and/or allied health professionals, will act as the local CFHealthHub researchers supporting patients with adherence behaviours. All relevant employment checks and approvals from individual Trusts will be gained prior to this change.

and delivery of adherence support. The contact with the CFHealthHub interventionist will be decided by the local participating site and may continue throughout the study;

6.3.1 Delivering the Behaviour Change Intervention

The CFHealthHub researcher and trained members of the CF team will support participants to use CFHealthHub, for example update information resources, problem solve and develop action plans. This may involve supporting patients intensively (e.g during an acute period of being unwell) or over a long period of being unwell. The style of support will vary between centres, the context and preferences of the patient and clinical team. Ongoing support may require patients to repeat the data collection (see table 3).

6.3.2 Troubleshooting

Participants may experience difficulties using the CFHealthHub and the associated technology during the project and may require support to resolve any issues. Queries may also arise from communication with the researchers (CTRU, University of Sheffield and Farr Institute, University of Manchester) which may require the local CFHealthHub researcher to follow up queries with the Participant in person or over the telephone.

6.4 Development of the CFHealthHub platform

The development of the CFHealthHub software is led by programmers at the University of Manchester, and supported by the Project management group. Local CFHealthHub researchers may be invited to meetings which discuss the development of the software. Local researchers may also identify opportunities to feedback development opportunities as the result of their ongoing engagement with CFHealthHub in routine care or resulting from local quality improvement work.

6.5 Quality Improvement (QI)

QI projects will support CF teams to use data within CFHealthHub as part of their routine care, in accordance with the conceptual idea that CF care and patient outcomes can be transformed with the availability of adherence data [18]. CF care is regarded as an exemplar healthcare context for QI [19], where the dynamic, iterative changes in healthcare processes are supported by a healthcare system which obtains regular data on indicators of patient health, for example FEV1 and BMI [20].

We will adopt a novel approach to QI within CF care adopting the process measure of adherence, usually unavailable to clinicians but collected within CFHealthHub, to understand the quality of care delivered by a CF centre. We hypothesise that CF centres where a greater number of patients self- manage their CF, achieving higher levels of adherence may experience fewer exacerbations resulting in fewer inpatient stays. This supports PWCF to stay well for longer and is more affordable to healthcare services (Fig. 3) Therefore QI projects focussed on understanding adherence behaviour and how to deliver healthcare which supports PWCF to self-manage, within an evidence based and replicable behaviour change framework (COM-B[1]) is highly valuable to the CF community.

We will obtain baseline information via a questionnaire from each participating site to understand their current adherence strategies with patients. Then CF teams led by the local CFHealthHub researcher will be supported by a team of QI coaches to undertake QI work throughout the project. As the number of sites participating in the Data Observatory increases, we will adapt the delivery of QI work, supporting CFHealthHub researchers to continue with QI work and tapering the face to face input from the QI coaches. We will adopt a QI collaborative approach, utilised widely in healthcare contexts (Øvretveit 2002), where a network of CF centres

will share change ideas for PDSA cycles and reflections on implementation, to generate best practice materials for future CFHealthHub QI projects.
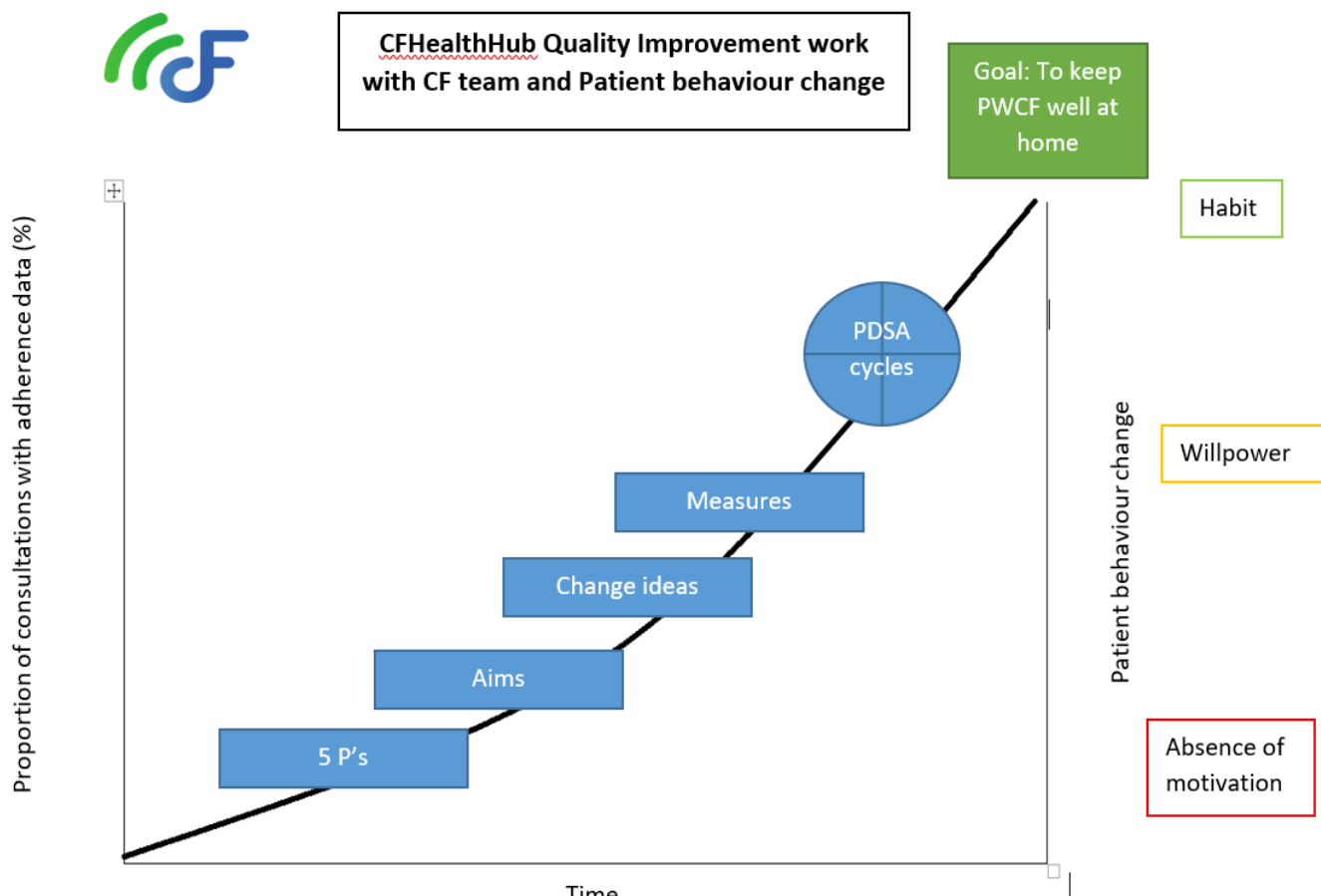
6.5.1 Microsystems Coaching

Quality improvement projects will utilise the Clinical Microsystem methodology developed by the Dartmouth Institute, USA (Nelson, Bataldan and Godfrey 2007) and adopted by the Sheffield Microsystem Coaching Academy (MCA). The Sheffield MCA (http://www.sheffieldmca.org.uk) has trained 143 microsystem coaches to deliver structured quality improvement based upon key quality improvement activities (figure 3). This approach advocates that complex health systems can be reduced to smaller building blocks called 'microsystems' where multidisciplinary teams deliver healthcare to patients. At each microsystem a number of QI projects may occur but the implementation requires the completion of four phases; Assessment, Diagnose, Treatment and Standardise, where tools such as assessment using the 5 P's (Purpose, Patients, Professionals, Processes, Patterns) process mapping, time series measurements, Plan Do Study Act (PDSA) cycles are utilised until the change idea has been adapted or has become embedded into the microsystem [21]

6.5.2 Metrics and tests of change

Quality improvement ideas will be generated by the CF centre team and developed with the QI coaches. However, we anticipate there are key metrics related to QI related to the overall adherence measured at centre level (pseudonymised aggregate data) and the proportion of patients who are willing to share individual identifiable data with the clinical team. We perceive the willingness of PWCF to share identifiable data is an indicator of the quality of relationship between PWCF and the clinical team. These aggregate data will not contain patient identifiers and will allow unit A to compare its performance with Unit B etc. The two metrics of adherence rate and the proportion of patients within a unit willing to share identifiable data with the clinical team will be made available as aggregate quality indicators of unit performance.

An example of QI projects might for example involve a test of change whereby teams might decide to change working patterns so that team members are available to support PWCF when at times which are more convenient to them, for example outside of normal working hours. An increase in overall unit adherence would support this change in practice as an improvement in the quality of care provided by the CF team.

Figure 3. CFHealthHub and Microsystems coaching

6.6 Trials within Cohorts (TWiCs) methodology

Data captured within CFHealthHub creates a cohort of CF patients to support future research via the adoption of a Trials within Cohorts methodology (also known as the cohort multiple RCT (cmRCT) design). The cohort will primarily support behaviour change research adopting a randomised design utilising data collected within the CFHealthHub Data Observatory procedures, for example adherence data, clinical indicators, and behaviour change metrics. However, the CFHealthHub cohort can also support studies of non-experimental designs such descriptive studies (cross sectional and qualitative) and observational studies.

TWiC's methodology is pragmatic, and may support researchers to overcome some of the traditional issues associated with conducting traditional RCT's designs in rare diseases, such as a low number of eligible participants, poor recruitment resulting in sub-optimal statistical power, poor external validity, and reduce the distress and anxiety which can result from randomisation to usual care [17,22,23]. The context of CF as chronic condition may also lend itself favourably to the adoption of TWiCs designs fulfilling criteria from Relton et al, such as; PWCF are an *easily defined and identified population, improvements to treatment is highly desired* due to the early age mortality rate and high costs of care and finally, *future pragmatic trials are likely to compare an intervention or treatment with 'usual care'* [23]

6.7 Procedures for the CFHealthHub Cohort

6.7.1 Participant Consent to future research

To perform the key function of TWiCs design which allows PWCF to be screened against study eligibility criteria and to be randomly allocated to the intervention or control group, PWCF will undergo a 'two-stage' consent process (figure 4). First, when consenting to the CFHealthHub Data Observatory PWCF could agree to be selected for future research (see table 2), which we term 'broad consent'. Second, if this participant meets the eligibility criteria for a hosted study and is randomised to the intervention group, they will be contacted by the CFHealthHub research team and provided with the new study invitation letter, participant information sheet and consent form. Consent to the new study must be provided to receive the intervention. Participants will be reminded throughout that they can decline participation to the new study with no impact on their chances to be selected for future studies. Participants can also decide to withdraw from the cohort for future research, without impacting their use of CFHealthHub or any other terms of consent.
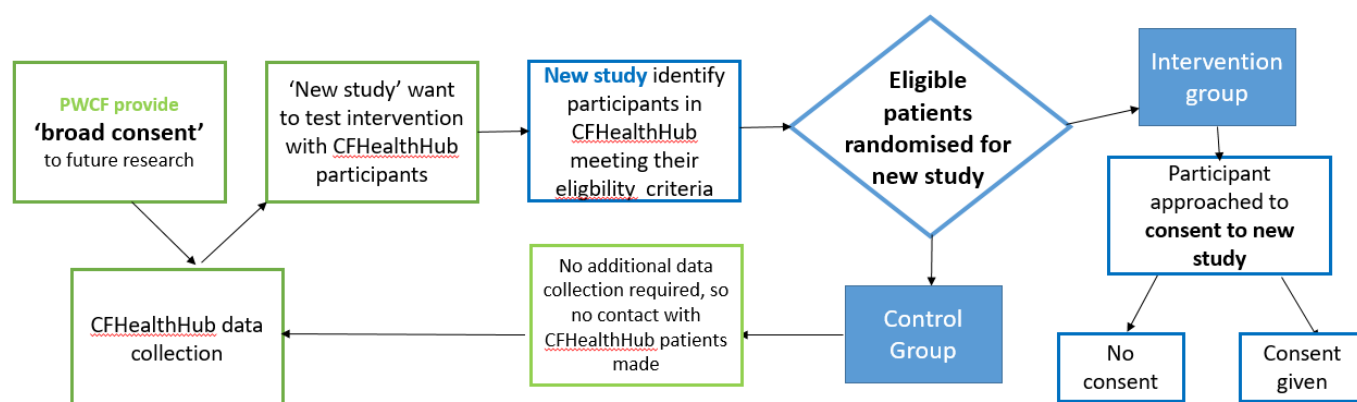
Figure 4. TwiCs two-stage consent procedure

Some participants who consent to future research will be randomised to the control group. If participation in the control group requires no change to their data collection within CFHealthHub these participants will not be approached for consent and they will not be informed of their participation in the control group. This is consistent with other cohorts [17,22], and on consultation with patient and public representatives was unanimously found to be an acceptable procedure. However a website will be maintained that publishes the results of studies carried out within the Data Observatory and publicity will provided periodically to allow patients to view study findings.

6.7.2 Quality assurance of supported research studies

Studies supported in CFHealthHub will be subject to a high level of appraisal which incorporates traditional research governance and ethical approval required for all studies and additional scientific appraisal from the CFHealthHub researchers. We envisage the CFHealthHub researchers will support research teams to develop high quality protocols, demonstrate a high level of scientific rigor, ensure the optimal security of the patient data, and are shaped by patient and public involvement. Researchers will then be required to obtain ethical approval from an NHS Research Ethics Committee, or other recognised Research Ethics Committee, along with other research governance requirements appropriate to the study design.

6.7.3 Data security and supported research studies

Where participants have consented to take part in future research studies they are required to provide their contact details to the CFHealthHub researchers. If a participant is randomised to receive an intervention thus requiring new study information to be posted to the participant, or contacted via the telephone, the initial invitation and any subsequent contact to recruit the patient to the study can be made by a member of their local CF team or the CFHealthHub researchers. Contact details will not be transferred to the new research team unless permission is obtained from the participant.

Data which is transferred from CFHealthHub for supported research will be pseudonymised and encrypted prior to transfer. Details of how the data will be transferred and stored within the new study will form part of their study protocol and patient materials which will undergo assessment to ensure patient confidentiality and data security is respected at all times.

6.8 Medicines Optimisation

The medicine possession ratio for high cost inhaled therapy in adults in the UK is reported as 63% whereas actual objectively measured adherence is reported as 36%. As homecare companies deliver a greater proportion of medicines there is the possibility of waste. The following work packages described here have been mandated as part of NHS England CQUIN funding for the Data Observatory.

CFHealthHub will develop modules to support the use of time and date stamped drug use data to guide homecare deliveries so that the MPR approaches actual use thus avoiding waste. This CFHealthHub functionality will also support patients in the Lind alliance survey priority of simplifying the administration of medications to ensure just in time availability. Based on initial analysis with CF pharmacists participating in the data observatory, the annual enduring saving is modelled at £708 per patient.

We will explore how CFHealthHub adherence data can support intelligent commissioning around new generation antibiotics. New generation inhaled antibiotics (Aztreonam and Levofloxacin) cost in the region of £12K per patient per year whereas colomycin costs in the region of £1.1K per annum. Specialised commissioning guidance suggests that patients should only escalate to the more expensive new generation inhaled antibiotics if patients cannot tolerate the first line antibiotics or are deteriorating.

 However, given that median adherence to inhaled antibiotics is in the region of 36%, a significant amount of treatment failure is likely to result from non-adherence. In the context of non-adherence, escalation from a twice daily £2k per annum drug to a more complex thrice daily regime with £12k per year drug is unlikely to deliver patient benefit. Reducing inappropriate variation in the use of high cost third and fourth line medication might save hundreds of thousands per annum. CFHealthHub can automatically provide adherence data to support escalation decisions.
There will be a number of stages in the EMBRACE project.

1. **Understanding system waste**: local pharmacists working as part of their hospital CFHealthHub team, will use local hospital records to calculate Medicine Possession Ratio (MPR), for participants consented into the Data Observatory. Objective adherence data will be available from CFHealthHub (if participants have data sharing switched on). Participant data will be only identifiable to the research team by their study ID. A cost comparison will be made between objective data and MPR, and an overall centre cost comparison will be reported.
2. **Developing 'just in time' drug delivery**: A sample of participants on 'Dornase only' prescriptions will be used to develop and test an algorithm for homecare delivery, based on objective adherence.
3. **Developing drug escalation protocols:** Local pharmacists working with the CF team will develop or adapt protocols for appropriate drug escalation using objective adherence data from CFHealthHub. A local PPI group will be consulted before this is implemented widely in the centre.

7 Process evaluation sub-study

7.1 Background and rationale

The Data Observatory is being used to drive up quality, in three NHS Trusts: Sheffield Teaching Hospital NHS Foundation Trust; University Hospital Southampton NHS Foundation Trust; and, Nottingham University Hospitals NHS Trust. Up to seventeen further trusts will join the observatory, subject to funding arrangements, in 2019.

The success of this multi-centre quality improvement exercise requires two steps:

1. NHS England-funded 'interventionists' work in centres to recruit participants to the observatory and influence multi-disciplinary teams to use adherence in their day-to-day practice.

2. Multi-disciplinary teams access data to benchmark their centre's performance and to inform the care of individual patients.

To inform that large scale process of change, we need to understand the potential sources of implementation failure based on activity at the three centres which are already initiated. The current process evaluation will provide that understanding, using the MRC Process evaluation framework[24].

The evaluation will involve interviewing health professionals and triangulating their views and experiences with quantitative data, already collected as part of the observatory.

7.2 Aims and objectives

We aim to answer the question: "What are the potential sources of failure for: (a) the observatory's implementation interventionists and site PIs; and, (b) for the uptake of adherence data in the management of people with CF by multidisciplinary teams?"

The objectives are:

1. To provide an overview of the experiences and views of site staff on this question; and,
2. To integrate those views with process data already collected by the observatory project.

7.3 Study design

The evaluation will use a mixed methods approach, following MRC process evaluation guidelines[25] to explore the activities and outputs documented on the logic model (appendix 1), specifically to identify the barriers and pathways to implementation. To capture the changing implementation of the Data Observatory this process evaluation will be repeated at yearly intervals, between 2018 to 2020.

7.3.1 Quantitative process data

1. **Study set up**

Collected by the central study team from study records. Data will include

- Date ethical and HRA approval was received.
- Critical path analysis of site set up using study manager notes

2. **Number and characteristics of eligible patients approached for this study**

Collected by centres in screening logs and transferred to Prospect database.

3. **Reasons for refused consent or ineligibility**

Collected by centres in screening logs and transferred to Prospect database.

4. **Reach**

Collected by screening and consent form transferred into the Prospect database. This will include the number of participants consented into the study, sub-grouped by socio-economic status (from CF Registry), as a proportion of:

- Those approached, expressed quantitatively, based on 'pre-screening' logs;
- Those known to be eligible, expressed quantitatively based on CF registry.

5. **Participant attrition rate and reasons for attrition**

Collected by centres in screening logs and transferred to Prospect database.

6. **Consent to optional statements relating to future research**

Collected by centres on consent forms and transferred to Prospect database

7. **CF registry data accessed**

Collected by the central study team from study records.

8. **Encounter based CFHealthHub Data Entry**

Encounter based data entry points are automatically collected on Prospect and will be compared against clinic information provided by the local administrators. Comparing the number of collected forms, versus the number of actual attended clinic visits will provide an understanding of the accuracy of data collected in the study, and identify any systematic patterns in missing data.

9. **Expertise at centre**

Collected in training records kept by the central study team. These records will be used to identify the number of staff and corresponding job role, at each centre, trained in:

- Quality improvement;
- Adherence support;
- CFHealthHub software.

10. **Number of delivered adherence sessions to participants, frequency of access to adherence data**

Evaluation of 'click analytics' exported from CFHealthHub for the:

- Completed 'Summary Review' page, used to record all adherence sessions with participants;

- Clicks onto 'How am I doing?' for each interventionist account.
- Other related CFHealthHub pages that indicate use of CFHealthHub / delivery of adherence support

11. Engagement with other research and TwiCs

Data collected in central study records, including details of the request to use the Data Observatory platform, and the study design.

12. PDSA cycles embed the use of adherence data in routine care

Collected on a standardised PDSA recording form by interventionists and MCA coaches.

13. Capability, Opportunity and Motivation barriers for CF Healthcare Professionals

Collected by way of questionnaire using the Theoretical Domains Framework and questions developed from the qualitative interviews in 2018. Health professionals at every CFHealthHub Data Observatory centre will be invited (by email) to take part on an online survey about their experience of implementing CFHealthHub in their centre. It is important to understand which elements of the CFHealthHub implementation strategy impacted on the overall implementation of CFHealthHub at each centre (see appendix 2). Implied consent will be obtained as part of the online survey. If participants provide their contact details, they may be selected for an in depth interview, within 12 months of completion of the questionnaire.

7.3.2 Qualitative process data

Logic model components (appendix 1) will be evaluated using data from semi-structured interviews with centre staff.

7.3.3 Sampling

We aim to sample at least six staff members from each of the three Cystic Fibrosis Centres already initiated. These will be selected for maximum variation[26] based on their role (consultant, physiotherapist, nurse). Consent to be interviewed will be sought by the University of Sheffield research team. Spontaneously-offered reasons for non-participation will be recorded. The eligibility criteria are as follows:

Inclusions:
1)   Member of staff employed by a CF centre involved in delivering the CFHealthHub Data Observatory (London-Brent REC 17/LO/0032) improvement collaborative study.

Exclusions:
1)   unavailable or unwilling to consent

7.3.4 Interview procedures

Identification of participants: Potential participants are study funded interventionists and healthcare professionals working in a Data Observatory study centre, who will be known to and identified by the study team. Invitations will be made face-to-face, by letter or by e-mail, by the Chief Investigator, study manager or research assistant. Invitations are made by letter or email, will be followed up by a telephone call from a member of the study team to ascertain interest, and where possible, arrange an appointment. Centres part of the phase 4 platform (previously in the RCT) will be purposively sampled based on responses of the Theoretical Domains Framework (TDF) questionnaire at baseline in 2019.

Timing and setting: Interviews will take place at a time and place convenient for consenting participants. Where it is not possible to conduct the interview face-to-face, interviews will be conducted over the telephone.

Informed Consent: Written or telephone (audio recorded) informed consent will be obtained from every participant. Those who agree to be interviewed will be met at a place convenient for them, by one of the study team who will read the information sheet through with them. If the participant is happy to continue they will be asked to sign the interview consent form. Those involved in taking consent and collecting data will have up-to-date training in Good Clinical Practice (GCP). Participants will be reassured that all data which are collected during the course of the research will be kept strictly confidential. Spontaneously offered reasons for non-participation will be recorded.

Interview guides: As the interviews aim to understand the potential barriers to implementing a multicentre quality improvement project, interviewers will follow a topic guide that draws upon the TDF[27,28]. In addition, interviewee's professional background, their role in the CFHealthHub Data Observatory project will be collected.

Recording: Encrypted digital recorders will be used and recordings sent securely to the research team for analysis. Once saved, recordings will be permanently deleted from the digital recorder. All interviews will be fully transcribed. At the end of the study audio recordings will be destroyed.

Field notes: Will be taken during and after interviews as required.

Duration: Interviews will last up to one hour. Transcripts will not be returned to participants for correction. Participants will be invited to participate in the interviews at future time points; there is no obligation to participate again. Different members of staff may be recruited at each time point.

Safety of the participants: As healthcare professionals, we do not consider the participants to be vulnerable. Interviews will be treated as confidential; information that identifies individuals will not be disclosed.

7.3.5 Analysis

Transcripts will be coded using the latest version of NVivo (QSR International). The theoretical framework for understanding intervention adherence is the Theoretical domains framework within the COM-B system[27]. This will be used within the thematic framework for this evaluation. We will use the process evaluation functions of context, mechanisms and implementation to frame the analysis. We will compare and contrast findings from each centre as the different contexts in which care is provided in each CF unit may affect implementation and acceptability of the intervention. We will use the logic model (Appendix 1) as a framework for summarising information at the programme level[29].

Summary statistics will be produced, the detail of which will be available in the Data Observatory Statistical Analysis Plan (SAP).

Using a modified triangulation protocol[30], we will integrate qualitative and quantitative datasets, summarising information based on logic model constructs at the programme level[29]. We will use a joint display table[31] to summarise data sets for logic model constructs in the Inputs. The fit of data integration will be categorised as: 'confirmation' (quantitative and qualitative data provide similar findings, enhancing credibility); 'expansion' (the datasets diverge, expanding insights/ addressing different or complementary aspects the phenomenon); or, 'discordance' (the datasets are contradictory)[32]. We will

summarise closeness of fit between data sets and differences in their contribution to the research question.

8 Data Collection and Management

8.1 Data collection sources

To ensure CFHealthHub is a useful tool for the CF team from the outset of the study, data will be collected retrospectively from CF Registry and patient medical records, existing patient data within CFHealthHub will also be retained and adherence data from existing nebuliser devices will be added to CFHealthHub.

Table 3. Sources of patient Data within CFHealthHub Data Observatory

Data Source	Data recorded	When will data be obtained?		
		Screening	Consent/ Baseline	Review
CF Registry	Pseudonymised ID, patient data; prescription , lung function, Body Mass Index, number of IV days, pseudomonas status diabetes status, deprivation index, lung transplant status)	x		
Patient medical records	Personal data; name, contact details, NHS number, DOB.		x	
	Lung function, prescription data, Height and weight, pseudomonas status, exacerbations, medication possession ratio		x	x
Existing nebuliser devices	Number of inhalations, date and time of inhalations		x	
CFHealthHub	Behaviour change data, usage metrics, adherence data.		x	x
Patient reported	COM- BMQ, habit score and effort score, participation in other research		x	x
Health Episode Statistics	NHS identifier, clinic appointment date and attendance, hospital admission date, length of stay.			x (if optional consent has been obtained)

8.2 **Data handling and record keeping**

The Sheffield CTRU will oversee data collection, management and analysis and ensure the study is undertaken according to Good Clinical Practice Guidelines and CTRU standard operating procedures. Data will be collected and retained in accordance with the Data Protection Act and General Data Protection Regulations. Patients will be reassured that all data which are collected during the course of the research will be kept strictly confidential

Data will be collected directly from the participants, CFHealthHub software, source documents (e.g. patient notes), or external sources (e.g. CF Registry). Pseudonymised screening and recruitment data will be collected for all participants, with patient contact details collected for those who consent to participation. Screening and recruitment data collected on CRF's will be entered into the Sheffield CTRU's electronic web-based data capture system (Prospect). Data from screening logs will be anonymised, encrypted and sent by the local CFHealthHub researcher via email to Sheffield CTRU for upload onto Prospect. All other data collected in the Data Observatory will be captured in CRF's and entered into Prospect locally, or a secure download from the CFHealthHub performed by data management staff at Sheffield CTRU.

Health Episode Statistics (HES) data will be stored securely at the University of Sheffield in accordance to data protection laws and requirements set out by NHS information centre (NHS digital). Data linkage procedures will be outlined in the data request application.

The Data Monitoring and Management Plan for the study will provide further guidance on the types and levels of data and how these will be monitored and verified. Some essential documents may be posted to the central team to facilitate this e.g. participant consent forms in which case this will be detailed in the appropriate participant PIS and consent forms.

Data capture will be monitored indirectly both by the local CFHealthHub researcher, CF team and central researchers at the University of Manchester and University of Sheffield. We envisage that where a patient treatment plan involves CFHealthHub they receive more intensive support to utilise the functionality or receive prompts for to review their data, outside of routine care encounters.

8.3 **Data Management**

8.3.1 **Clinical Trial Unit (CTRU), University of Sheffield**

Pseudonymised data and anonymised patient data will be transferred from CFHealthHub to Sheffield CTRU's Prospect system for analysis to an agreed specification between the Chief Investigator and Sheffield CTRU. The Prospect system has a full electronic audit trail and will be regularly backed up. Members of the central research team at the CTRU and local research teams can have access to the anonymised data on the database through the use of usernames and encrypted passwords. The necessity of access and appropriate permission to access data in accordance with the agreed data management plan, and local delegation log will be considered. Privilege management features can be used to ensure that users have access to only the minimum amount of data required to complete their tasks and will restrict access to personal identifiable data. Consent forms posted to Sheffield CTRU will be stored securely in accordance with GCP physical data storage guidance.

Quality control procedures to validate the data will be incorporated which will produce data queries for clarification this will require the Sheffield CTRU team to work with the local researchers. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Prospect provides a full electronic audit trail, as well as validation and verification features which will be used to monitor data quality, in line with CTRU SOPs and the Data Management Plan (DMP). Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator.

Prospect stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS.

8.3.2 University of Manchester

Any participant data held within CFHealthHub will be stored on a secure server at the University of Manchester. CFHealthHub complies with the Data Protection Act and follows best practice guidelines on security and information governance and has been subject to rigour security testing. Encrypted channels are used to transfer any data to and from the web and mobile application platforms. All user interaction with the CFHealthHub server and each action performed by a user will be logged. An audit log contains the username of the user performing the action, the date & time of the action, short description of the action performed. All users are authenticated via a secure password with access to the system restricted on a role basis.

8.3.3 Not- for- profit CFHealthHub Company

In 2019, the CFHealthHub platform will transition from the University of Manchester, Sheffield Teaching Hospitals and ScHARR to a standalone Community Interest Company (CIC) which will function on a not for profit basis. This change will ensure the legacy of CFHealthHub is secured for the future. The community interest company is required to ensure that all the staff needed to maintain CFHealthHub are employed into the future and extensive work with NIHR has led to the conclusion that the optimum strategy to ensure implementation is via a not for profit CIC. The CIC ensures that any revenues that accumulate must be used for the community which is defined at the time the CIC is set up. For which, the CF community have been defined as the beneficiaries of the CIC. CFHealthHub board members responsible for the oversight and day to day running of the CIC will ensure the future of the platform. The CIC will be governed by exactly the same data security and protection arrangements as within the period prior to the establishment of the CIC and operational functions will be contracted to the Farr Institute and the Clinical Trials Research Unit at ScHARR with a board and governance arrangements that will ensure resilience and continuity.

8.4 Data Analysis

The analysis will be performed at regular intervals by a CTRU statistician under the supervision of the senior study statistician who will develop a statistical analysis plan with the input of the CI and the wider research team As the study is observational and also has quality improvement functions, data will be reported and presented according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) statements [33,34]. The main analysis will be mainly descriptive and focus on confidence intervals rather than formal hypothesis testing. Analyses will be performed for the entire cohort (i.e. every individual in the Data Observatory analysed as a single group) and also at a centre-level for the purpose of comparing the different CF centres within the Data Observatory.

We will report rates of consent and follow-up by centre and process outcomes (prescription checks, duration of inhalation). The primary outcome of interest is objective nebuliser adherence. 3-monthly and annual adherence for each individual will be calculated as unadjusted adherence, normative adherence [35] and total nebuliser used per week [36]. Centre-level adherence over the same duration (3-monthly and annual) will also be summarised as median (IQR) since adherence data is not normally distributed.

The variability of each individual's adherence data is likely to be important, since previous studies have demonstrated the relationship between variability in adherence with outcomes [37,38]. Therefore, the annual adherence data for each individual will also be clustered based on the magnitude and variability of adherence.

The proportion for each adherence cluster at the centre-level will be reported. In addition, proportion of adults at the highest adherence cluster will also be compared between centres using funnel plots [39].

Other outcomes of interest include FEV1 (a form of lung function), and baseline IV antibiotics use will be stratified according to unadjusted FEV1 (Johnson et al). For the purpose of centre-comparison, FEV1 will be adjusted for age using Generalised Linear Model due to the non-linear relationship between FEV1 and age. Centre-level use of IV will be summarised as median (IQR) due to non-normal distribution, whilst centre-level age-adjusted FEV1 will be summarised as mean (SD). Funnel plot analyses for IV use and age-adjusted FEV1 will also be carried out, to understand the relationship between process measures (nebuliser adherence and IV use) and outcome measures (FEV1) at a centre-level. For example, we would expect that a centre that is a positive outlier for nebuliser adherence to be a positive outlier for age-adjusted FEV1. Pseudomonas status will also be collecting using the Leeds criteria and clinician derived status to understand the utility of the measures long term within the Data Observatory.

Further analyses with the objective nebuliser data will be performed to explore the process of habit formation with the delivery of the adherence intervention [40–45]. The analyses will include:
(a) generating objective habit scores by taking into account time of nebuliser use
(b) using statistical process control to identify when periods of stability are achieved
(c) other time-series methods, including cross-correlation between habit scores and adherence.

9 Monitoring and Oversight

9.1 Management of the study

A Data Monitoring and Ethics Committee will not be convened in this study due to the low risk nature. Sheffield Teaching Hospitals NHS Trust and the sponsor of the study, have overall responsibility for the study and are the study data controller.

At each participating site, the PI local Principal Investigator (PI) will be responsible for the study, which will be registered and approved by each R&D department. The study will be conducted in accordance with the protocol, GCP and Sheffield CTRU Standard Operating Procedures

The Project Management Group (membership listed on the p3) will govern the conduct of the study on a day to day basis. The Study Manager will be jointly supervised by the CI and the Assistant Director of CTRU via the form of regular meetings (face to face and telephone calls). The Study Manager will be responsible for liaising with the whole project team.

Monitoring procedures will be assessed based on the level of risk of the study. The Site Monitoring Plan will outline the types and frequency of site monitoring activities for the study and this will be agreed with the Sponsor prior to the start of the study.

9.2 Harms (safety assessments)

It is not anticipated that there will be SAEs related to the use patient use of CFHealthHub, the collection of their data in a Data Observatory.

9.3 Auditing

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The investigator will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

9.4 Finance and indemnity

The project has been financed by NHS England CQUIN funding. Details have been drawn up in a separate agreement. This is an NHS sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10 Ethics and dissemination

10.1 Approvals

The project will be conducted subject to Health Research Authority and Research Ethics Committee favourable opinion. The approval letter from the ethics committee and copy of approved patient information leaflets, consent forms and any ethically approved questionnaires will be present in the site files before

initiation of the study and patient recruitment. Local research governance approvals will be sought from all participating research sites. The project will be conducted in accordance with Good Clinical Practice Guidelines and CTRU standard operating procedures.

10.2 Amendments to the project

The categorisation of amendments as substantial or non- substantial will be guided by the Sponsor, and implemented in accordance with the HRA amendment classification. It will be agreed with each local R&D whether a letter of permission to continue is required prior to the date of amendment implementation as recommended by the HRA. The local PI and researchers will be updated following an amendment to the ethical approval, protocol or study documents. The new documents, REC approval, R&D approval and any other appropriate documentation surrounding the amendment will be sent to the site via a "site file update". Local researchers will be required to fulfil the implementation of the amendment per guidance provided by the CTRU.

10.3 Consent procedures

Please refer to 'Informed Consent' in section 5.5 and section 6.7.1

10.4 Confidentiality

Participant confidentiality will be respected at all times. Access to personal details and identifiable data will be highly restricted to key members of the study team, with all other researchers using pseudonymised data. All data transfer and will be pseudonymised.

Trial documents (paper and electronic) will be retained in a secure location at the local participating site during and after the trial has finished. All source documents will be archived for a period of 5 years following the end of the project. Each site is responsible for ensuring records are archived, in accordance with their local procedures and CTRU Archiving procedures.

10.5 Declaration of Interests

There are no interests to declare.

10.6 Dissemination policy

A dissemination plan will be developed with the CI and Sheffield CTRU appropriate to needs of the wider research programme.

11 References

1. Michie S, van Stralen M, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6(42).
2. Parham R, Thomas S, Mills R, Al E. CF patient's beliefs about nebuliser treatment: implications for adherence to treatment. J Cyst Fibros. 2012;11 (Suppl(S9).
3. Bucks RS, Hawkins K, Skinner TC, Horn S, Seddon P, Horne R. Adherence to treatment in adolescents with cystic fibrosis: The role of illness perceptions and treatment beliefs. J Pediatr Psychol. 2009 Sep;34(8):893–902.
4. George M, Rand-Giovannetti D, Eakin M, Borrelli B, Zettler M, Riekert K. Perceptions of barriers and facilitators: self-management decisions by older adolescents and adults with CF. J Cyst Fibros. 2010;9:425–32.
5. Dziuban E, Saab-Abazeed L, Chaudhry S, Streetman D, Nasr S. Identifying barriers to treatment adherence and related attitudinal patterns in adolescents with cystic fibrosis. Pediatr Pulmonol. 2010;45:450–8.
6. Bregnballe V, Schiøtz P, Boisen K, Pressler T, Thastum M. Barriers to adherence in adolescents and young adults with cystic fibrosis: a questionnaire study in young patients and their parents. Patient Prefer Adherence. 2011;5:507–15.
7. Modi A, Quittner A. Barriers to treatment adherence for children with cystic fibrosis and asthma: What gets in the way? J Pediatr Psychol. 2006;31:846–58.
8. Abbott J, Dodd M, Bilton D, Webb A. Treatment compliance in adults with cystic fibrosis. Thorax. 1994;49:115–20.
9. Abbott J, Dodd M, Webb A. Health perceptions and treatment adherence in adults with cystic fibrosis. Thorax. 1996;51:1233–8.
10. Abbott J, Dodd M, Gee L, Webb K. Ways of coping with cystic fibrosis: implications for treatment adherence. Disabil Rehabil. 2001;23:315–24.
11. Conway S, Pond M, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. Thorax. 1996;51:29–33.
12. Jones S, Curley R, Wildman M. 345 Systematic review of qualitative studies investigating barriers to adherence in patients with cystic fibrosis using framework analysis structured by a conceptual framework of behaviour change. J Cyst Fibros. 2013;12 (Suppl(S136).
13. Kettler L, Sawyer S, Winefield H, Greville H. Determinants of adherence in adults with cystic fibrosis. Thorax. 2002;57:459–64.
14. Lask B. Non-Adherence to Treatment in Cystic Fibrosis. J R Soc Med. 1994;87 (21 Sup:25–7.
15. Latchford G, Duff A, Quinn J, Conway S, Conner M. Adherence to nebulised antibiotics in cystic fibrosis. Patient Educ Couns. 2009;75:141–4.
16. Horne R, Weinman J, Barber N, Elliott R. Concordance , Adherence and Compliance in Medicine Taking: Report for the National Co-Ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO). 2005.
17. Kwakkenbos L, Jewett L, Baron M, Bartlett S, Furst D, Gottesman K, et al. The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: protocol for a cohort multiple randomised controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context. BMJ Open. 2013;3(e003563).
18. Wildman M, Hoo Z. Moving CF care from rescue to prevention by embedding adherence measures in routine care. Paediatr Respir Rev. 2014;15(sUPPL 1:16–8.
19. Quon BS, Goss CH. A story of success: continuous quality improvement in cystic

fibrosis care in the USA. Thorax. 2011;66:1106–8.

20. Schechter MS, Fink AK, Homa K, Goss CH. The Cystic Fibrosis Foundation Patient Registry as a tool for use in quality improvement. BMJ Qual Saf. 2014;23(Suppl 1):i9.

21. Sheffield MCA. 2016.

22. Uher R, Cumby J, Mackenzie LE, Morash-Conway J, Glover JM, Aylott A, et al. A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. BMC Psychiatry. 2014;14:344.

23. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. BMJ. 2010;340:c1066.

24. Moore G, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions UK Medical Research Council (MRC) guidance. [cited 2017 Nov 10]; Available from: http://decipher.uk.net/wp-content/uploads/2014/11/MRC-PHSRN-Process-evaluation-guidance.pdf

25. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015 Mar;350(mar19 6):h1258–h1258.

26. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? J Adv Nurs. 1997;26(3):623–30.

27. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci [Internet]. 2017;12(1):107–12. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0895435604002562

28. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci [Internet]. 2011;6(1):42. Available from: http://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-6-42

29. Yin RK. How to Start Your Analysis , Your Analytic Choices , and How They Work. Case Study Res Des Methods [Internet]. 2013 [cited 2017 Dec 11];127–64. Available from: https://www.sagepub.com/sites/default/files/upm-binaries/24737_Chapter_5.pdf

30. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and Implementing a Triangulation Protocol for Qualitative Health Research. [cited 2017 Dec 11]; Available from: http://journals.sagepub.com/doi/pdf/10.1177/1049732305285708

31. Guetterman TC, Fetters MD, Creswell JW. Integrating Quantitative and Qualitative Results in Health Science Mixed Methods Research Through Joint Displays. Ann Fam Med [Internet]. 2015 Nov 1 [cited 2017 Dec 11];13(6):554–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26553895

32. Fetters MD, Curry LA, Creswell JW. Achieving Integration in Mixed Methods Designs—Principles and Practices. Res Quest Mix Methods Heal Serv Res [Internet]. [cited 2017 Dec 11]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097839/pdf/hesr0048-2134.pdf

33. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet (London, England). 2007;370(9596):1453.

34. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): Revised Publication Guidelines from a Detailed Consensus Process. Can J Diabetes. 2015;39(5):434–9.

35. Hoo ZH, Curley R, Campbell MJ, Walters SJ, Hind D, Wildman MJ. Accurate reporting of adherence to inhaled therapies in adults with cystic fibrosis: methods to

calculate "normative adherence." 2016;

36. Hoo Z, Curley R, Walters S, Campbell M, Wildman M. Improving nebuliser adherence in an adult CF centre - differences in unadjusted adherence vs normative adherence. 2016;

37. Pollock-barziv SM, Finkelstein Y, Manlhiot C, Dipchand AI, Hebert D, Ng VL, et al. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. Pediatr Transplant. 2010;14(8):968–75.

38. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. Pediatr Transplant. 2008;12(1):67–72.

39. Spiegelhalter DJ. Funnel plots for comparing institutional performance. Stat Med. 2005;24(8):1185–202.

40. Hoo Z, Gardner B, Curley R, Wildman M. Part I : Understanding the variation in adherence with nebulised treatment in Cystic Fibrosis. J Improv Sci. 2013;9(1–10.3).

41. Hoo Z, Gardner B, Curley R, Hinchliffe C, Wildman M, Zhe A, et al. Part II: Methods to Deliver a "Personalised" Behaviour Change Intervention to Support Adherence with Nebulised Treatment. J Improv Sci. 2013;10:10.

42. Hoo Z, Gardner B, Curley R, Wildman M. Part IV: Using Process Behaviour (XmR) Charts of I-neb Adherence Data to aid the "Personalisation" of a Behaviour Change Intervention. J Improv Sci. 2013;13:1–12.

43. Hoo Z, Wildman M, Curley R, Hinchliffe C, Gardner B. Part V: Time of Nebuliser Use and the Process of Habit Formation. J Improv Sci. 2014;16:1–10.6.

44. Hoo Z, Wildman M, Curley R, Gardner B. Part VI: Delivering a "Personalised" Behaviour Change Intervention to Support Adherence with Nebulised Treatment with the "PDSA cycle" at an Individual Level. J Improv Sci. 2014;17:1–7.5.

45. Hoo Z, Gardner B, Curley R, Wildman M. Part III: constructing a process behaviour (XmR) chart with I-neb adherence data for people with cystic fibrosis. J Improv Sci. 2013;12:1–12.4.

Appendix 1. Logic Model
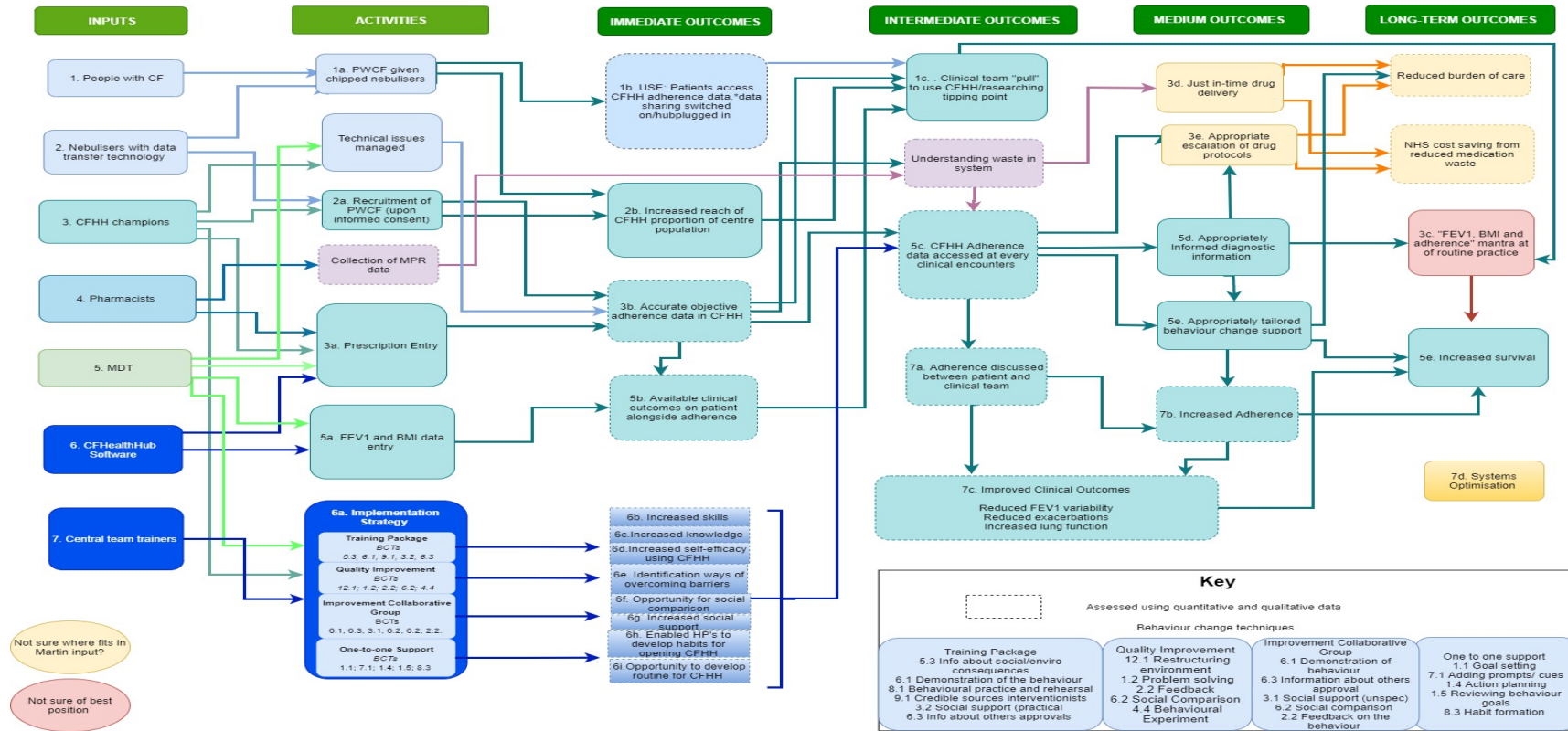
Appendix 2.

Implementation Strategy (publication submitted for review)

Module	COM-B	Intervention functions	Proposed BCTs
Training package: CFHH training and adherence support training: Training resources, refresher training, shadowing, fidelity assessment by lead interventionist	Physical capability Psychological capability Social opportunity	Training Education Persuasion	5.3 Information about social/enviro consequences 6.1 Demonstration of the behaviour 8.1 Behavioural practice and rehearsal 9.1 Credible sources 3.2 Social support (practical) 6.3 Information about others approval
Quality Improvement work: PDSA cycles and continuous metrics feedback	Physical opportunity Reflective motivation Automatic motivation	Education Environmental restructuring Enablement	12.1 Restructuring physical environment 1.2 Problem solving 2.2 Feedback on behaviour 6.2 Social comparison 4.4 Behavioural experiments
Improvement Collaborative group: Peer support, multicentre events, share success stories, problem solve together	Reflective Motivation Social Opportunity	Persuasion Modelling Enablement	6.1 Demonstration of behaviour from influential figures 6.3 Information about other approval 3.1 Social support (unspecified) 6.2 Social comparison 2.2 Feedback on the behaviour 1.2 Problem solving 15.3 Focus on past success
One to one support from trained interventionist: Goal setting, identifying prompts/cues, action planning	Psychological capability Reflective motivation	Training Enablement Environmental restructuring	1.1 Goal setting 7.1 Adding prompts/cues 1.4 Action planning 1.5 Review behaviour goals 8.3 Habit formation

12 Appendix. 3

12.1 Using the CFHealthHub digital learning health system to support preventative self-care for patients with Cystic Fibrosis (CF) during the COVID-19 emergency

12.2 Background

- During the COVID-19 pandemic, optimum adherence to preventative inhaled medication will reduce exacerbations and, in the event of COVID-19 infection, likely improve outcomes.

- During the COVID-19 pandemic, clinic visits will be minimised and CFHealthHub (CFHH) provides a tool that offers an alternative to clinic visits which is proven to significantly increase self-care to inhaled preventative therapies. This can be delivered via web and app.

- This protocol outlines how the CFHealthHub infrastructure will be reconfigured to provide bespoke support to individual CF teams across the UK. This is intended to allow the provision of uninterrupted self-care support throughout the pandemic, despite local teams managing high emergency workloads & staff sickness.

- Central resource will be configured in such a way that even when an individual CF centre has minimal staff availability, people with CF (pwCF) will continue to see accurate self-care data and receive self-care support as needed.

12.3 Aim

- To support pwCF to maintain and optimise lung health via potent inhaled preventative medication throughout the COVID-19 emergency.

- To support pwCF to monitor medicine supply and ensure medications are always available.

- To provide encouragement to maintain motivation and to ensure pwCF using CFHH feel supported in the daily challenge of staying well.

- To input patient prescriptions on CFHH for expected treatment regimens for the next 3-6 months.

- To deliver a robust and well-supported digital platform that can be refined to meet the changing needs of pwCF and clinical teams during the COVID-19 emergency.

12.4 **Objectives**

- Central team[3] to take on the task of ensuring that data within CFHH is as accurate as possible.
- Central team to work with local teams to provide flexible support to patients who are not taking optimal treatment.
- Central team to work with local teams to facilitate the delivery of inhaled medications to pwCF using CFHH.
- Central technical team to ensure the ongoing stability and maintenance of the CFHH digital platform and deliver software refinements and updates as needed.

---

[3] Central team who are either NHS employed or trained in a healthcare role e.g. Allied Health Professional

12.5 **Contents**

12.6 Description of revised CFHH support

12.6.1 Initial phase

Excess COVID-19 admissions remain low & CF teams not pulled to other duties.

- All participants will be contacted to inform them of the changes to CFHH relating to COVID-19 and how we plan to continue managing their care. We will explain how their data will be managed and that they may be contacted by a member of the central team where the local team are unavailable. All participants will be offered the opportunity to opt out of being contacted by the central team. Participants who opt out will be recorded on CFHealthHub.

- Local interventionist to continue to support CF patients using CFHH.

- Support provision of nebulised preventative medication to the patient.

- Endeavour to ensure prescriptions outlining expected treatment are inputted for the next 3 to 6 months.

- Local teams develop strategies to continue to provide CFHH support as the emergency escalates (e.g. could team members self-isolating deliver CFHH input with coaching as required from the Central team).

- Central team establish a cascade of contacts with local CF centres so that the Central team have a robust communication strategy if local teams need to pass CFHH support on to them. The aim is to have 1 local CF centre team member & 2 'buddies' who are able to commit 3 hours per week in total "whatever happens", with contact arrangements with the central team in place.

- Interventionists to prioritise recruitment of pwCF to CFHH, ensuring the maximum number of pwCF access CFHH throughout the COVID-19 emergency.

- Central team will support interventionists in providing:
  - CFHH technical support
  - CFHH recruitment support
  - Regular CFHH support for patients to develop habits and routines for treatment-taking that emphasises the benefits of preventative self-care during the COVID19 emergency.

- Identify and implement all software refinements to support pwCF throughout the COVID-19 crisis, and to support the work of the Central team (e.g. delivering

COVID-19 clinical dashboards for the Central team that enables prioritisation of pwCF with greatest need).

12.6.2 Intermediate phase

COVID-19 admissions start to impact clinical teams with cross-cover & self-isolation reducing resource.

- Central team will liaise with local teams and likely start to take on tasks such as prescription checking and identifying pwCF in local centres with falling or low adherence.
- Central team may pick up the task of checking CFHH inhaled therapy stocks for pwCF on CFHH.
- Hospital teams may move to "emergency CFHH delivery" in this phase so that only 3 hrs of "local CFHH time" is available.
- Any Central team contact with patients will be recorded in the Summary page on CFHH.
- Data of patients not engaging with the Central team for adherence or prescription purposes will be recorded centrally. CFHH pseudonym identifiers will be used. Identifiable information will not be recorded, as per usual data protection guidance.

12.6.3 Peak phase

COVID19 admissions are at the peak and hospital services are only just coping. There will be major concern in the population at this time. Local teams may no longer have any resource to support CFHH, though they may have team members at home self-isolating.

- Central team will take on the responsibility for ensuring data accuracy, technical and adherence support for the entire CFHH collaborative, including updating prescriptions.
- Any Central team contact with patients will be recorded on the Summary page on CFHH, with relevant information fed back to the local CF MDT by email. Identifiable information will only be shared between secure nhs.net email addresses.

52

- Central team will continue to aim to deliver adherence support to patients not managing to take optimum treatment.

- Central team will support data accuracy, reviewing CFHH prescriptions and reacting to prescriptions alerts.

- Patients will be identified for a CFHH call if:
  - They are not taking optimum treatment, prioritising those who are taking the least treatment.
  - There is a prescription problem.
  - There is a request for support from the local team.

- Where prescriptions require updating, this will be undertaken by the central team.

12.6.4 'Hand back' Phase

There will be a period of transition of CFHH back to the local team once the epidemic calms and interventionist duties return to their normal activities. We may need to potentially address training needs at this point.

12.7 Patients using I-neb nebuliser devices

It is anticipated that the visibility of adherence data on CFHH for patients using I-neb devices will reduce and potentially cease during the COVID-19 emergency, as patient-clinician face-to-face contact diminishes and clinicians will be unable to download adherence data from patient I-nebs. I-neb patients will receive prescription and technical support from the central team depending upon local team resource as outlined above. Patients will also have to opportunity for adherence support telephones calls from the Central team, although this will be limited in the absence of any recent adherence data. Options for patients to download ineb data from home will be explored. Guidance will be updated as this progresses.

12.8 Setting up of new participants

Consent visits have been face-to-face as approved by our ethics. We will move to amend this protocol to enable remote consent and set up of new participants. Sites

will also move to an opportunistic approach, consenting and setting up if or when new potential participants are seen (e.g. as inpatients or at home).

12.9 Functions of the Central team

- To be a point of contact for sites to relay information regarding their ability to carry out CFHH activities and duties.
- To support sites to continue with their current CFHH duties for as long as possible.
- In the event that the interventionist(s) at a site are no longer able to carry out their CFHH duties, the Central team will assume control of prescription updates, technical support, and providing remote adherence support to patients.

12.10 Central team resilience strategy

We will build a team with the resources, knowledge and experience to move fluidly in response to rapid changes in roles and responsibilities at site-level. All scheduled face-to-face meetings amongst the Central team will now take place over teleconference.

12.11 Resources

12.11.1 Central team

- Protected time for a Central team of people who are experienced with CFHH to optimise data accuracy and deliver adherence support interventions.
- All central team members will:
  - Be experienced or trained in delivering adherence support interventions
  - Be GCP trained
- Include a technical support team at University of Manchester to maintain the digital platform throughout the crisis, provide updates to the platform as required, and provide technical support to pwCF and the clinical teams. The technical team will also act as liaison with third party suppliers for nebuliser and spirometer devices, ensuring on-going data transfer from devices.

12.11.2   Local CF centres

- Aim for protected time for each site interventionist of around 3 hours per week for essential communication with the central team for patient adherence support purposes.

- Clinical, administrative and technical support will be offered from the Organisational Development team at Sheffield Teaching Hospitals to support data collection or analysis.

12.12   Equipment

- If working from home, the central team will require:
  - Laptop with internet access
  - Mobile phone, ideally with speaker function or headphone
  - Phone line for Central team communication to avoid face to face meetings, to allow multiparty teleconferences
  - Contact log access for mobile and emails accounts

12.13   Risks

What are the risks if CFHH is not available?

12.13.1   Context

- Cystic Fibrosis is an inherited life-limiting disease in which the lungs are damaged by repeated infections, making pwCF a critically vulnerable group in whom COVID-19 will be especially dangerous, since respiratory reserve is already reduced.

- Randomised controlled trials (RCTs) and meta-analyses of RCTs show that inhaled preventative therapy can protect the lungs of pwCF, improve lung function and reduce infectious exacerbations. However, median adherence to inhaled therapies is around 30%.

- The CFHealthHub platform was built and designed to support adherence to inhaled therapies and is currently in use across >60% of adult Cystic Fibrosis centres in the UK, reaching a major portion of the overall adult CF population.
- The 'Data Observatory Platform', an ongoing collaborative research project (supported by University of Manchester CFHealthHub platform) and digital learning health system, is continuing to recruit and support patients across >60% of adult CF centres.
- During the COVID-19 pandemic, the platform will be supported by NHS England and by a national coordinating CFHH central group.

The evidence we draw upon to understand the risks come from a 19-centre RCT involving 608 pwCF which was completed at the end of December 2019. This trial was led by Martin Wildman (Chief Investigator and Principle Investigator at Sheffield Teaching Hospitals), and the CFHH digital platform was developed by the Centre for Health Informatics, Digital Health Software team (leads: Prof John Ainsworth & Dr Pauline Whelan). This was the largest CF trial ever conducted in the UK and provides the most recent evidence-base to draw on.

12.13.2 Why is CFHH valuable to pwCF?

- CFHH was developed by clinicians and pwCF to provide feedback (objective adherence data) to pwCF about their use of inhaled therapies. It also provides a comprehensive behaviour change intervention which has been proven to significantly increase the use of preventative inhaled therapy compared to a control group not using CFHH.

12.13.3 What are the risks if CFHH is not available?

- If pwCF are not supported by CFHH, their adherence to inhaled preventative therapies will fall and their lungs will deteriorate, making them at greater risk if they contract COVID-19. They will also be more likely to have a "standard" exacerbation leading to hospital admission which will almost certainly increase the risk of COVID-19 exposure.

- PwCF have used CFHH for the past couple of years and for it to fail during the COVID-19 emergency can be expected to create panic and anxiety, and reduce resilience at a very difficult time.

12.13.4   Levels of distress to patients and the clinical team

- Frontline CF teams have worked hard over the past 3 years to create CFHealthHub as a potent tool to support vulnerable patients and they have come to depend on it as a way of keeping patients well.
- Frontline teams have felt incredibly reassured that CFHH will help them to support patients virtually in the most challenging circumstances any healthcare team has ever faced. If CFHH was taken away when it was most needed, it would create a sense of betrayal and increased anxiety as clinicians feel unable to support pwCF when they most need that support.
- Where patients require general guidance on COVID19 they will be directed to their local care team and the care team alerted if possible, to the query. All notes will be recorded on the summary review page.

12.14 Central team

The central team will be made up of a core of staff who have experience working with CFHH and/or working in a CF clinical environment. These staff members will sign a central delegation log, have GCP training and be specifically trained for the task by the CI. Their role in the study will be to provide a number of the following roles to sites:

- Adherence support
- Prescription checking
- Triaging data
- Technical support