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Health Research**

Sheffield Teaching Hospitals 
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Clinical
Trials
Research
Unit.

**Sheffield
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University**


CFHealthHub

Development and evaluation of an intervention to support Adherence to treatment in adults with Cystic Fibrosis

**A randomised controlled trial and
parallel process evaluation**

WP 3.2 and WP 3.3

RESEARCH PROTOCOL

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1. 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.

We have designed an intervention to help adult PWCF see how much treatment they use. We use dose-counting nebulisers to collect data and send it to a website, called CFHealthHub, where it can be displayed. We have worked with PWCF to make the information easy to understand. The website has modules which teach PWCF how to build successful treatment habits. We have developed a toolkit to help PWCF and a health professional (interventionist) work together to form habits of adherence to treatment. This trial will assess whether use of the CFHealthHub intervention, which includes the toolkit and website, reduces the amount of unscheduled emergency care PWCF require compared to those receiving standard care.

We will recruit PWCF for seven months at up to 20 CF units. We intend to recruit 556 PWCF overall. A computer will decide whether people who consent to be in the study will receive usual care alone or also receive the intervention. Both groups have a short period of two to four weeks when data is collected through their nebulisers and fed back to the website. It is only after that period that those allocated to the CFHealthHub group are allowed to use the website and receive enhanced care from the interventionist. After that point, all participants are followed up for 12 months. Participants will complete a series of questionnaires at the outset and at 12 months.

Quantitative data will be collected from the RCT CFHealthhub group, asking about acceptability of the intervention.

2. Introduction

2.1 Background

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) [9] 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.

2.2 Rationale

The National Institute for Health Research have commissioned a Programme Grant for Applied Research to systematically develop and evaluate an adherence intervention for PWCF. The Programme Grant has three work packages

Work package 1: Build IT infrastructure to capture adherence data from nebulisers. Co-produce a web-portal, 'CFHealthHub', with PWCF and clinicians, in order to display routinely collected adherence data for the use of both groups.

Work package 2: Develop a toolkit based on psychological theory that can support PWCF to adhere to treatment. This will include feedback of measured adherence data and personalised interventions to increase adherence delivered through CFHealthHub. Manualise a Behaviour Change Intervention (BCI) for use by health professionals and PWCF.

All five work packages have received a favourable opinion from an NHS REC:

- Work package 2.1A: A study of the views of people with cystic fibrosis about their condition and treatments (Hampshire A REC: 14/SC/1455; IRAS: 171049);
- Work package 2.1C: A study to produce videos for the CFHealthHub website (Camden & Kings Cross REC: 15/LO/0944; IRAS: 182367);
- Work package 2.2B: A study to develop a Behaviour Change Intervention (BCI) to help patients with CF manage treatment adherence ((South Yorkshire REC: 15/YH/0332; IRAS: 184477); and,
- Work package 2.2B(1): A study to understand how to use the eTrack and Bi-neb nebuliser to help people with CF to manage their inhalation treatments (West of Scotland REC 5: 15/WS/0089; IRAS: 177900).
- Work package 3.1: A feasibility study comprised of an external pilot randomised controlled trial and process evaluation (London Brent REC: 16/LO/0356; IRAS 199775).

- Work package 3.2 and 3.3: A randomised controlled trial and parallel process evaluation to determine the efficacy of CFHealthHub and Manuals and conduct a parallel process evaluation
- Work package 3.5 Health economic assessment: a formal health economic evaluation to assess the incremental costs and benefits of the adherence intervention versus usual care.

3. Aim and objectives

3.1 Aims

The aims of this RCT with parallel process evaluation are to determine whether the complex intervention is more effective than standard care in improving outcomes for PWCF and to determine the best way to deliver the intervention.

3.2 Objectives

1. A randomised controlled trial to determine the effect of the intervention on both clinical and participant related outcomes.
2. A process evaluation to facilitate interpretation of the RCT results and offer insights about how best to deliver the intervention in the real world.

4. Design

Mixed-methods study comprising of:

- Quantitative component: two armed, efficacy, parallel group, superiority open labelled, RCT;

and,

- Mixed methods process evaluation: analysis of audio-recorded consultations to assess fidelity of the intervention delivery; qualitative interviews with PWCF, interventionists and PIs to explore context, implementation, mechanisms of action, and longer-term acceptability of the intervention; quantitative data collected as part of the RCT questionnaire to measure acceptability of the intervention; and quantitative data from CFHealthHub on use of the intervention over time.

5. Participants and study settings

5.1 Settings and locations where the data will be collected

Nebuliser adherence data and information derived from CFHealthHub will be automatically uploaded by participants nebulisers in their own home. Data collection involving patient notes and patient reported outcome measures will take place in up to 20 specialist CF units which have not been involved in the development of the intervention. Exacerbation data will be collected by the ACtiF trial interventionist and clinicians at sites from participant notes.

5.2 Eligibility

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. Willing and able to take inhaled mucolytics or antibiotics via a chipped nebuliser (e.g. eTrack)

5.2.2 Exclusion criteria for participants

1. Post-lung transplant
2. People on the active lung transplant list
3. Patients receiving palliative care
4. Lacking in capacity to give informed consent
5. Using dry powder devices to take antibiotics or mucolytics

5.2.3 Eligibility criteria for study centres

1. Adult CF Centre;
2. Recognised by commissioners to receive funding

5.2.4 Eligibility criteria for interventionists

1. Health care professional e.g. registered nurse, physiotherapist or other appropriately skilled individual (band 6 or above) or other candidates such as a psychology graduate (band 4 or above) with significant post registration experience.

6. Interventions

6.1 Summary

PWCF are allocated to either a complex intervention or usual care. A ‘complex intervention’ is defined as one with several interacting components [17]. The complex intervention under evaluation has three broad categories of components (Figure 1):

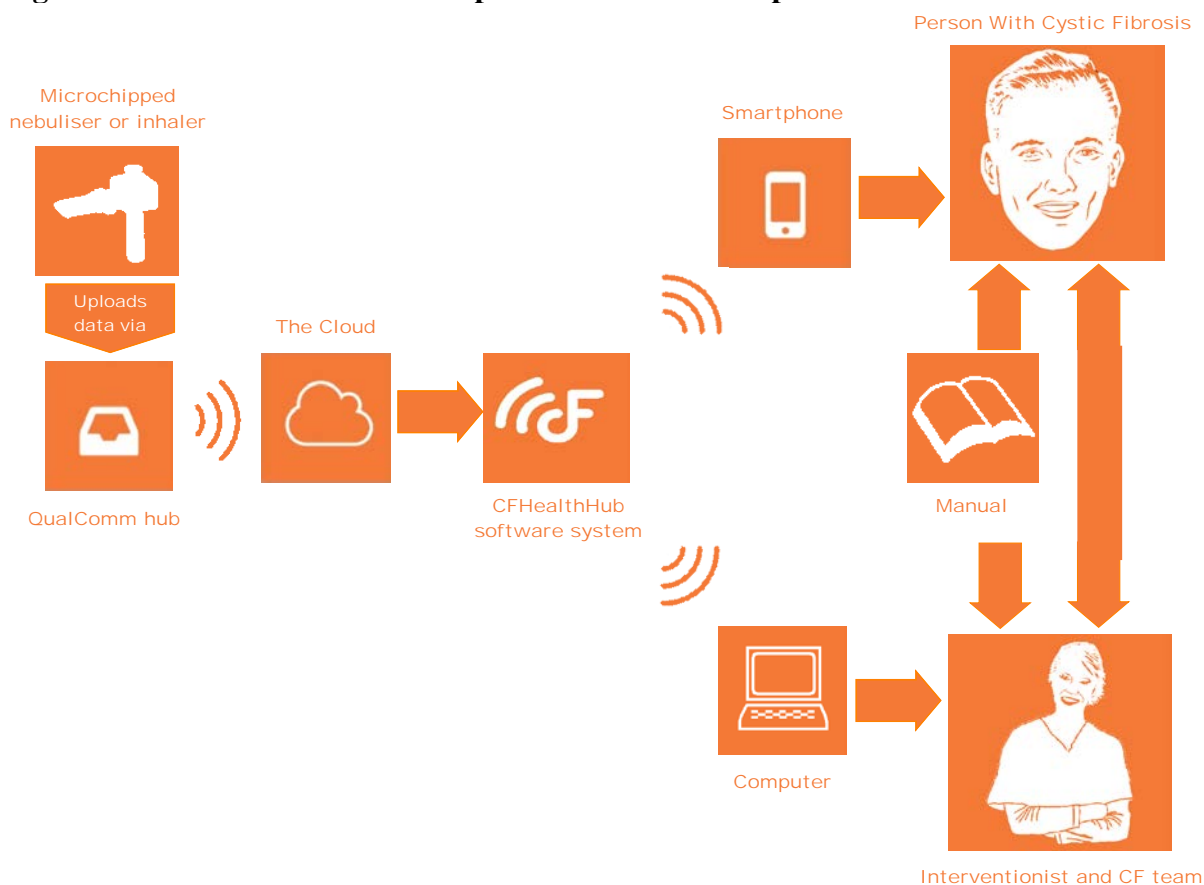
(a) *a microchipped device* (nebuliser) for delivering inhaled medications, which are routinely prescribed for the control of cystic fibrosis (Section 6.2);

(b) *information technology infrastructure* to capture and store adherence data from the nebulisers and display it to PWCF and the CF team (Section 6.3); and,

(c) *the behaviour change intervention*, comprising a software platform (‘CFHealthHub’ mobile apps and website) offering adherence feedback and tailored modules of content and tools used by the health professional in interactions with PWCF (Section 6.4) and accessed independently by PWCF via CFHealthHub

Services received as usual care described in Section 6.5.

Figure 1. Interaction between complex intervention components



6.2 Microchipped devices

Depending on treatment strategies at different centres the participant may use an eTrack nebuliser system (Section 6.2.1), .

6.2.1 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 nebuliser or Altera nebuliser. 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.

6.3 Information technology infrastructure

The information technology infrastructure for the complex intervention comprises:

- i. The Qualcomm hub (Section 6.3.1)
- ii. CFHealthHub (Section 6.3.3).

6.3.1 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.

6.3.3 CFHealthHub

CFHealthHub is a web-portal which displays adherence data and provides resources and tools to people with cystic fibrosis and health professionals in order to support improved nebuliser adherence. It is available on-line via computers, tablets or mobile phones.

A qualitative study (WP 2.1A) to identify the barriers and facilitators of nebuliser use in PWCF informed the development of an intervention designed to increase nebuliser adherence. Analysis of the interview data was conducted using the COM-B framework, and these findings were used to inform the development of a complex intervention centred around the feedback of objective adherence data. The intervention was further developed and refined in consultation with PWCF and clinicians. An iterative study (WP2.2B) in which prototype versions of the intervention were delivered to and reviewed by PWCF was conducted. In that iterative study we interviewed PWCF and interventionists about the usability and tailoring of the intervention, and made improvements to the process and materials based on this feedback. The system has been developed to ensure it meets the requirements of the Data Protection Act 1998. It is intended that data on maintenance and relapse will be generated during the full scale trial.

CFHealthHub has a number of modules addressing barriers to adherence based on the COM-B system described in greater detail in Section 6.4.1. The objectives of the modules as mapped to the COM-B are outlined in Table 1 below.

Table 1. Learning objectives of the CFHealthHub modules

COM-B model component	Objectives
Physical capability	- Have the skills to be able to use the nebuliser correctly
Psychological capability	- Understand the importance of nebuliser use in CF treatment - Be able to remember to use nebuliser - Be able to self-monitor nebuliser use - Be aware of a need to improve nebuliser use
Physical opportunity	- Have a realistic medication plan - Have a working/functioning nebuliser - Have a suitable place to use nebuliser - Have the time to use nebuliser
Social opportunity	- Be/feel supported by others to use nebuliser
Reflective motivation	- Perceive benefits of nebuliser use - Perceive few/no concerns about nebuliser use - Understand the health consequences of use/non-use - Feel confident about nebuliser use - Intend to use nebuliser
Automatic motivation	- Have an established routine for nebuliser use - Have a habit to use nebuliser

6.4 The Behaviour Change Intervention (BCI)

6.4.1 Rationale and theory

The rationale of the BCI is to help CF patients to self-manage their condition and to form habits that will improve adherence to their medication, thereby extending life and improving quality of life. The MRC framework for developing and evaluating complex interventions recommends that intervention development should be informed by a suitable theoretical framework and evidence base [17]. The theoretical model adopted is the COM-B model [18] which describes a ‘behaviour system’ of the essential and interacting conditions of Capability, Opportunity, and Motivation [18]. The model posits that non-adherence is either non-intentional (a problem of capability or opportunity) or intentional (a problem of motivation). The model has been adapted to nebuliser adherence on the basis of evidence about the factors influencing nebuliser adherence in PWCF [19–32], input from expert clinicians currently delivering services to PWCF, as well as from the PPI panel and exploratory research conducted in Sheffield. It is important that interventions are tailored to individual needs and use a multi-modal approach [33]. Each of the conditions of Capability, Opportunity and Motivation has been considered in turn in the development of our intervention. The primary component of the intervention is adherence feedback

delivered via the CFHealthHub. Evidence suggests that while personalised feedback can have an effect size of up to 20% in increasing adherence [34, 35], feedback is most effective when combined with additional behaviour change techniques [34].

Figure 2. Interactions between capability, opportunity and motivation

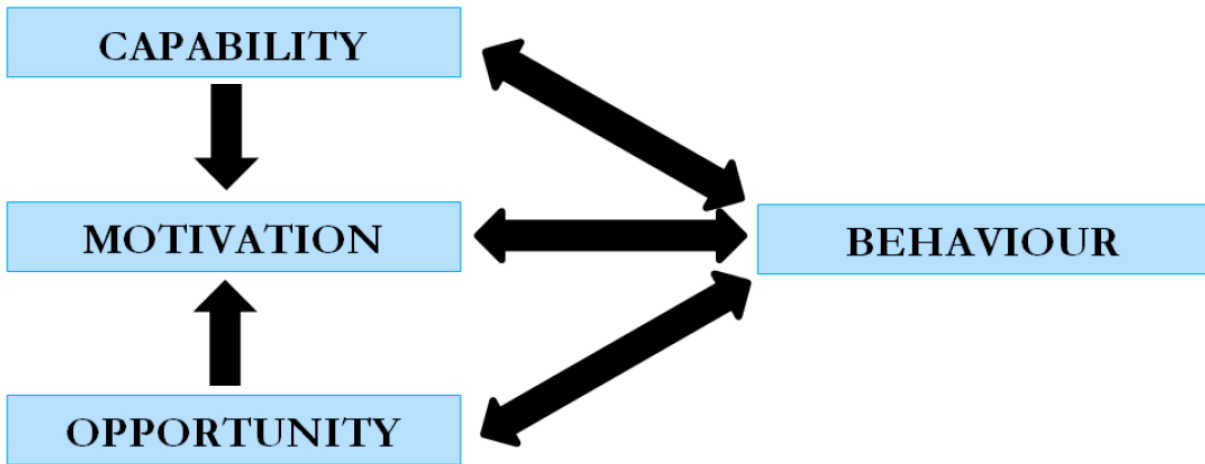


Figure 3. Habit formation incorporating COM-B and necessities and concerns

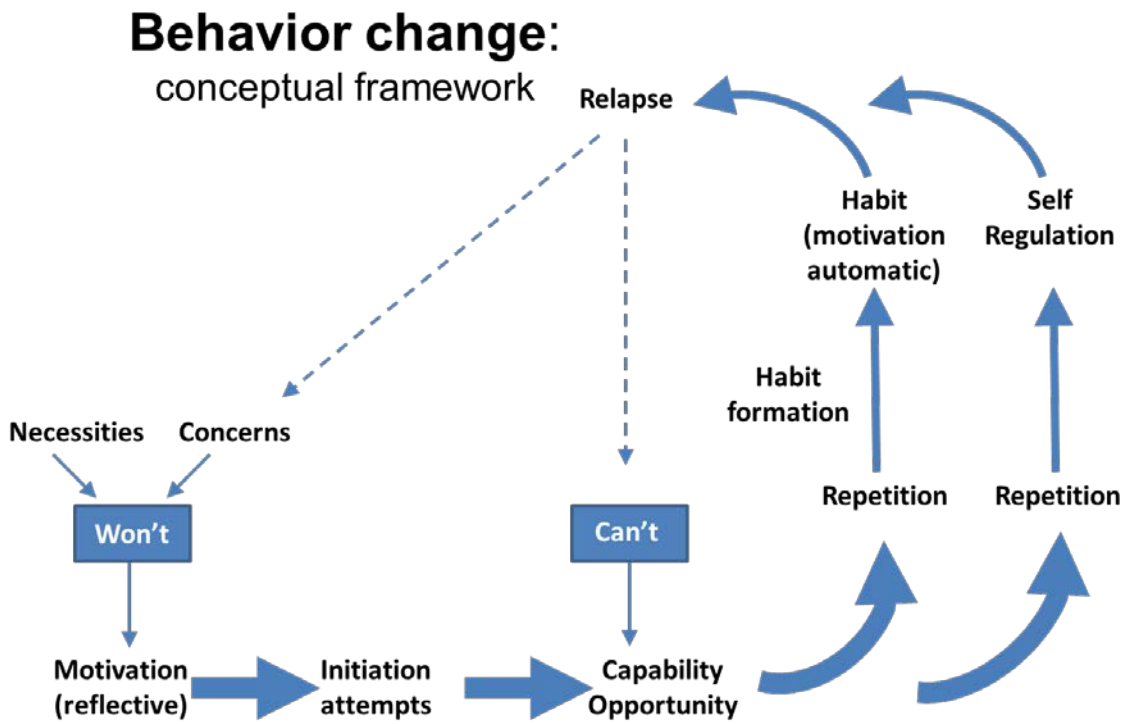
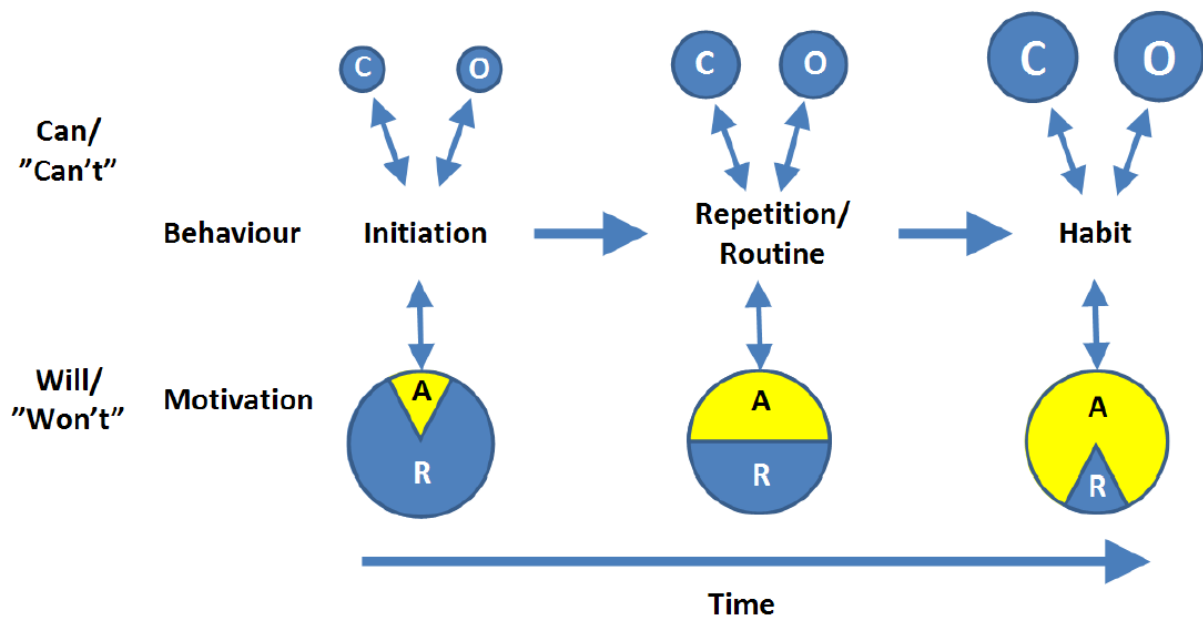


Figure 4. Interplay between COM-B components during habit formation



A= Automatic, R= Reflective, C= Capability, O=Opportunity

The identification and choice of appropriate behaviour change techniques has been driven by the Behaviour Change Wheel framework for the development of interventions [Michie, S. F., Atkins, L., & West, R. (2015). *The behaviour change wheel: a guide to designing interventions.*] which outlines a process of intervention design using the COM-B model "through the systematic evaluation of theory and evidence" (p. 13). In brief, the process involved the following steps:

1. In depth identification and analysis of the factors influencing nebuliser adherence in PWCF through an examination of the existing literature, and a qualitative study in which participants viewed charts of their objective nebuliser adherence data within an interview about factors affecting their motivation, capability and opportunity to adhere to their nebuliser treatment (study 2.1). The Theoretical Domains Framework (TDF; [36]) which analyses Capability, Opportunity and Motivation in greater detail was used as a framework to guide the analysis.
2. Identification and evaluation of potential intervention functions (e.g. education, persuasion, enablement, environmental restructuring, modelling) to address the identified factors influencing nebuliser adherence in consultation with the research team, clinicians and PPI.
3. Development of intervention modules to include specific Behaviour Change Techniques to deliver intervention functions, selection of mode of delivery, and mechanism for tailoring of BCI delivery to meet individual needs with regard to Capability, Opportunity and Motivation. The module contents have been discussed and refined as a result of discussions with clinicians and PPI.
4. Identification of potential mediators of behaviour change, and identification of tools to measure each mediator.

The intervention arrived at through this process is described in Table 2.

Table 2: Intervention modules

Module	COM-B	Intervention functions	Behaviour Change Techniques	Mode of Delivery
<i>Universal parts of the intervention</i>				
Self-monitoring	Psychological capability Reflective Motivation	Education Environmental restructuring Enablement	<ul style="list-style-type: none"> • Self-monitoring of behaviour • Adding objects to the environment (CFHealthHub) 	<ul style="list-style-type: none"> • Charts of objective adherence data presented within CFHealthHub
Goal setting & review	Psychological capability Automatic motivation	Enablement Incentivisation	<ul style="list-style-type: none"> • Goal setting (behaviour) • Feedback on behaviour • Discrepancy between current behaviour and goal • Review behavioural goals • Graded tasks • Social reward 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Action planning • Habit formation • Prompts/cues (tailored) 	<ul style="list-style-type: none"> • Action planning tool within CFHealthHub • Option to set reminders
Confidence building	Reflective Motivation	Persuasion	<ul style="list-style-type: none"> • Focus on past success 	<ul style="list-style-type: none"> • Interventionist encouraging focus on periods of higher adherence on charts

Module	COM-B	Intervention functions	Behaviour Change Techniques	Mode of Delivery
<i>Tailored parts of the intervention (based on baseline COM beliefs and barriers questionnaire (COM-BMQ)¹ and consultation with interventionist)</i>				
My treatment	Reflective Motivation Psychological capability	Education Persuasion Modelling	<ul style="list-style-type: none"> Information about health consequences Credible source Saliency of consequences Demonstration of the behaviour Vicarious consequences Self-talk 	<ul style="list-style-type: none"> Q&A linked to information within CFHealthHub (tailored by baseline beliefs and prescription data) Presentation through 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	<ul style="list-style-type: none"> Demonstration of behaviour 	<ul style="list-style-type: none"> '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	<ul style="list-style-type: none"> 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) 	<ul style="list-style-type: none"> 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

6.4.2 Intervention providers

Interventionists may already be working at, or be new to participating organisations or be the ACTiF interventionist employed to deliver the trial locally at the site. Externally appointed staff will be recruited through a formal job interview. Suitable individuals will fulfil the job description and may include registered nurses or other member of the multidisciplinary team or a graduate in a suitable subject such as psychology or, other relevant profession who holds relevant skills / experience. Candidates for the post will ideally have a minimum of three years postgraduate experience which might include delivering a research project to time and target. They will be employed on the Project to work to NHS Agenda for Change Band 6 or above. They must have access to a car for work purposes e.g. participant home visits.

Interventionists will be supported in the delivery of the intervention by members of the Multidisciplinary team (MDT) at the site in which they are based.

Training for interventionists in how to deliver the intervention according to the specifications of the behaviour change manual will be provided by Marlene Hutchings, Madelynne Arden and Judy Bradley. A comprehensive training manual and training programme will be developed to facilitate this. A certificate of competence, based on both the theoretical and practical aspects of the intervention, will be provided prior to the interventionist being able to use CFHealthHub with participants.

The central research Physiotherapist (Marlene Hutchings) will offer support to trial sites as and when required. This on occasion will involve input to patients (face-to-face or telephone contact), and assisting with problem solving via liaising with the nebuliser company. They will be named on the local site delegation log.

6.4.3 Materials

The BCI contains two broad categories of components:

- i. CFHealthHub behaviour change modules including adherence feedback used by PWCF and health professionals
- ii. The behaviour change manual and toolkit used by the interventionist in interactions with PWCF in order to understand the specific barriers to adherence for that individual, and to tailor and personalise delivery of the behaviour change modules accordingly.

6.4.4 Procedures

Based on the findings and feedback from the Pilot trial, from participants, interventionists and our PPI group, we have made amendments to the way the intervention is delivered. A new CFHealthHub RCT Manual and participant User guide have been written incorporating these changes. The BCI will be delivered over the participant follow up period through a combination of face-to-face sessions, contact via telephone or video calling with an interventionist, and through participant interaction with different modules of content available on CFHealthHub. The interventionist will discuss participant data with members of the MDT to ensure that care is informed by objective adherence data. If any concerns become apparent

as the interventionists collect data and work with participants, these concerns will be passed onto the clinical team. The clinical team will follow their standard procedures in relation to any concerns raised. The intervention content and delivery flow are outlined in Figure 5 and described below.

6.4.4.1 Consent Visit (all participants)

At the consent visit, participants will be given a chipped nebuliser (eTrack) and Qualcomm hub. The eTrack will connect to CFHealthHub which will enable adherence data be collected. The interventionist will input the participant's prescription details into CFHealthHub. Together these will allow the system to generate adherence charts for that participant. At this visit participants will complete a range of baseline measures (see Table 3) including the COM beliefs and barriers questionnaire (COM-BMQ) which will be entered into CFHealthHub. The responses to this questionnaire will be used to populate the 'My toolkit' section of CFHealthHub with specific tailored elements from the 'My treatment' modules prior to the Initial Intervention Visit. The participant's *Pseudomonas* status will be clarified at baseline and confirmed by the PI with the opportunity to compare the participant's prescription with the *Pseudomonas* status.

6.4.4.2 Initial Intervention Visit (CFHealthHub Group)

Participants will be introduced to CFHealthHub. They will be asked to complete an online consent form in which they will specify what additional data they would be willing for CFHealthHub to record and display (e.g. name, and uploaded photographs) and what functional options they would like access to (e.g. push notifications). Permissions may be changed at any time. The interventionist will discuss their motivation to adhere to their nebuliser treatment, will address beliefs associated with poor adherence and will refer back to answers on the COM-BMQ to elicit the participants beliefs associated with adherence. Participants will be shown 'My toolkit' which will have been prepopulated with tailored motivational content (see consent visit).

The interventionist and participant will look at and discuss the adherence charts on CFHealthHub with a focus on period of higher adherence. The interventionist will note any barriers raised by participants during this discussion.

The interventionist will support the participant to identify where and when additional nebuliser treatments could be fitted into their schedule and support them to make an action plan using the online tool available on CFHealthHub. This action plan will be saved to the 'My toolkit' zone. The interventionist will then agree a % adherence goal for the next four to six weeks based on the number of additional treatments that have been planned. This will be recorded on CFHealthHub and will be represented by a target line on the adherence charts.

If motivation is so low that participants are reluctant to set an action plan/goal then the interventionist will spend further time discussing motivation and will skip to confidence building (see below).

The interventionist will encourage participants to focus on likely problems or issues that might disrupt the achievement of the adherence goal and will use the Problem-solving module on CFHealthHub to address each of these anticipated problems. The Problem-solving module includes solutions based on educational content, practical support (e.g. model letters to employers) and interactive tools such as coping plans. Relevant solutions will be saved to the 'My Toolkit' zone of CFHealthHub.

The interventionist will discuss the participant's confidence to meet their goal and will identify 2-3 'talking heads' videos showing other people with CF addressing and overcoming similar barriers to nebuliser adherence. The visit will conclude with a review of the goal and the tailored and personalised contents saved to the 'My toolkit' zone of CFHealthHub. The interventionist will encourage a learning mindset, emphasising that even if adherence doesn't increase starting to think about adherence will produce learning that will make subsequent attempts to change easier.

6.4.4.3 Participant Independent access to CFHealthHub (CFHealthHub Group) Participants will have independent access to CFHealthHub at all times following the Initial Intervention Visit. They can, at any time, access their adherence charts, 'My toolkit' contents, and can browse the other areas of content as they wish. Frequency of access to each area of CFHealthHub will be monitored and recorded.

Adherence charts will provide colour -coded feedback about participant achievement towards their adherence goal so that they are provided with immediate, easy to recognise information about their achievements. Subject to consent, participants will be sent a weekly summary of their percentage adherence and encouraging messages via push notifications, or alternatively when they access CFHealthHub, to match the progress made e.g. congratulations on achieving their goal, congratulations on having made progress towards their goal, encouragement to remember their action plan.

6.4.4.4 Review visit(s) (Visit 3 till end of study - CFHealthHub Group)

Following the first intervention session, the amount of interaction which each PWCF has with the interventionist will be tailored to their needs and requirements. Where possible, a review visit will be attempted by the interventionist around the participant's routine clinic visits or if the participant is in hospital for any other reason (e.g. as a result of an exacerbation).

There are three types of review visits which will be implemented as shown in Figure 5 below:

1. Intermediate review
2. Phased review
3. Triggers for new phase

Which type of review each participant requires will be based on a combination of their current adherence and the presence of any "triggers" e.g. an exacerbation episode or a drop in adherence by more than 20%.

At the review visit, the interventionist and participant will look at and discuss the adherence charts on CFHealthHub and goal achievement with a focus on progress made and periods of higher adherence. If the adherence goal was met then the participant will be encouraged to set a new higher adherence goal or to a goal to maintain their current level of adherence which will be recorded on CFHealthHub. Following this the participant and interventionist will review the contents of 'My toolkit' and revise action plans, problems/solutions as required. If issues of motivation are still a concern the interventionist may recommend additional/alternate elements of content from 'My treatment' or 'Talking heads' to go into 'My toolkit'.

If the adherence goal was not met then the interventionist and participants will discuss the barriers to goal achievement (motivation, capability, opportunity). The interventionist will address beliefs associated with poor adherence and will add/revise the elements of content from 'My treatment' or 'Confidence building' to go into 'My toolkit'.

If no goal was previously set then the interventionist will review motivation and confidence and then will consider if the participant is ready to action plan and set a goal. If not they will spend more time reviewing motivation and confidence.

The participant will be encouraged to set a realistic % adherence goal for the next four to six weeks and this will be recorded on CFHealthHub. The interventionist will support the participant to revise their action plan as needed and save this to the 'My toolkit' zone. Based on the earlier discussion about the barriers that prevented goal achievement the Problem-solving module on CFHealthHub will be used to address each of the problems encountered, and any that are anticipated. Relevant solutions will be saved to the 'My Toolkit' zone of CFHealthHub.

The visit will conclude with a review of the goal and the tailored and personalised contents saved to the 'My toolkit' zone of CFHealthHub. The interventionist will re-emphasise a learning mindset, emphasising that the participant cannot fail, but can learn from the process so that they can work together on the adherence challenge.

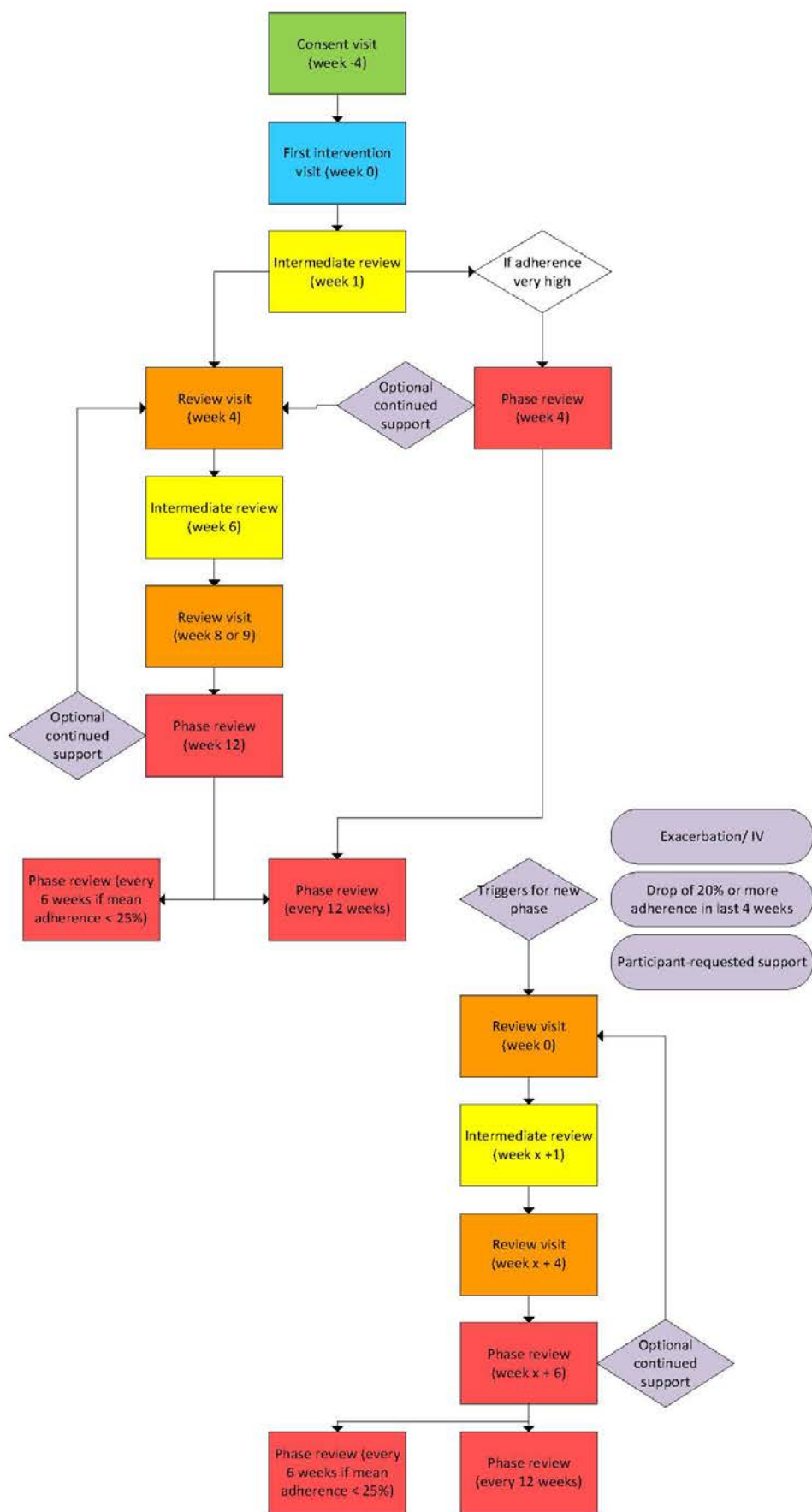
Participating centres will provide participants with contact details, typically telephone numbers, but other methods may be volunteered by centres. Contact details will be provided so that participants can contact the centre if they have queries or problems regarding CFHealthHub between visits. The interventionist will be able to feedback any information from the intervention delivery **after** the baseline intervention visit to members of the wider CF team. This may include adherence data from sessions with the participant's clinician and MDT particularly if the participant raises any concerns or issues e.g. side effects of a drug to allow their usual clinician to discuss this with them at their next clinic visit.

6.4.4.6 Final research visit (12 months from consent)

All participants will complete a final research visit 12 months from the date of consent. At this visit, the interventionist will collect primary and secondary outcome data as outlined in table 3. At this final research visit, the interventionist will perform a system check with the eTrack device to ensure that adherence data has been transferred to CFHealthHub. The eTrack can store approximately 6 months of treatment data, ensuring all the data is transferred at this visit should help to prevent missing data.

Following the final 12-month research visit, we will continue to collect: adherence data from CFHealthHub; exacerbations; FEV1 and ask participants the subjective adherence question until, 30th June 2019. At this point, the study closes and the involvement of all participants ceases. After the trial ends (30/6/19), participants will have the option to enter into further CFHealthHub research should they wish..

Figure 5. Behaviour change intervention delivery plan



6.5 Usual care

Patients in both arms will receive usual care. Usual care is heterogeneous within and between centres, based on the needs of patients and the skills and interests of CF Unit staff.

Participants in the control group will use a microchipped nebuliser but will not be able to access adherence data or other content and tools through CFHealthHub, nor will they receive the structured CFHealthHub intervention as described in the intervention manual. Members of the MDT will not have access to the graphs/data generated by CFHealthHub for control arm participants although we will, centrally, follow participants up for troubleshooting missing data/ data errors.

6.6 Criteria for discontinuing or modifying allocated interventions

There are no criteria for discontinuing treatment. Participants will be made aware that their participation is voluntary and they may discontinue study interventions, should they wish, at any time.

If a participant wishes to withdraw from treatment they will be able to speak to a member of the site study team i.e. ACtiF interventionist. This will be documented on a participant withdrawal form, within the Case Report Form. Any data already collected during the course of the trial up to the point of withdrawal will be used in the final analysis. We will ask the participants for their permission to continue to collect the primary outcome data i.e. CF exacerbations. The participant or clinician can make the decision to discontinue the allocated study intervention for any reason.

Participants will have the following options if they wish to withdraw:

1. Withdraw from the intervention i.e. intervention delivery visits only but will remain in the study. Patients can continue to use CFHealthHub. All study data will continue to be collected at subsequent follow up time points as per protocol.
2. Withdrawal from the study. Unless the patient objects, any data collected up to this point would be retained and used in the study analysis. The local interventionist would ask the participant if they agree to the collection of primary outcome data as defined in the protocol and or adherence data if they agree to collection of adherence data, CTRU and or interventionist will continue to follow up participants for adherence data.
3. Withdrawal from the trial entirely. Unless the patient objects, any data collected up to this point would be retained and used in the study analysis. If the patient does not wish to be contacted with regard to primary outcome data or adherence data, no further contact with regard to the study will be made. If the participant does specifically request for all their data to be removed information regarding the participant will be retained at site, as part of the patient notes, along with their withdrawal form and request to delete the data.

A participant would be classed as complete if they have continued in the study until the last protocol defined visit, however there may be missing visits and / or data.

Loss to Follow-Up

A participant would be classed as lost to follow-up if the participant has 1) not completed the study or 2) been withdrawn despite attempts for further contact, as per protocol, having been made. Unless the participant withdraws from the study entirely we will continue to collect the primary outcome data when possible (i.e. from medical notes).

This withdrawal section has been developed in accordance with the CTRU Participant Discontinuation and Withdrawal of Consent Standard Operating Procedure (SSU003).

6.7 Strategies to improve adherence to intervention protocols

6.7.1 For health professionals

The intervention protocols will be described in detail in an intervention manual. Interventionists will be trained to deliver the intervention according to the manual protocols at a 2-day workshop and through an online learning platform. Tutorial support will also be offered. Interventionist training (as a form of behaviour change) will focus on Capability, Opportunity and Motivation. It will utilise evidence about the importance and likely effectiveness of the intervention and will challenge common misconceptions about adherence. Skills training and an introduction to the tools available on CFHealthHub will increase staff capability, and we will work with clinics and clinicians to ensure that the practical requirements for intervention delivery are in place: space, time etc (opportunity).

CFHealthHub will record interventionist access to the site. It will also automate some of the tailoring of the intervention according to the COM-BMQ which will be completed online. The contents of 'My Toolkit' will be recorded for each participant so that we will have records of what content they have been recommended. Interventionists will also be required to complete session records each time that they deliver the intervention to record the decisions made and the reasons for these.

6.7.2 For patients

Where participants provide consent, we will send optional push notifications to encourage engagement with CFHealthHub. For example, we will send congratulatory messages when adherence improves, encouraging messages to remind participants to engage with the content. Face-to-face visits will, where possible be arranged to coincide with clinic visits as per usual care, therefore minimising the additional burden on participants.

6.8 Relevant permitted / prohibited concomitant care

No concomitant care will be denied based on the research protocol.

7. Outcomes

7.1 Clinical outcomes and covariates

The time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants can be found in Section 7.4, Table 3 and Table 4 below.

7.1.1 Primary clinical outcome

The primary clinical outcome is the number of pulmonary exacerbations in the 12 month post-baseline follow-up period, defined according to the modified Fuchs criteria [37]. An exacerbation of respiratory symptoms will be said to have occurred when a patient was treated with parenteral antibiotics for **any one of the following 12 signs or symptoms** [38]:

1. change in sputum;
2. new or increased hemoptysis;
3. increased cough;
4. increased dyspnea;
5. malaise, fatigue, or lethargy;
6. temperature above 38 °C;
7. anorexia or weight loss;

8. sinus pain or tenderness;
9. change in sinus discharge.
10. change in physical examination of the chest, derived from notes by site staff.
11. decrease in pulmonary function by 10 percent or more from a previously recorded value, derived from notes by site staff; or,
12. radiographic changes indicative of pulmonary infection, derived from notes by site staff.

The trial interventionist or prescribing clinician/nurse will collect data on the “exacerbations” form at the point of a participant starting a course of IV antibiotics whether these are planned or unscheduled.

7.1.2 Secondary clinical outcomes

1. **Body Mass Index (BMI).**
2. **Forced expiratory volume in 1 second (FEV₁):** standardised spirometry as a measure of condition severity [39].
3. **EuroQol EQ-5D-5L:** generic health status measure which will be used to inform the health economic analysis [40].
4. **The Patient Activation Measure (PAM-13) (Health Style Assessment):** assessment of patient knowledge, skill, and confidence for self-management [41]. *PAM-13 was labelled as “Health Style Assessment” following a request from the licence owners to ensure the purpose of the questionnaire is clear for participants.
5. **Assessment of routine:** measure of life chaos [42].
6. **Self-Report Behavioural Automaticity Index (SRBAI):** automaticity-specific subscale of the Self Report Habit index to capture habit-based behaviour patterns [43].
7. **Cystic Fibrosis Questionnaire-Revised (CFQ-R):** disease specific health-related quality of life instrument [44].
8. **The Patient Health Questionnaire depression scale (PHQ-8):** severity measure for depressive disorders [45].
9. **MAD (Medication Adherence Data-3 items) :** medication adherence measure
10. **The General Anxiety Disorder 7-item anxiety scale (GAD-7):** severity measure for anxiety [46].
11. **The Capability Opportunity Motivation Behaviour Beliefs Questionnaire (COM-BMQ):** This questionnaire incorporates:
 - a. **The Beliefs about Medicines Questionnaire - specific (Nebuliser adherence) (BMQ 21-item):** a validated self-report tool[47], customised by the author to identify perceived necessities and concerns for nebuliser treatment.
 - b. The following project-specific items: one additional belief item, one intention item, one confidence item, and a list of barriers. These will serve as a tailoring tool for the intervention and also as a secondary outcome measure.
12. **Subjective adherence single question:** self-report estimate of adherence as a percentage. Self-reported problems: identification of capability and opportunity barriers to nebuliser adherence

13. **Resource use form:** interventionist collects data from a combination of hospital notes and the NHS patient electronic system to determine 1) inpatient IV days 2) Routine clinic visits 3) Unscheduled outpatient contacts 3) unscheduled inpatient stays.
14. **Exploratory analysis of habit formation:** analyses with the objective nebuliser data will be performed to explore the process of habit formation with the delivery of the adherence intervention
15. **Prescription:** a monthly prescription check to both check for data transfer to CFHealthHub and review for an indication that the prescription has changed or indication of microorganism e.g. Pseudomonas (please see Table 3 and 4 and refer to Section 10.1.1).
16. **Adherence to prescribed medication (see 7.4.3)**
17. **Any treatment with IV antibiotics**
18. **11 item questionnaire on acceptability of intervention**

7.1.3 Adherence to prescribed medication

Adherence to prescribed medication will be defined in several ways including:

1. Unadjusted adherence
2. Simple normative adherence (without numerator adjustment)
3. Sophisticated normative adherence (without numerator adjustment)
4. Simple normative adherence (with numerator adjustment)
5. Sophisticated normative adherence (with numerator adjustment)

Further detail about the outcomes will be reported in the trial statistical analysis plan.

7. 2 Process data relating to the implementation of the trial

1. Number and characteristics of eligible patients approached for the study

Collected by centres in screening logs and transferred to Prospect database

2. Reasons for refused consent

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

3. Reach

How many participants are 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 completed by ACTiF interventionist;
- Those known to be eligible, expressed quantitatively based on CF Registry.

4. Participant attrition rate

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

5. Reasons for attrition

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

6. Maintenance:

The processes by which participants are kept involved in the collection of key secondary outcome data research data:

- The extent to which adherence data is successfully uploaded from the chipped nebulisers, described quantitatively using CFHealthHub

7. Number of missing values/incomplete cases

Assessed by data management team, based on data in Prospect database.

8. Participant,/interventionist and PI views on research protocols

Assessed through qualitative interviews and to include:

- Barriers to recruitment, problems encountered in reaching participants [48];
- Perceived problems with trial procedures such as recruitment, informed consent etc
- Acceptability
Perceived utility and burden of outcome assessments

9. A survey on the content of usual care at participating centres

To better understand the configuration of usual care at participating centres a survey tool will be administered by the local interventionist at two time points 1. within one month of the study start at the site and 2. after the last participant has been followed up for 12 months.. This will identify the spectrum of clinical and behaviour change interventions that are in use in the management and self-management of CF.

7.3 Process data relating to the implementation of the intervention

1. Context

Definitions of ‘context’ tend to cluster around setting, roles, interactions and relationships [49]. It is important that context is understood as diachronic and emergent rather than synchronic and static [50, 51]. Frameworks for process evaluation have defined ‘context’ as:

- “aspects of the larger social, political, and economic environment that may influence intervention implementation” [52];
- “factors external to the intervention which may influence its implementation, or whether its mechanisms of impact act as intended” [53].

The context, and its interaction with implementation, mechanisms of impact, outcomes, the description of the intervention and its causal assumptions [53] will be described using qualitative data from research interviews, reflection notes, study management logs, and audio recordings of intervention visits,. The focus will be how the context of individual CF Units affects implementation of the intervention and its potential outcomes.

4. Training:

The comprehensiveness and effectiveness of the training component of the intervention for the health professionals delivering the intervention will be assessed by a combination of an evaluation questionnaire, competency assessments (with feedback), and assessment of drift over the course of the RCT - see fidelity. Additional training will be offered during the RCT where delivery of the intervention is identified as requiring improvement.

5. Fidelity –

“The extent to which the intervention was delivered as planned. It represents the quality and integrity of the intervention as conceived by the developers. Fidelity is a function of the intervention providers.”[52]
The fidelity assessment will be developed and based on a tool used by Borelli et al [54] that considers five domains of fidelity: Design, Training, Delivery, Receipt, and Enactment. Fidelity will be assessed using a combination of:

- Data from CFHH about what tools and content have been recommended by the interventionist
- Data from CFHH about how participants have interacted with CFHH tools and content
- Session reports/checklists completed by interventionists during preparation for and delivery of intervention sessions in accordance with the procedures outlined in the intervention manual
- Audio-recordings of all intervention sessions from the CFHealthHub group which a sample of 20% of participants, selected by site, by interventionist, and recruited in the early, mid and late phases of the RCT (to assess drift) will be analysed to triangulate with data from CFHH and session reports, and to assess the quality of the interaction.
- Semi-structured interviews with a sample of participants (see section 10.2.2) to assess comprehension of the intervention, and how they utilised the content and tools available.

A separate Fidelity Assessment protocol will be developed for the RCT.

6. Use [48] / *dose received* [52] of intervention

Use of CFHealthHub by participant, as proposed by interventionist, determined by data capture by CFHealthHub, including the online activities started and completed, minutes spent on recommended pages and which parts the participant has picked out and put in a “my toolkit” page. The number of times, frequency over time and duration with which users log on to CFHealthHub, as well as the activities they perform while logged in, described quantitatively using data from CFHealthHub.

A record of the discussion between the interventionist and the MDT will be kept. This will include who was there, brief notes of what was discussed and any agreement of treatment goals made.

7. Acceptability

The acceptability of the intervention to PWCF assessed through a 11 item questionnaire in the RCT and interviews with interventionists and PWCF.

8. Perceived benefits and harms

Assessed through semi-structured interviews with interventionists, PIs and PWCF.

7.4 Clinical outcomes and covariates

Table 3. Individual-level data derived from PWCF and sites

+ Pseudomonas (or other microorganism) status will be checked together with the monthly prescription* Only required where PWCF indicates they have received parenteral antibiotics

** EQ5D-5L collected at: the start and end of every exacerbation episode; between 7 and 14 days of the end of a period of exacerbation and at

	Where?	Completed by?	Consent visit	Baseline (intervention) visit	At clinic visits	Exacerbations episode	12 months from consent visit
Enrolment							
Pre-screening form (before 1 st visit)	Prospect	Site	-	-	-	-	-
Confirmation of eligibility form	Prospect	Site	●	-	-	-	-
Informed consent	Prospect	Site	●	-	-	-	-
Intravenous days in last registry year	Prospect	Site	●	-	-	-	-
Pseudomonas status +	Prospect	Site	●	-	-	-	-
Primary outcome							
Exacerbations form including:	Prospect	Site	●	-	-	●	●
Parenteral antibiotics							
Change in sputum*							
New or increased hemoptysis*							
Increased cough*							
Increased dyspnea*							
Malaise, fatigue, or lethargy*							
Temperature above 38 °C*							
Anorexia or weight loss*							
Sinus pain or tenderness*							
Change: sinus discharge*							
Change: phys. exam. chest*							
Decrease: pulmonary function *							
Indicative radiographic changes*							
Secondary outcomes							
BMI (height and weight)	Prospect	Site	●	-	-	-	●
FEV ₁	Prospect	Site	●	-	●	-	●
EQ-5D-5L**	Prospect	PWCF	●	-	●	●	●
PAM-13 (Health Style Assessment)	Prospect	PWCF	●	-	-	-	●
Assessment of Routine	Prospect	PWCF	●	-	-	-	●
SRBAI	Prospect	PWCF	●	-	-	-	●
CFQ-R	Prospect	PWCF	●	-	-	-	●
PHQ-8	Prospect	PWCF	●	-	-	-	●
GAD-7	Prospect	PWCF	●	-	-	-	●
MAD-3 (Medication Adherence Data-3 items)	Prospect	PWCF	●	-	-	-	●
COM-BMQ	Prospect	PWCF	●	-	-	-	●
Objective adherence	CFHH	CFHH	●	-	●	-	●
Subjective adherence single question	Prospect	PWCF	●	-	●	-	●
Concomitant medications	Prospect	Site	●	-	-	-	●
Other SAEs	Prospect	Site	-	-	●	-	●
Resource use	Prospect	Site	-	-	-	-	●
Behavioural question	Prospect	Site	●				●
Behavioural questionnaire	Prospect	Site			●		

every standard clinic visit. Where participants have not attended the hospital for a period of over 3 months, the Interventionist will administer the Clinic visit behavioural questionnaire and the EQ5D-5L over the phone every 3 months.

Table 4. CFHealthHub data (CFHealthHub group only)

	Completed by?	Baseline (intervention) visit	At intervention visit s with interventionist	Between sessions	At clinic visits	At 12 months
Clinician metrics						
Adherence data*	PWCF	●	●	●	●	●
Recommendation of modules by interventionist	Interventionist	●	●	-	●	-
Feed back to participant their adherence data screens (data click)	Interventionist	●	●	-	●	-
Check prescription with participant	Interventionist	●	●	-	●	-
Order of clicks	CFHH	●	●	-	●	-
Interventionist responds to patient changing prescription	Interventionist	-	●	●	●	●
Monthly check on prescription +	Interventionist / CTRU	●	●	●	●	●
Time in and out preparation	Interventionist /CFHH	●	●	-	-	●
Time in and out with patient	Interventionist /CFHH	●	●	-	-	●
Time in and out review	Interventionist /CFHH	●	●	-	-	●
Patient metrics						
Adherence (number of nebulized doses taken per day.) ¹	PWCF	●	●	●	●	●
Duration of inhalation	Nebuliser	●	●	-	-	-
Accessing CFHealthHub – look at adherence data	PWCF	●	●	-	-	-
Accessing CFHealthHub – look at ‘My Toolkit’	PWCF	●	●	-	-	-
Accessing CFHealthHub problem solving / education / talking heads pages outside of ‘My Toolkit’	PWCF	●	●	-	-	-
Accessing CF HealthHub – first to last click in a session	PWCF	●	●	-	-	-
	PWCF					x

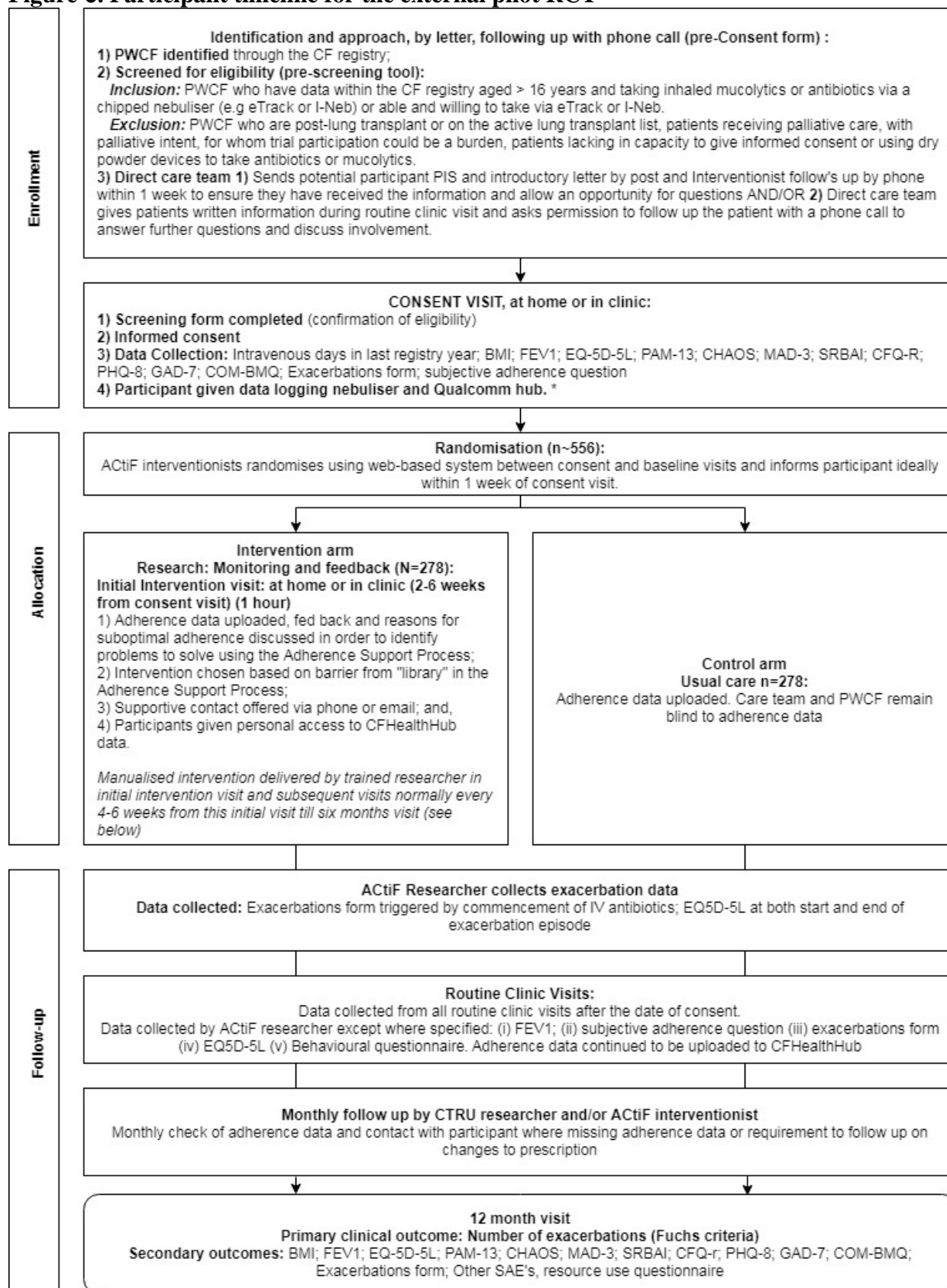
*Adherence data collected for both research and control arms

+ Monthly prescription checked by CTRU centrally to alert local interventionists to any potential changes

¹To be broken down in statistical analysis plan.

Data at the 12 month follow up visit may be collected by the interventionist within+/-4 weeks of the due date.

Figure 6. Participant timeline for the external pilot RCT



Interventionists should make every effort to collect secondary outcome data at 12m (-2w to + 4w). However, data which comes in afterwards will be used in the analysis and will not be considered a protocol non-compliance.

8. Sampling

8.1 Quantitative components

8.1.1 Sites

Up to 20 specialist CF centres have been screened for their ability to recruit participants based on the number of participants they have on their CF registry and their motivation to participate in the main RCT.

8.1.2 Sample size

The sample size from the main trial has been revised from $n=688$ to $n=556$. The primary outcome measure will be the mean number of Pulmonary Exacerbations (PE) per patient treated with IV antibiotics that meet at least one of the Fuch's criteria in the 12 month post-randomisation follow-up. We shall use the Fuch's criteria for defining a PE in patients with CF, as used in the trials by Elkins et al and McIlwaine et al.

The Elkin's et al trial, with 162 patients with CF, using a stricter definition of PE of exacerbations requiring IV antibiotic therapy plus 4 out of 12 of the Fuch's criteria reported a mean number of exacerbations over 48 weeks of 0.89 and 0.39 respectively in the control and intervention groups, a difference of 0.5 (95% CI: 0.14 to 0.86), with an estimated standard deviation of 1.2.

Based on the pilot data with six months' follow-up we observed 60 exacerbations in 60 patients; a mean of $60/60 = 1$ exacerbation per patient; extrapolating this to 12 months gives a mean of 2 exacerbations per year; assuming the number of exacerbations in a year follows a Poisson distribution then the standard deviation is 1.5 (rounded up).

At an individual patient level we can only observe integer values for the number of exacerbations per year (e.g. 0, 1, 2, 3 etc.) and the smallest difference an individual patient can have is a change of one exacerbation per year. At a group or population level smaller differences than one exacerbation per year are likely to be clinically or practically important. Our original sample size calculation assumed a target difference of 0.9 exacerbations per year based on an average of around 3 exacerbations a year and made an allowance for contamination at the treating centre level of around 10% i.e. a likely reduction in the target difference of around 10% to allow for contamination effects at the centre (i.e. from 1.0 to 0.9 exacerbations per year). A reduction of 1 exacerbation per year is around 33% of the originally assumed baseline level of 3 exacerbations per year. With a lower baseline level of around 2 exacerbations per year a 33% reduction would equate to a reduction of difference of 0.66 exacerbations per year. If we allow for contamination at the treating centre level (of around 24% reduction in the target difference) and assume a smaller target difference of 0.5 exacerbations per year is of clinical and practical importance.

Therefore assuming a mean difference of 0.5 PE over a 1 year follow-up between the intervention and control groups is the target difference we wish to detect; a SD of 1.5; 90% power and two-sided significance level of 5%; a design effect of 1.16 to allow for any clustering of outcomes by physiotherapist (ICC of 0.01 and cluster size of 17) then we require 222 subjects per arm (444 in total) to detect this difference. If we assume a 20% loss to follow-up by 12 months then we would need to recruit 556 patients (278 per arm). Meta-analysis level evidence indicates that date and time stamped data improves adherence. Patients recruited to the active limb of the trial will receive feedback of time and dated stamped adherence data which the meta-analysis evidence suggest will be beneficial. We have been provided with sufficient funded chipped nebulisers to allow us to recruit up to 35 patients in each centre which may allow us to exceed our study targets based on our power calculations. We consider that it is in patients best interests to recruit them if the opportunity arises since the evidence suggests this will benefit their adherence and RCT evidence supports that the treatments prescribed are beneficial. In addition power calculations are an inexact since so increasing

our power will reduce the chance of a false negative trial result. Thus since over recruitment is associated with patient benefit we think that if the opportunity arises we should do this.

8.1.3 Approach, non-participation and recruitment

Approach: Health professionals involved in approaching and screening PWCF and collecting data will be trained in the study protocol and procedures. Additionally those taking consent will have up-to-date training in Good Clinical Practice (GCP). All study personnel will be named on the study delegation log. Health professionals working with the CF team will identify a sample of PWCF registered at the centre via the CF registry database locally. The CF Clinical team member at each site will send an encrypted excel file containing Registry number, gender, age and number of IV days (in home and hospital), via email to the Sheffield CTRU Study Manager; the password will be communicated separately via a telephone call. The encrypted excel file will be saved on an access restricted University Network Folder; it will be unencrypted and uploaded to Prospect. Alternatively, each site will be able to input screening information directly into Prospect from their CF registry data. All inclusion and exclusion criteria will be assessable via patient records and they will exclude any patients who do not fit the eligibility criteria.

A member of the participant's direct clinical team will send the potential participant a PIS and introductory letter by post or give the written information during a routine clinic visit. If information is provided in a routine clinic visit, the clinical care team will seek permission for the ACTiF Interventionist to follow up with a phone call in order to answer any further questions and discuss involvement. Written informed consent may be conducted at this visit where the participant is happy to take part as this is a low risk trial.

Telephone call: Up to a week after posting out the information, the ACTiF Interventionist will telephone or text the PWCF to discuss the study over the phone and answer any questions. If the potential participant is happy to take part, the ACTiF Interventionist will arrange an appointment to gather written informed consent.

Non-participation: Spontaneously offered reasons for non-participation in the trial will be recorded.

8.2 Qualitative components

All intervention visits in each centre will be audio recorded with permission from the patient to assess the fidelity of implementation of the intervention and mechanisms of action throughout the trial. Encrypted digital recorders will be used at each site and recordings sent securely to the research team for analysis.

- Interview with the interventionist in each centre (n=20)
- Interviews with 16-20 PWCF: 8-10 PWCF within 2-3 months of starting the intervention to explore changes made since the pilot and 8-10 PWCF 6-12 months after being introduced to the intervention to understand their views of the intervention in the longer term
- Interviews with 6-8 PIs sampled based on sites with specific issues e.g. not recruiting, large number of withdrawals to understand how the context may impact the RCT and/or intervention

Written informed consent will be obtained from both the interventionist and the PWCF participating in the audio recording when they consent to be in the study. Separate consent will be sought from PWCF, interventionists and PIs for semi-structured interviews.

9. Assignment of interventions

9.1 Sequence generation

Participants will be allocated in equal proportions to one of the two groups using a computer generated pseudo-random list, stratified by centre and the number of days participants have been on IV antibiotics in the previous 12 month period as collected at consent visit, with random permuted blocks of varying sizes. The two categories for stratification within the number of IV days will be (i) less than or equal to 14 days and (ii) greater than 14 days.

9.2 Allocation concealment

The allocation sequence will be hosted by the Sheffield CTRU in accordance with their standard operating procedures and will be held on a secure server. Access to the allocation sequence will be restricted to those with authorisation. The sequence will be concealed until recruitment, data collection, and analyses are complete.

9.3 Implementation

The allocation sequence will be created by a Sheffield CTRU statistician who is not otherwise associated with the trial. At the consent visit, a health professional who is named on the delegation log, will go over the patient information sheet again with the study candidate and answer any questions. If the PWCF is still willing to enter the trial, they obtain full written consent and complete the eligibility form. If the participant is eligible, then baseline assessments will be taken. The recruiting health professional will log into the remote, secure Internet-based randomisation system and enter basic demographic information, after which the allocation will be revealed.

9.4 Blinding

After revelation of the allocation, only the statisticians will be blinded to allocation as per CTRU SOPs (ST001 and ST005).

10. Data collection, management and analysis

10.1 Quantitative data

10.1.1 Data collection methods

Data handling and record keeping. The Sheffield CTRU will oversee data collection, management and analysis and ensure the trial 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 1998. Patients will be reassured that all data which are collected during the course of the research will be kept strictly confidential.

The study team will train those collecting data in the study procedures before the trial begins. Data will either be collected directly from the participants, carers, interventionist, CFHealthHub or from source documents (e.g. patient notes) and input onto the CRF or Sheffield CTRU's electronic web-based data capture system (Prospect). 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.

The CTRU will perform checks on the data to ensure data is being captured and alert the local interventionist if there is an indication of a prescription change and a need to check pseudomonas (or other microorganism) status. This is required for the correct denominator to assess “normative adherence”. Data will be extracted from the CF registry to understand exacerbations in the preceding 12 months since prior exacerbations can have a bearing on the optimum target regimen.

Plans to promote participant retention and complete follow-up.

Participant retention will be ensured by the following procedure:

1. At each point of contact, the interventionist will check with the participant that the Qualcomm hub or Smartphone hub is plugged in and turned on. A member of CTRU who is performing data and prescription checks may alert the interventionist. They will remind the participant of the proximity required for data transfer (10 metres)
2. In the event of no data being displayed in CFHealthHub for the first two weeks of trial participation, (and the participant is not known to be on holiday) the interventionist will make contact with the participant (Email/Text/Telephone call) and follow the troubleshooting procedure (see section below)

Troubleshooting:

Data capture will be monitored both by interventionist at the site and centrally by the CTRU. In the event of data not being uploaded patients will be contacted to trouble shoot problems. Troubleshooting includes (but it not limited to) checking:

- That the Qualcomm hub is plugged in
- That the Qualcomm hub is working (showing solid green and yellow lights on the display)
- That they have been within range of the Qualcomm hub sufficient to facilitate data transfer (10 metres)
- The interventionist may perform a home visit to run a test nebulisation with the participant and inform CTRU of the date this occurred. This will help assist with technical issues in patients in this group.

Patients will be offered support to suit their circumstances including home visits (conducted by the members of the site research team) where necessary. Documentation for assisting participants with troubleshooting issues will be incorporated in the CFHealthHub manual. Troubleshooting will be conducted extensively in the first 2 weeks from participant entry into the study (consent visit) for both control and intervention arm participants. Beyond this point:

1. there will be a 6-month data check for control arm participants performed by CTRU. CTRU will follow up with local interventionist’s, cases where data has not been coming through to CFHealthHub and facilitate troubleshooting
2. intervention arm participants will have ongoing data checks throughout the trial period
3. both control and intervention arm participants will be asked to complete a manual data transfer at the 12 month research visit

10.1.2 Data Management

Anonymised trial data will be entered onto a validated database system designed to an agreed specification between the Chief Investigator and Sheffield CTRU. The research staff at sites (mainly the ACTiF interventionist) will be responsible for data entry locally. The Sheffield CTRU Trial Manager, research assistant and the Data Management Team will work with sites to ensure the quality of data provided. The study manager, research assistant, data manager, PI’s, any research nurses and site interventionist will have

access to the anonymised data on the database through the use of usernames and encrypted passwords. The system has a full electronic audit trail and will be regularly backed up. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator.

Trial documents will be retained in a secure location during and after the trial has finished. The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of participant data. 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. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This can be used to restrict access to personal identifiable data.

Participants who give consent to the qualitative part of this study will also give consent to their name and address to be given to the University of Sheffield qualitative research staff in order to be contactable.

10.1.3 Data quality assurance

Prospect provides a full electronic audit trail, as well as validation and verification features which will be used to monitor study data quality, in line with CTRU SOPs and the Data Management Plan (DMP). Error reports will be generated where data clarification is required. Rates of missing data and data points which are out of the expected or allowed range will be presented to the team at monthly management group meetings.

10.2 Qualitative data

10.2.1 Audio recordings of consultations

All intervention visits at each centre will be audio recorded with permission from the patient from which a sample will be selected to assess the fidelity of implementation of the intervention and mechanisms of action throughout the trial. A purposive sample will be selected for analysis to ensure assessment at site and interventionist level and during early, mid and late phases of recruitment into the RCT. Encrypted digital recorders will be used at each site and recordings sent securely to the research team for analysis.

10.2.2 Semi-structured interviews: PWCF

From 3-6 centres we will interview a total of 16-20 PWCF. Initial approach will be made via email or post where the information sheet, consent form and invitation letter is sent to the participant. Following this, the qualitative researchers will email/phone or text the participant to discuss the study and if the participant is happy will arrange a suitable time (based on the participants preference) to seek informed consent and conduct the interview. We will interview 8-10 of them around 2-3 months of starting the intervention to gain feedback on changes made since the pilot trial, and 8-10 of them around 6-12 months into the intervention to seek longer term views of the intervention. This will build on the qualitative research in the feasibility study where PWCF were interviewed around 1 month and then 3-6 months into the intervention process. We will sample based on baseline adherence levels and maximum variation of socio-demographic characteristics.

10.2.3 Semi-structured interviews: interventionists

We will interview the interventionist in each centre (n=20). The interventionists may have different lengths of experience of working with CF, nebulisers, or behaviour change and we will consider the influence of differences in backgrounds on their ability to implement the intervention. The interventionists will work in different centres and we will consider how context has affected implementation and feasibility. Interviews will take place between 3 and 8 months into the RCT.

10.2.4 Semi-structured interviews: PIs

We will interview the PI in some centres (n=6) where there are specific issues identified during the trial to understand how the context of different centres may be affecting implementation and feasibility of the RCT and the intervention. Interviews will take place between 3 and 12 months into the RCT.

10.2.5 Undertaking the interviews

We will use an encrypted digital recorder. Reflexive notes will be made during and after the interviews. We expect interviews to last around one hour.

11. Data analysis

11.1 Quantitative analysis

The analysis will be performed after data lock by a CTRU statistician under the supervision of the senior study statistician. As the trial is a pragmatic parallel group RCT data will be reported and presented according to the CONSORT 2010 statement [55]

Clinical outcome measures will be summarised overall and by randomized group. Baseline demographic (age, gender), physical measurements (e.g. weight, height, BMI), and patient reported outcome measures (EQ-5D-5L, PAM-13, Assessment of Routine, MAD-3, SRBAI, CFQ-R, GAD-7, COM-BMQ, PHQ-8), and clinical measurements (e.g. FEV1, IV days in last registry year) will be described and summarised overall and for both treatment groups. We will report rates of consent, recruitment and follow-up by centre and by randomised group.

The primary outcome is the number of pulmonary exacerbations treated with IV antibiotics over the 12 month post-consent follow-up period.

Secondary continuous outcomes such as 12-month post consent FEV1, BMI EQ-5D-5L, PAM-13, Assessment of Routine, MAD-3, SRBAI, CFQ-R, GAD-7, COM-BMQ, PHQ-8) will be analysed with a multiple linear regression model with the baseline value of the outcome and randomised group as covariates. The treatment group coefficient and its associated 95% confidence interval will be reported from the various multiple linear regression models. The mean level of adherence (to prescribed medication) between the CFHealthHub and control groups over the 12 month post-consent follow-up period will also be reported and compared between the groups and a 95% confidence interval (CI) for the mean difference in this parameter between the randomised groups will also be calculated.

Further analyses with the objective nebuliser data will be performed to explore the process of habit formation with the delivery of the adherence intervention. 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 is achieved
- (c) other time-series methods, including cross-correlation between habit scores and adherence.

Adverse events will be based on serious adverse events (SAE) case report forms. A serious adverse event is defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. The following summaries will be presented as overall rates and stratified by AE classification:

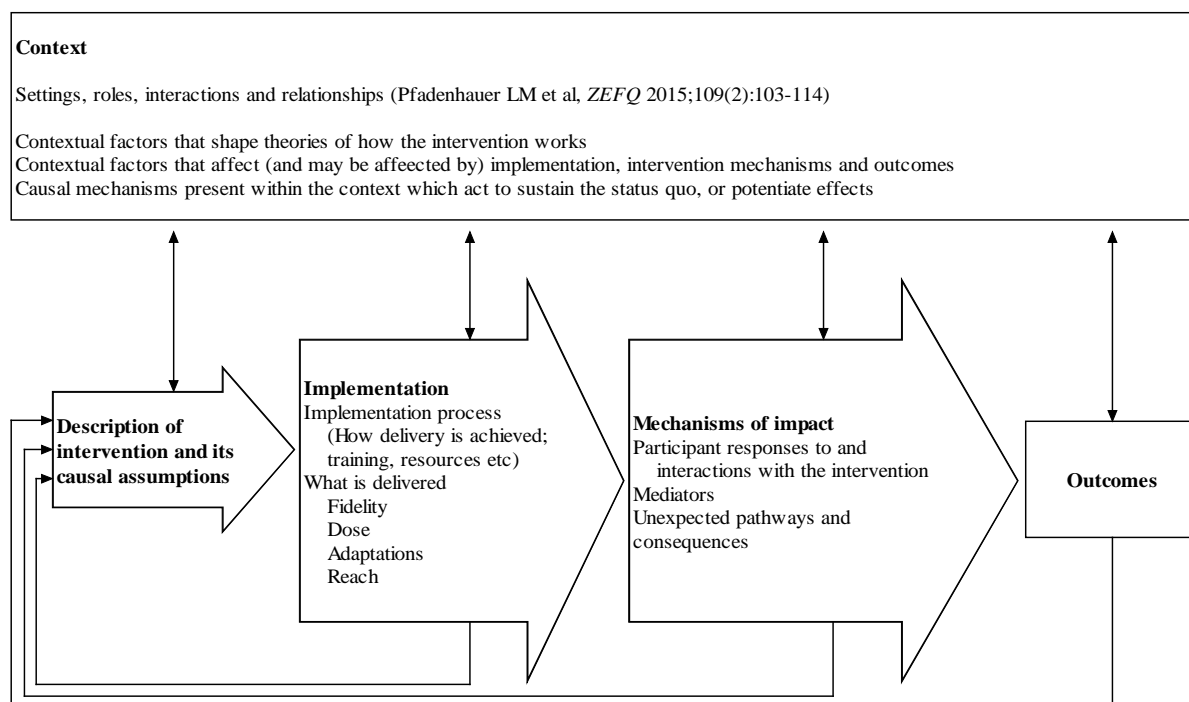
- the number and percentages of patients reported as having Serious Adverse Events (SAE) in each treatment group; and,
- the number and percentages recorded as having all forms of Adverse Events (AE) in each group.

11.2 Qualitative analysis

Transcripts will be coded using the latest version of NVivo (QSR International). The analysis will use the National Centre for Social Research ‘Framework’ approach [56]. AO’C and SD will undertake the following stages of the analysis of patient transcripts: familiarisation; identifying a thematic framework; indexing; charting; and, mapping and interpretation. We will use the process evaluation functions of context, mechanisms and implementation to frame the analysis [53]. Within mechanisms we will use the COM-B system [1]. The Normalisation Process Theory is likely to be relevant to the analysis of the interventionists’ interviews [57].

Figure 7. Assumptions of the MRC Guidance on Process Evaluation

[49, 58]



11.3 Combining data and findings from the different components

We will use Farmer’s triangulation protocol to display the findings from each component of the study together and discuss as a team the extent to which findings converge,

complement each other or contradict each other [59, 60]. For example, we will display all findings about acceptability of the intervention.

12. Monitoring

12.1 Oversight

The CTRU SOP GOV003 Data Monitoring and Ethics Committee states “A DMEC does not need convening in studies that carry low risk to patients”. This project involves delivering a behaviour change intervention through the website CFHealthHub and would therefore be classified as low risk.

The overall responsibility for the study will be with Sheffield Teaching Hospitals NHS Trust who will act as sponsors for the study. The local Principal Investigator (PI) will be responsible for the study at each participating site and it will be registered and approved with each local R&D department. The study will be conducted in accordance with the protocol, GCP and Sheffield CTRU Standard Operating Procedures. The two committees which will govern the conduct of the study are:

1. Programme Steering Committee (PSC)
2. Project Management Group (PMG)

The PSC will be responsible for the overall conduct of the trial and consists of an independent chair and four other independent members including a statistician and PPI representative. The committee will meet every 6 months to monitor the study.

The PMG will comprise of the trial manager and the core research team. The PMG will meet on a monthly basis to monitor the day-to-day running of the trial. The Trial 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 Trial Manager will be responsible for liaising with the whole project team. Trial 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.

12.2 Description of any interim analyses and stopping guidelines

There are no planned interim analyses or stopping guidelines for this study.

12.3 Harms (safety assessments)

12.3.1 Serious Adverse Events

Trial sites are to report SAEs in conjunction with the CTRU standard operating procedure PM004 (Adverse events and serious adverse events). The definition of an SAE is as follows:

- results in death;
- is life-threatening* (subject at immediate risk of death);
- requires in-patient hospitalisation or prolongation of existing hospitalisation;**
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or,

- is another important medical event that may jeopardise the subject.***

* 'life-threatening' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

It is not anticipated that there will be many SAEs related to the behaviour change intervention. We will report any SAEs which are deemed related to the trial intervention and unexpected to the Sponsor within the specified timeframes below (12.3.4).

12.3.2 Adverse events we require reporting:

We do require that sites report any new diagnosis of depression and/or anxiety which requires treatment with medication or psychological therapy e.g. Cognitive Behavioural Therapy (CBT).

12.3.3 Expected SAEs and adverse events

Certain adverse events are common to CF and associated medications. Expected SAEs must be reported in the annual safety report. Hospitalisation as a result of an exacerbation will be recorded in the study database and not be reported as an SAE.

Expected AEs in relation to medications or common in patients with CF

1. Acute FEV₁ drop >15% after 1st dose of medication
2. Increased productive cough
3. Nasal congestion or stuffy nose
4. Chest congestion
5. Wheezing
6. Chest pain or chest discomfort
7. Voice alteration/change
8. Dyspnea (breathlessness)
9. Haemoptysis (coughing blood)
10. Rhinitis
11. Headache
12. Crackles in lung
13. Throat irritation/ sore throat
14. URTI
15. Sinusitis
16. Deafness
17. Indigestion / reflux

18. Tonsillitis
19. Joint pain
20. Decreased appetite
21. Fatigue
22. Headache
23. Distal intestinal obstructive syndrome
24. Fever
25. Otitis media or ear infection
26. Conjunctivitis
27. Pneumothorax
28. Decreased exercise tolerance
29. Pyrexia
30. Abdominal pain
31. Influenza
32. *Pseudomonas* infection
33. Vomiting
34. Diabetes
35. Pneumonia

12.3.4 Reporting

Adverse events and SAEs can be reported for participants at any stage of their trial participation. A member of the site study team (interventionist, clinician or other) will enquire about any adverse events at routine clinic appointments. These will be recorded on the adverse event section of the paper CRF and database. The event will be assessed by the local Principal Investigator and the form will be kept in the site file. Serious adverse events will be reported in the periodic safety reports to the research ethics committee and Trial Steering committee.

All adverse events (serious or other based on the definitions above) will be recorded on the case report form and details will be **entered on the study database within 1 week of completing the paper form**. Any SAEs which are deemed related to the trial intervention, the site will complete the paper CRF and **fax this form to the CTRU within 24 hours of becoming aware of the event** in order for the CTRU to report this event to the Sponsor and the main REC within the required timeframes (15 days).

12.4 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.

12.5 Finance and indemnity

The trial has been financed by the NIHR and 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.

13. Ethics and dissemination

13.1 Approvals

The trial will be conducted subject to Research Ethics Committee favourable opinion including any provisions for site specific assessment. The application will be submitted through the IRAS central allocation system. 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. This clinical trial will be conducted in accordance with Good Clinical Practice Guidelines and CTRU standard operating procedures. MHRA approval is not required for this study.

13.2 Protocol amendments

The investigator will be updated following an amendment to the protocol or study documents. The new documents, REC approval, R&D approval, HRA assessment letter and any other appropriate documentation surrounding the amendment will be sent to the site via a “site file update”. The sites will receive the documents with a site file update sheet, detailing where to file the amended documents and which documents to supersede. If there are any significant changes to the study procedures or eligibility criteria sites will be notified by a combination of email, telephone, newsletters or additional project training when required.

In relation to informing REC, if any study documents require amending, the changes will be discussed with the sponsor and either a substantial (via IRAS and HRA) or minor amendment (notification via email) will be submitted to REC and HRA. Following REC acknowledgment and approval (when applicable) other appropriate approvals will be obtained i.e. HRA and R&D approval.

If a protocol amendment requires participants to be re-consented they will be informed of the amendment by an updated participant information sheet and will be asked to re-consent to the study. Trial registries, journals and regulators will be updated regarding protocol amendments when appropriate.

13.3 Consent

Consent for the main trial:

The ACTiF trial interventionist or local PI at the site will be responsible for taking informed consent from potentially eligible trial participants face to face at home or in clinic. Any

researcher or clinical member of the team taking informed consent will be trained in study procedures and GCP. Participants will have the option to specify whether they are interested in being approached for the qualitative interviews and audio recordings. However, they do not have to consent to these to be involved in the main study.

Consent for the interviews:

Consent for interviews (participant, interventionist or MDT member) will separately be taken by the qualitative researcher. Participants can participate in the main trial but choose to not take part in the qualitative research.

13.4 Confidentiality

Participant confidentiality will be respected at all times. Participant names and contact details will be collected and entered on the prospect database. Access to these personal details will be restricted to users with appropriate privileges only. All users who do not require access to identifiable data will only identify data by participant ID number, and no patient identifiable data will be transferred from the database to the statistician.

Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 5 years following the end of the trial. Where trial related information is documented in the medical records – those records will be retained for 5 years after the last patient last visit. Each site is responsible for ensuring records are archived and the information supplied to the Chief Investigator.

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. 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.

13.5 Declaration of Interests

Martin Wildman has received funding from Zambon who market the Ineb to carry out research to understand the performance of the Ineb and in the past we received funding from Zambon to carry out work to understand barriers to adherence.

13.6 Access to data

The central ACTiF study team alone will have access to the final dataset details of which will be outlined in the study DMP.

13.7 Ancilliary and post-trial care

Centres will be able to continue to use CFHealthHub if they wish to do so after the end of the pilot and feasibility study. If so, participants in the control group will be able to cross over to use the intervention at this stage.

13.8 Dissemination policy

It's main interest will be to potential researchers and funding bodies. Data will be reported according to the revised CONSORT statement (Schultz, 2010). The findings of this research will be available to NIHR, patient groups and other interested bodies. It will also be offered for presentation at medical meetings and will be offered for publication in peer reviewed medical journals.

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Appendix 1. W.H.O. Trial Registration Data Set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	To be added
Date of registration in primary registry	To be added
Secondary identifying numbers	NIHR: RP-PG-1212-20015 Sponsor (STH):
Source(s) of monetary or material support	National Institute for Health Research (NIHR) Programme Grants for Applied Research programme.
Primary sponsor	Sheffield Teaching Hospitals NHS Foundation Trust. STH19692
Contact for public queries	Chin Maguire Trial Manager Clinical Trials Research Unit University of Sheffield Regent Court 30 Regent Street Sheffield S1 4DA Tel: (+44) (0)114 222 0717 Fax: (+44) (0)114 222 0870 email : c.maguire@sheffield.ac.uk
Contact for scientific queries	Dr Martin Wildman Adult CF Centre Northern General Hospital Herries Road Sheffield S5 7AU Tel: (0114) 2715212 Fax: (0114) 222 0870 email : Martin.Wildman@sth.nhs.uk
Public title	<u>Adherence to treatment in adults with Cystic Fibrosis (ACtiF)</u>
Scientific title	RCT and parallel process evaluation
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Cystic Fibrosis
Intervention(s)	Usual care plus a microchipped nebuliser with or without a complex intervention. The complex intervention consists of: <ul style="list-style-type: none"> - A software platform, CFHealthHub mobile apps and website, which allows access to medication adherence data and education modules intended to remove barriers

	<p>to adherence</p> <ul style="list-style-type: none"> - A manual containing a ‘behaviour change toolkit’ to guide interactions between health
Key inclusion and exclusion criteria	<p>Inclusion criteria for participants</p> <ol style="list-style-type: none"> 1.Diagnosed with CF and with data within the CF registry 2.Aged 16 years and above 3.Willing to take inhaled mucolytics or antibiotics via a chipped nebuliser (e.g. eTrack) <p>Exclusion criteria for participants</p> <ol style="list-style-type: none"> 1.Post-lung transplant 2.People on the active lung transplant list 3.Patients receiving palliative care, 4.Lacking in capacity to give informed consent 5.Using dry powder devices to take antibiotics or mucolytics
Study type	RCT and process evaluation
Date of first enrolment	Anticipated: 11/9/2017
Target sample size	556 participants in total (CFHealthHub group n=344, control group n=344).
Recruitment status	Not yet open.
Primary outcome(s)	Exacerbations of cystic fibrosis as defined by the Fuchs criteria (<i>N Engl J Med</i> 1994, 331:637–42.)
Key secondary outcomes	None.