Study title: ACtiF

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

WP 3.2 RCT [ISRCTN55504164]

Statistical Analysis Plan Version 2.0
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Authored by

_____ ___/___/_____
Laura Sutton *Date*
ACtiF Trial Statistician
Clinical Trials Research Unit, University of Sheffield

Approved by

_____ ___/___/_____
Dr Martin Wildman *Date*
Chief Investigator
Sheffield Teaching Hospitals NHS Foundation Trust

_____ ___/___/_____
Professor Stephen Walters *Date*
Senior Trial Statistician
ScHARR, University of Sheffield

_____ ___/___/_____
Professor Kathy Rowan *Date*
Chair, Project Steering Committee
London School of Hygiene and Tropical Medicine

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List of abbreviations used

AE	Adverse Event
BMI	Body Mass Index
CF	Cystic Fibrosis
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTRU	Sheffield Clinical Trials Research Unit
FEV1	Forced Expiratory Volume
HTA	Health Technology Assessment
ICC	Intra-cluster Correlation Coefficient
IQR	Interquartile Range
IRR	Incidence Rate Ratio
ITT	Intention to Treat
PE	Pulmonary Embolism
PWCF	Person with cystic fibrosis
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

Summary Table

Trial title	Development and evaluation of an intervention to support Adherence to treatment in adults with Cystic Fibrosis (ACtiF)
Trial design	A multi-centre parallel group, superiority open labelled randomised controlled trial (RCT)
Trial participants	People with cystic fibrosis (CF)
Sample size	556
Centres	19
Follow-up	12 months (with option to continue collection of primary outcome and adherence after 12 months)
Primary analysis	A comparison of the number of exacerbations over the 12 month follow up period in intervention vs control arm using a generalised linear model adjusted for study centre and IV days in the previous 12 months.
Secondary analyses	Secondary outcomes (including adherence to CF medication and FEV1) will be compared between treatment arms using regression models selected based on the distribution of the outcome.

Change control

SAP version	**Date approved**	**Modifications (with section)**	**Prior to/after blind review, prior to/after database lock**
2.0	22 Aug 2019	Clarification to derivation of numerator-adjusted normative adherence (section 9.2.1.3, p25)	After unblind review, prior to database lock
		Addition of Hoo *et al*. (2016) reference (section 13, p33)	After unblind review, prior to database lock

1 Introduction

This document outlines the detailed statistical analysis plan (SAP) for ACtiF and is intended to be read in conjunction with the current study protocol (v3). This SAP is written in conjunction with the International Conference on Harmonisation topic E9 (Conference et al. 1999), applicable statistical standard operating procedures (SOPs) from the University of Sheffield Clinical Trials Research Unit (CTRU) and trial documents (Protocol and Data Validation Specification). The trial will be conducted in accordance with Good Clinical Practice in Clinical Trials (ICH Harmonised Tripartite Guideline 1996) and Medicine for Human Use (Clinical Trials) Regulations (UK Statutory Instruments 2004).

This SAP will guide the Trial Statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study. It excludes the health economic evaluation (which will be described elsewhere).

All analysis will be performed in a validated statistical software package such as R (Team 2012).

1.1 Study Outline

The ACtiF study is a two-armed, parallel group, superiority, open-labelled randomised controlled trial (RCT) that will evaluate the efficacy of a complex intervention for people with cystic fibrosis (CF). The primary outcome will be the number of pulmonary exacerbations in a 12 month period. The study will take place across 19 centres in the UK. People with CF (PWCF) will be allocated to either the intervention or usual care. The intervention comprises a microchipped device (nebuliser), an information technology infrastructure to capture and store adherence data and a behaviour change intervention software platform offering adherence feedback and tailored modules of content to be used by PWCF and health professionals in interactions with PWCF. A more detailed description of the intervention and inclusion and exclusion criteria can be found in the study protocol.

This project was funded by the Programme Grants for Applied Research programme (RP-PG-1212-20015) and will be published in full in the NIHR Journals Library.

1.2 Primary Objectives

- To determine the efficacy of CFHealthHub and Manuals in the primary outcome (Section 7.7)
- To carry out a process evaluation to facilitate interpretation of the RCT results and offer insights about how best to deliver the intervention in the real world.

1.3 Secondary Objectives

- To determine the efficacy of CFHealthHub and Manuals in secondary outcomes (section 7.8) including adherence to medication, quality of life and habit formation.

2 Outcome measures

2.1 Primary outcome measure

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 (Fuchs et al. 1994). 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** (Ratjen et al. 2012)**:**

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.

2.2 Secondary outcome measures

Secondary outcome measures as described in the study protocol (v3) include:

Key secondary outcomes

1. **Body Mass Index (BMI).**
2. **Percent predicted forced expiratory volume in 1 second (FEV_1), calculated using the GLI equation:** standardised spirometry as a measure of condition severity (Miller et al. 2005).
3. **Adherence to prescribed medication (see 7.4.3)**

Other secondary clinical outcomes

1. **EuroQol EQ-5D-5L**: generic health status measure which will be used to inform the health economic analysis (Herdman et al. 2011).

2. **The Patient Activation Measure (PAM-13) (Health Style Assessment)**: assessment of patient knowledge, skill, and confidence for self-management (Hibbard et al. 2005). *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.

3. **Assessment of routine:** measure of life chaos (Wong et al. 2007).

4. **Self-Report Behavioural Automaticity Index (SRBAI):** automaticity-specific subscale of the Self Report Habit index to capture habit-based behaviour patterns (Verplanken and Orbell 2003).

5. **Cystic Fibrosis Questionnaire-Revised (CFQ-R):** disease specific health-related quality of life instrument (Quittner et al. 2000).

6. **The Patient Health Questionnaire depression scale (PHQ-8):** severity measure for depressive disorders (Kroenke et al. 2009).
7. **MAD (Medication Adherence Data-3 items) :** medication adherence measure

8. **The General Anxiety Disorder 7-item anxiety scale (GAD-7):** severity measure for anxiety (Spitzer et al. 2006).

9. **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(Horne, Weinman, and Hankins 1999), 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.

10. **Subjective adherence single question:** self-report estimate of adherence as a percentage. Self-reported problems: identification of capability and opportunity barriers to nebuliser adherence
11. **Behavioural question-** single question asking the participant to rate the effort of nebuliser treatments.

12. **Resource use form:** interventionist collects data from a combination of hospital notes and the NHS patient electronic system to determine 1) inpatient IV days unrelated to an exacerbation 2) Routine clinic visits 3) Unscheduled outpatient contacts 3) unscheduled inpatient stays.

13. **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.

14. Any treatment with IV antibiotics with 0 Fuchs’ criteria

15. 11 item questionnaire on acceptability of intervention (Intervention arm only)

All outcomes listed will be collected in both arms unless otherwise stated.

3 Sample Size Estimation

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 Fuchs criteria in the 12 month post-randomisation follow-up. We shall use the Fuchs criteria for defining a PE in patients with CF, as used in the trials by Elkins et al. 2006 and McIlwaine et al. 2013.

The (Elkins et al. 2006) 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 Fuchs 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 (SD) 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 SD 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 a mean 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 suggests 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 science 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.

4 Randomisation & Blinding

4.1 Sequence generation

Participants will be allocated in equal proportions to one of the two groups using a computer generated pseudo-random list, stratified by site 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.

4.2 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.

4.3 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.

4.4 Blinding

The trial statistician(s) will remain blinded throughout the study, but will be unblinded at database freeze, for analysis. Any changes to the SAP will be documented in detail and will include the date of change in relation to database freeze. Reports to the TMG and TSC will be prepared by Data Management but will not require any summaries by treatment arm.

5 Interim Analysis & Study Monitoring

The following committees will be established:

1. **Trial Steering Committee (TSC)** - consist of an independent chair and 3 other independent members. The committee will meet approximately every 6 months from the start of the trial.
2. **Trial Management Group (TMG)** – oversee the day-to-day management of the trial and will meet monthly. The TMG will include the core members of the team (Chief Investigator, Study Manager and direct research staff).

ACtiF is a low risk to participants as it is a behaviour change intervention and therefore there will be no Data Monitoring and Ethics Committee to monitor the study.

6 Data Collection

6.1 Data Sources

The randomisation list will be held on the CTRU's randomisation system. Trial data will be extracted from source documents and entered onto the CTRUs in house data management system (PROSPECT). The data management team in the Sheffield CTRU will validate and query electronic data for inconsistencies during the course of the trial (as stipulated in SOP DM005), The trial statistician will conduct any additional validation checks where appropriate before the data lock and sign off (as guided by ST003, DM005 and DM012). Details of data collected at each time point are given in Table 1 and
Table **2**.

Table 1 Individual-level data derived from PWCF and sites

	Where?	Completed by?	Consent visit	Baseline (intervention) visit	At clinic visits	Exacerbations episode	12 months from consent visit
Enrolment							
Pre-screening form (before 1st 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	●	-	●	-	●
Other SAEs	Prospect	Site	-	-	●	-	●
Resource use	Prospect	Site	-	-	-	-	●
Behavioural question	Prospect	Site	●				●
Behavioural questionnaire	Prospect	Site			●		

+ Pseudomonas (or other microorganism) status will be checked together with the monthly prescription. This will be via administration of three different clinical criteria: Leeds Criteria; Clinician Judgement and CFHealthHub (CFHH) Criteria
* 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 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 2 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
[1]To be broken down in statistical analysis plan.

Data at the 12 month follow up visit may be collected by the interventionist within+/-4 weeks/1 calendar month of the due date.

7 Statistical Analysis

7.1 General Considerations

Data will be reported according to the Consolidated Standards Of Reporting Trials (CONSORT) statement for individually randomised parallel group trials (Schulz, Altman, and Moher 2010).

Summaries of continuous variables will comprise the number of observations used, mean, median, SD, inter-quartile range, minimum and maximum as appropriate for the distributional form of the data.

Summaries of categorical variables will comprise the number of observations used, and the number and percentage of observations in each category. Tables containing the results of the statistical modelling will present the overall difference between treatment groups with two-sided 95% confidence intervals (CI) and p-values. Hypothesis tests will use a two sided 5% significance level.

Complete details of data derivations and methods of handling missing data are covered in sections 9 and 8.1.

7.2 Participant flow

A CONSORT style flow diagram will be used to show the flow of participants through the trial (Figure 1). In addition to the flow diagram, tables showing more detailed summaries of the reasons for refused consent and reasons for withdrawal will be presented.

7.2.1 Attrition

There are several reasons that a participant may not complete outcome data collection. These include withdrawal of consent, loss to follow up and death. The number and proportion in each category will be presented by intervention arm.

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. The number of each type of withdrawal will be presented as part of the CONSORT flow diagram and will be summarised in more detail in a separate table which will include the timing and type of withdrawal (Table 4).

7.3 Baseline Characteristics

The baseline demographics and clinical characteristics of the participants will be reported. Separate tables will be produced for those randomised and those analysed (participants with primary outcome data). For the continuous variables (e.g. age) either mean and SD will be presented or median and inter quartile range (IQR) depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries. For the categorical variables, (e.g. sex), the number and percentage of participants in each of the categories and the total number of observations will be presented.

All baseline summaries will be presented and reported for each treatment arm and in total (Table 6, Table 7, Table 8). No statistical significance testing will be done to test baseline imbalances between the intervention arms but any noteworthy differences will be descriptively reported.

The following summaries will be presented:

Demographics:	Age, Sex, IMD quintile
Physical measurements:	Weight, Height, BMI
Clinical measurements:	FEV1 percent predicted, IV days in last registry year, Pseudomonas status (Leeds criteria, clinician's judgment and consensus definition) , Adherence to CF medication in first 2 weeks, Subjective adherence to CF medication, Medication, Treatment burden
Patient reported: outcomes	EQ-5D-5L, PAM-13, CHAOS, MAD-3,SRBAI, CFQ-R, GAD-7, COMBMQ, PHQ-8

7.4 Intervention Fidelity

Health professionals delivering the intervention will be assessed for fidelity at the following stages:

- **At certification**- each interventionist will be assessed for fidelity in each of the 3 types of review: 1st intervention visit; review visit and phase review visit. Interventionists must score above a certain threshold in each assessment to become certified.
- **During the study**- interventionists will be assessed for drift. Not all interventionists will be assessed for but a target selection will be identified by the fidelity team based on data from the CRF that has been entered into PROSPECT.

Data collected on fidelity worksheets will be entered into PROSPECT and simple summaries will be produced. These will include:

- Summary of the number of interventionists assessed at each stage
- Summary of the number of times interventionists were assessed before becoming certified (once, twice, more than twice)
- Descriptive statistics of fidelity scores for each type of intervention delivery at each stage
- The number of interventionists who were targeted for assessment and the reasons for assessment
- The number of interventionists who were randomly selected for assessment
- A summary of the number of times interventionists were assessed for fidelity after certification (due to drift) (from 0 to 10)
- The number and proportion of interventionists who received at least one 'booster' training session
- The number and proportion of interventionists who did not achieve at least 80% fidelity in drift assessment at least once
- Descriptive statistics of overall fidelity score by centre (described below)

The summaries described above will also be calculated by site where appropriate

Overall fidelity will be calculated at centre level so as to reflect the primary analysis method. As interventionists will not be assessed consistently, an overall score for each centre for the study will be calculated as follows:

Weighted score for interventionist= $\sum$ score x weight

Weight (w)=$\frac{number\ of\ days\ score\ is\ valid}{total\ days}$

Centre mean=$\frac{\sum\ Weighted\ score}{n}$

To summarise the whole fidelity assessment process, a line graph showing overall fidelity scores by interventionist over time will be plotted. The timing of assessments and training will be indicated with symbols and threshold scores (90% at certification and 80% during the study) will be indicated with horizontal lines.

As interventionists were rated independently, fidelity scores will be compared between raters using Bland Altman plots (Bland and Altman 1986) and calculating an intraclass correlation coefficient.

7.5 Adherence to the Intervention

The intervention can be described as a complex intervention as it has several interacting components. These components can be measured by a number of different metrics and will be summarised across all participants in the intervention arm. The metrics fall into 3 broad categories

1. **Interventionist sessions**- Interventionists and participants will have one-to-one intervention sessions where they will interact with CFHH together. These sessions may occur face-to-face or over the phone.
2. **Participant CFHH interaction**- Participants can access CFHH online and each click in these interactions is logged with the date and time.
3. **Interventionist CFHH interaction**- Interventionists can also access a participant's adherence summaries and module summaries.

The specific metrics that will be summarised across the 12 month follow up period by participant will include:

Interventionist sessions

- The total number of interventionist sessions received by the participant whether face-to-face or via telephone *(continuous)*
- Whether a participant attended at least 1,3, and 5 interventionist sessions *(categorical)*

Participant CFHH interaction:

- The number of sessions in CFHH (*continuous)*
- The number of days with sessions in CFHH (*continuous)*
- Total duration in minutes of CFHH sessions (*continuous)*
- Mean duration of a participant's CFHH sessions (*continuous)*

- Whether a participant had at least 1, 5,10 and 15 CFHH sessions *(categorical)*
- Whether a participant interacted with specific CFHH modules including 'Action Plan', 'Coping Plan' and 'Rewards' *(categorical)*
- The number of clicks in each of the CFHH modules across all participants (*continuous)*
- The number of CFHH sessions with at least 1 click by CFHH module (*continuous)*
- The number of participants who accessed CFHH via the mobile application (app) (categorical)
- The number of notifications sent by participant for in those participants who had the app (continuous)

Interventionist CFHH interaction:

- The number of interventionist sessions in CFHH (*continuous)*
- The number of days with interventionist sessions in CFHH (*continuous)*
- Total duration in minutes of interventionist CFHH sessions (*continuous)*

Detailed descriptions of how these metrics will be derived can be found in section 9. For the continuous variables either mean and SD will be presented or median and IQR depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries. For the categorical variables, the number and percentage of participants in each of the categories and the total number of observations will be presented.

Nebuliser data will be used to calculate adherence to CF medication. The analysis of this data is described in section 7.8.1.

7.6 Analysis Populations

7.6.1 Intention to treat

To avoid any potential bias in the analysis, Intention to treat (ITT) will be the primary analysis population (including primary, secondary and safety outcomes) unless otherwise stated. This is defined as participants being analysed as they are randomised regardless of the treatment they received. Participants will not be included in the analysis if they withdraw consent and do not want their data to be used. As the primary outcome is defined as the number of events all participants will be included regardless of their follow-up duration. Details of the analysis of the primary outcome can be found in section 7.7.

7.6.2 Per protocol

A per protocol analysis will be conducted as a secondary analysis on the primary outcome. This population will include the following:

- A first intervention visit (to include a visit to the CFHH 'How am I doing?' page).
- A review session (to include a visit to the CFHH 'How am I doing?' page).

CACE analysis will also be used (section 7.7.3).

7.7 Analysis of the primary outcome

7.7.1 Estimating treatment effect

For the primary outcome, the between group difference, and its associated 95% confidence interval and p-value will be calculated using a mixed effects Poisson model. The duration of follow-up for each individual participant (in days) will be included as an exposure or offset in the model, number of IV days in previous 12 months (less than or equal to 14 days and greater than 14 days) and treatment arm will be included as fixed effects and centre will be included as a random effect.

For a Poisson model the estimated treatment effect is an incidence-rate ratio (IRR). The total number of person-years and exacerbations will be presented by treatment arm to aid interpretation (Table 9).

7.7.2 Model and data checks

As an additional assessment, the mean (and variance) of the number of exacerbations in the 12-month follow-up will be calculated along with the ratio of the mean number of exacerbations to its variance. In the event of this ratio being less than unity (variance ≥2*mean)), then we will consider using a negative binomial model as an alternative to the Poisson model to analyse the count data.

Data checks on the rate of exacerbations across the study will be carried out to assess whether the assumption of a constant rate is met. The rate in each four month period will be plotted by treatment arm and overall.

7.7.3 Sensitivity analysis

The following analyses will be presented alongside the primary analysis (Table 9) to assess the consistency of the results (Thabane et al. 2013).

7.7.3.1 Treated and untreated exacerbations

Exacerbation data will be collected even when an event is not treated with IV antibiotics so does not fit the definition of the primary outcome. These events will be included in a sensitivity

analysis which will follow the same method as the primary analysis and will be presented alongside it.

7.7.3.2 Imputation

As participants will be included regardless of the length of follow up, we will examine the effect of the missing data on our estimates. The methods of imputation have been described in section 8.1.

7.7.3.3 CACE analysis

CACE analysis will allow us to examine the effect of the intervention in a subgroup of participants defined as compliers. A detailed description of this analysis can be found in section 8.2.

7.7.3.4 Per protocol

As described in section 7.6.2, the results of the per protocol analysis will be presented with the primary analysis.

7.7.3.5 Multiple event analysis

An Andersen-Gill model, which is an extension of the Cox proportional hazards regression model for censored time to event outcomes, will be used to assess the robustness of results if distributional assumptions have not been met by the observed data. Poisson and negative binomial models assume a constant event rate. The Andersen-Gill model does not require this assumption. The hazard ratio, its 95% confidence interval and p-value will be presented.

7.8 Analysis of the secondary outcomes

7.8.1 Adherence to CF medication

As adherence to prescription medication is a key secondary outcome, more detailed analysis will be conducted. Three separate measures of adherence will be reported (defined in section 9.2.1).

1. Total weekly inhalations
2. Numerator adjusted adherence
3. Numerator adjusted normative adherence

7.8.1.1 Summaries of adherence

Simple line graphs will be plotted over the whole study period showing mean weekly adherence by treatment arm (Figure 3) to examine the overall trend in each of the 3 types of adherence. Mean and standard deviation will be presented by treatment arm for the baseline period (first 2 weeks) and over 6 and 12 months.

7.8.1.2 Estimating treatment effect

To examine the effect of the treatment on adherence across the 12 month study period, we will use a repeated measures analysis. A linear mixed effects model with participant ID and site as random effects and treatment arm, time in weeks, baseline adherence (first 2 weeks) and previous IV days (less than or equal to 14 days and greater than 14 days) as fixed effects and mean weekly adherence repeated across the whole study period as the outcome measure. An interaction between treatment and time will be included in the model to examine the rate of change in adherence by treatment arm. An exchangeable autocorrelation structure will be used. This is an exploratory analysis which will be conducted on numerator-adjusted normative adherence only.

7.8.1.3 Missing adherence data

It is worth noting that a participant may not have any inhalations recorded on any given day. Extensive checks will be carried out so we can be confident that these days without inhalations are genuine zeros i.e. the participant has not taken any CF medications and data are not simply missing.

7.8.1.3.1 Withdrawal from adherence data collection

Participants will have the opportunity to withdraw from adherence data collection and where this is the case the date of withdrawal and reason for withdrawal will be recorded. If a participant has withdrawn from adherence data collection, their adherence will then be recognised as missing from the date of withdrawal.

If a participant withdraws from adherence data collection, the data they have contributed up to the point of withdrawal can still be included in data analysis. For the line graphs, data will be contributed to the weekly mean adherence until the point of withdrawal. For the estimation of treatment effect, the benefit of using a mixed effects model is that data can be included for a participant to the point of withdrawal.

7.8.2 Estimating treatment effect of other secondary outcomes

Secondary outcomes will be analysed with a mixed effects model with the baseline value of the outcome, number of IV days in previous 12 months (stratification variable) and randomised group as fixed effects and interventionist as a random effect. The treatment effect and its associated 95% confidence interval and p-value will be presented (Table 13) for each of the secondary outcomes. The analysis will be conducted on the ITT population.
Adherence to CF medication is a key secondary outcome but the analysis of this measure is described in section 7.8.

7.9 Safety

Safety will be assessed by recording adverse events (AEs). All those working on the trial will notify the Sheffield CTRU about any AEs during home visits, entering data, interventions etc. Those judged to be serious will have an expedited reporting procedure. Details of definitions of AEs and serious adverse events (SAEs) are outlined in the study protocol.

The following figures will be presented overall and by treatment arm (Table 18):

- The number and percentage of participants reporting an AE;
- The number and percentage of participants reporting a SAE;
- The number and percentage of participants reporting a treatment related AE;
- A list of all AEs and their details.

Safety outcomes will be reported for all participants who are randomised (i.e. the ITT populations)

8 Detailed Statistical Methods and Calculations

8.1 Missing Spurious & Unused Data

8.1.1 Missing primary outcome data

A simple method of imputation will be implemented to impute the missing primary outcome data. This will only be carried out on participants who have not died by the end of the 12 month follow-up period.

- *Multiple imputation by chained equation (MICE)*- a multiple imputation model will be used to impute any the number of exacerbations experienced in the remaining follow up period. This model will use data collected in other participants with age, sex, previous 12 months IV days, FEV1 percent predicted, previous exacerbations (recorded up to discontinuation) and pseudomonas status as predictors. As the primary outcome is a count, the R package ‘countimp’ will be used. This package allows multiple imputation of incomplete count data (Kleinke et al. 2011).
- *Best case scenario*- assume that the participant would not have experienced any exacerbations in the remaining follow up period.

The results of these sensitivity analyses will be presented alongside the primary analysis to examine the impact of missing data on the primary outcome.

8.1.2 Missing items within a questionnaire

Scoring of questionnaires will be conducted following guidance from the developers of the measure. Where instructions include a method for handling missing items, these will be

adhered to. Details of scoring of questionnaires including how missing items are to be handled can be found in section 9.

8.2 CACE analysis

CACE analysis is an attempt to compare the 'protocol compliers' in the intervention arm to those in the control arm who are 'likely' to have complied to the intervention had they been randomised to the intervention arm. A complier in the intervention arm will meet the following criteria:

- A first intervention visit (to include a visit to the CFHH 'How am I doing?' page).
- A review session (to include a visit to the CFHH 'How am I doing?' page).

CACE analysis will be performed in the following steps (Peng, Little, and Raghunathan 2004):

1. Using participants in the intervention arm, derive a logistic regression model to predict the probability of being a non-complier (defined above). Possible predictor covariates will include baseline demographics (e.g. age and sex), baseline questionnaire scores (e.g. PAM-13) and baseline clinical measures (e.g. FEV1 percent predicted and IV days in the previous 12 months)
2. Apply these predictions to the control arm, so that each participant is given a probability of receiving the intervention as planned (if they had been randomised to receive it) which is based on their covariates.
3. For each participant in the control arm, calculate a re-weighted outcome defined as the original outcome multiplied by the predicted probability of receiving as planned.
4. Compare the subset of participants in the intervention arm that are deemed to have complied with intervention with the re-weighted outcomes amongst participants in the control arm.

CACE analysis will be conducted by a two stage regression, the first will use mixed effects logistic regression including site as a random effect. The second model used in step 4 will be the mixed effects model as used in the primary analysis (Section 7.7).

9 Data manipulations and definitions

9.1 Primary outcome

The primary outcome will be collected on the 'Exacerbations' form. To meet the criteria, the exacerbation must have been treated with IV antibiotics and meet at least one of the 12 Fuchs criteria. The exacerbation must also have taken place within 12 calendar months from the date of consent. Participants who withdrew their consent and did not want their data to be used will

be excluded. In addition to the number of exacerbations, the length of follow up in days will be calculated. This will be the number of days from consent to 12 calendar months from consent. If the participant died, withdrew consent or was lost to follow up, the follow up period will be calculated as the number of days from the date of consent to the date of withdrawal (death, withdrawal of consent or date of last contact).

9.2 Other outcomes

9.2.1 Adherence to CF medication

Adherence will be calculated using data from chipped nebulisers which will be used by both the intervention and control groups. The number of doses prescribed will be decided by the interventionist in CFHealthHub in agreement with the participants. Each participant will have a daily adherence measure calculated using the total number of doses taken that day as a percentage of the total expected doses. The number of expected doses will differ depending on the type of adherence being calculated. Three measures of adherence will be calculated and are described below.

9.2.1.1 Total doses per week

As a basic, unadjusted measure of adherence, the total number of doses taken per week will be calculated.

$$\sum_{j=1}^{n} Dose\ taken_j$$

where

n= number of days in specified time period.

Due to potential differences in attrition between treatment arms, the doses will be summarised per week.

9.2.1.2 Numerator adjusted adherence

Adherence is typically calculated as the following:

$$Unadjusted\ Adherence_i = \frac{\sum_{j=1}^{n} Dose\ taken_j}{\sum_{j=1}^{n} Dose\ prescribed_j}$$

where

- *n= number of days in specified time period.*

For our purposes, the specified time period will be 12 months (the full duration of the study). Numerator adjustment occurs only if a daily adherence measure is greater than 100%, thus the maximum daily adherence is set at 100%.

9.2.1.3 Numerator adjusted normative adherence

Adjustments are made to treatment prescriptions to measure adherence to what may be considered an ideal regimen for treatment effectiveness, based on the following rules:

- All patients should receive a mucolytic
- All patients with chronic pseudomonas should receive both a mucolytic and an antibiotic

(Hoo *et al.*, 2016)

Pseudomonas status (chronic/non-chronic) is determined by consensus definition (Hoo *et al*., 2018). The number of doses taken is capped at the number of prescribed doses, as with basic numerator-adjusted adherence. The denominator is then adjusted based on the patient's pseudomonas status and antibiotic regimen as follows:

1) For all patients, if a mucolytic is not prescribed, a daily dose will be added to the prescription, giving a minimum denominator of at least 1. For a patient with a prescription of 2 doses of antibiotic, the denominator would be raised to 3, for example.
2) For patients identified at baseline as having chronic pseudomonas infection, variables are created to indicate the presence of antibiotics in the prescription, and specifically the use of Tobramycin, Aztreonam or Levofloxacin to indicate potential on/off treatment regimens.
    a. If one of those specific antibiotics is not detected, the antibiotic treatment regimen is assumed constant and must include 2 daily antibiotic doses at all time. If no antibiotic is prescribed, 2 doses will be added to the denominator, giving a minimum daily denominator of 3. For a patient on 2 doses of non-antibiotic, the denominator would be raised to 4, for example.
    b. If Tobramycin, Aztreonam or Levofloxacin are present in the prescription, it will be adjusted to ensure 1 mucolytic and 2 antibiotic doses per day (3 for Aztreonam) for 28 days, giving a minimum daily denominator of 3 (4 for Aztreonam). After that period, if another antibiotic is prescribed, the adjustment of at least 1 mucolytic and 2 antibiotic doses is continued, as per constant antibiotic treatment regimen. If no antibiotic is prescribed after 28 days, an on/off cycle will be assumed and just 1 mucolytic required for the subsequent 28-day period, giving a minimum daily denominator of 1. The 28-day on/off periods of denominator adjustment will be repeated unless other antibiotics are prescribed.

A sensitivity analysis will be conducted using the pilot study definition in which pseudomonas status is determined by the worst case between the Leeds criteria and the clinician's judgement. This will give a status of chronic pseudomonas, intermittent pseudomonas, pseudomonas-free or unknown. For intermittent, pseudomonas-free and unknown cases, the above rule 1 will be followed. For chronic pseudomonas cases, the above rules 1 and 2 will be applied.

9.2.2 Participant questionnaires

Questionnaires will be completed by participants and scores will be calculated by the Sheffield CTRU database (PROSPECT). The scoring algorithm will be checked independently by the trial statistician. The scoring and interpretation of these scores are outlined in Table 3.

Table 3 Scoring of questionnaires used in the ACtiF study

Name	Score range	Description	Score calculation (including handling of missing items)*	Interpretation of score
EQ-5D-5L		The measure comprises 6 questions. The main EQ-5D-5L health utility is based on questions 1-5 (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which are scored on a five point scale (1: best response, 5: worst). The final question is a stand-alone item, a 0-10 self-assessed thermometer scale scored in units of 0.1 (0=worst, 10=best).	**Scoring:** The van Hout scoring algorithm will be used (Van Hout et al. 2012) **Missing items:** the health utility is defined only if Q1-Q5 are non-missing	0 = equivalent to death 1 = full health negative score = state worse than death **Direction of a positive effect:** increase
PAM-13	0-100 Levels 1-4	Measures patient activation e.g. ability and willingness to manage their health. A score from 0-100 is calculated and a PAM level from 1-4	**Scoring:** 13 items with scoring spreadsheet **Missing items:** scores only calculated if 12/13 items are present	0= low patient activation 100= high patient activation Level 1- does not believe they have an active role Level 4- Maintaining behaviours **Direction of a positive effect:** increase
CHAOS-6	0-24	Measures confusion, hubbub and order. 6 item questionnaire	**Scoring:** Six items are scored from 0-4 and all items are summed to give a single total score **Missing items:** scores only calculated if all items are present	0= low level of chaos 24= high level of chaos **Direction of a positive effect:** decrease

SRBAI	0-28	Measure of habit and automaticity 4 item, 7 point likert scale	**Scoring:** 4 items are scored from 0-7 and all items are summed to give a single total score **Missing items:** scores only calculated if all items are present	0= low level of automaticity 28= high level of automaticity **Direction of a positive effect:** increase
CFQ-R	0-100	8 domains each score 0-100. The domains are: Physical, Emotion, Social, Eating, Body, Treatment Burden, Respiratory, Digestion	**Scoring:** Scores are calculated for each domain by using a scoring algorithm provided by http://www.psy.miami.edu/cfq_QLab/scoring.html	0= lower level of health 100= higher level of health **Direction of a positive effect:** increase
PHQ-8	0-24	Measure of depression. 8 item questionnaire, 0-3 for each item	**Scoring:** 8 items are scored from 0-3 and are summed to give a single total score **Missing items:** scores only calculated if 7/8 items are present	0= No or minimal depression 24= Severe depression **Direction of a positive effect:** decrease
GAD-7	0-21	Measure of anxiety. 7 item questionnaire	**Scoring:** 7 items are scored from 0-3 and are summed to give a single total score **Missing items:** scores only calculated if 6/7 items are present	0= No anxiety 21= Severe anxiety **Direction of a positive effect:** decrease
COM-BMQ				
Specific Necessities	2-5	Measure of perceived personal need for medication	**Scoring:** The detailed scoring algorithm can be found in 14.2.1.	**Direction of a positive effect:** increase
Specific Concerns	1-3	Measure of perceived concerns about the negative effects of the medicine they are taking	**Scoring:** The detailed scoring algorithm can be found in 14.2.1	**Direction of a positive effect:** decrease
MAD-3	3-15	Specifically made 3 item questionnaire to measure perceived medication adherence	**Scoring:** 3 items are scored from 1-5 and are summed to give a single total score	3= low perceived medication adherence

			Missing items: scores only calculated if all items are present	15= high perceived medication adherence **Direction of a positive effect:** increase

*Guidance from the developers has been used to score the questionnaires unless otherwise stated

9.2.3 FEV1 Percent Predicted

FEV1 percent predicted values will be derived using FEV1, sex, age and height (Quanjer et al. 2012)

9.2.4 Intervention Metrics

Interventionist sessions

- The number of interventionist sessions- collected as part of the CRF
- The number and percentage of participants who attended at least 1,3, and 5 interventionist sessions- collected as part of the CRF

Participant CFHH interaction:

- The number of sessions in CFHH- a session is defined as a series of clicks with no more than a 15 minute break in between clicks.
- The number of days with sessions in CFHH- a count of the number of days in the study period with a CFHH session
- Total duration in minutes of CFHH sessions- a total of all CFHH sessions from the time of the first to last click
- Mean duration of a participant's CFHH sessions- a mean of all sessions from the first to last click by participant
- The number of participants who had at least 1, 5,10 and 15 CFHH sessions
- The number and percentage of participants who interacted with each of the CFHH modules- the number and associated percentage of participants who clicked on the specified module at least once
- The number of clicks in each of the CFHH modules across all participants- the total number of clicks in the specified module
- The number of CFHH sessions with at least 1 click by CFHH module- a total of the CFHH sessions that included a click in the specified module

Interventionist CFHH interaction:

- The number of interventionist sessions in CFHH- a session is defined as a series of clicks with no more than a 15 minute break in between clicks
- The number of days with interventionist sessions in CFHH – the total number of days in the study period that had at least 1 interventionist CFHH session by participant
- Total duration in minutes of interventionist CFHH sessions- the total time spent in all sessions from first to last click by participant

9.2.5 IMD scores

IMD score can be ascertained using postcode data. This will be done via the Sheffield CTRU database (PROSPECT) and IMD scores and quintiles will be exported. As the study includes data from England, Scotland, Wales and Northern Ireland, an algorithm will be used to standardise the IMD scores so they can be combined and summarised together (Abel, Barclay, and Payne 2016).

10 Additional Analyses

10.1 Subgroup analysis

As suggested by the literature, the subgroup analysis will be restricted to the primary analysis and subgroups will be defined by baseline data i.e. data that is not dependent on the intervention. The subgroup analysis will be performed using mixed effects linear regression with the primary outcome. An interaction statistical test between the randomised treatment group and subgroup will be used to directly examine the strength of evidence for the difference between treatment arms varying between subgroups. Subgroup analysis will be performed regardless of the results of the primary analysis. The IRR (and 95% CI) will be computed for each subgroup category and visually displayed using a forest plot. The regression coefficient for the interaction between treatment group and subgroup will be presented with the associated confidence interval and P-value. We will not calculate separate p-values within each subgroup category (Wang et al. 2007). Results will be presented as shown in Table 19.

The subgroups of interest are described below. Groups defined below may be combined where numbers are low

10.1.1 Socioeconomic status

Socioeconomic can be derived from postcode data as described in Section 9.2.5. IMD score can be categorised into one of five quintiles (most deprived to least deprived).

10.1.2 Age category

Participants will be categorised into four subgroups based on age at consent:

- ≤ 18 years;
- 19-25 years;
- 26-34;
- ≥35 years.

10.1.3 Depression score

PHQ-8 scores at baseline can be categorised into depressed or not.

- PHQ-8 score ≥ 10 = Depressed

- PHQ-8 score <10 = Not Depressed

10.1.4 Anxiety score (Anxiety High/Low)

GAD-7 scores at baseline can be categorised into levels of anxiety.

- GAD-7 score ≥ 6 = Moderate to Severe anxiety
- GAD-7 score < 6 = No to Mild anxiety

10.1.5 Adherence to CF medication

Adherence to CF medication at baseline (defined as the first two weeks of data collected) can be categorised into levels of adherence.

- Low (≤ 25%)
- Medium (26-50%)
- High (51-75%)
- Very High (>75%)

Numerator adjusted normative adherence will be used.

10.1.6 Lung function (FEV1 percent predicted)

FEV1 percent predicted at baseline will be used to categorise participants into categories as defined by international convention (Morgan et al. 2016).

11 Implementation of the Analysis Plan

This SAP will be used as a work description for the statistician involved in the trial. All analyses should ideally be performed by the same statistician (under the supervision of senior trial statistician) and consequently none of the investigators involved in the trial will perform any of the statistical analyses.

Initially, the data manager will provide blinded data for preliminary checks by the statistician. Following database freeze, unblinded data will be delivered to the statistician to define analysis sets and test statistical programs. Any queries will be communicated to the data manager prior to database lock, and any changes to the database during this time will be documented. The database will be locked after agreement between the statistician, data manager and study manager. It is expected that no data amendments should be required following database lock. However, if an amendment is required, the process is documented in CTRU SOP DM012.

12 Modifications to the Original Protocol Analysis Statement

Not applicable

13 References

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Trial Documents

Title	Version	Date	Location
Study Protocol	3	15th February 2019	X:\ScHARR\PR_ACTIF\Admin\WP 3.2 RCT\1 Study Documents\1.1 Approved protocol
Data Management Plan	1	30th August 2017	X:\ScHARR\PR_ACTIF\Admin\WP 3.2 RCT\Data Management\Study Documents

CTRU Standard Operating Procedures

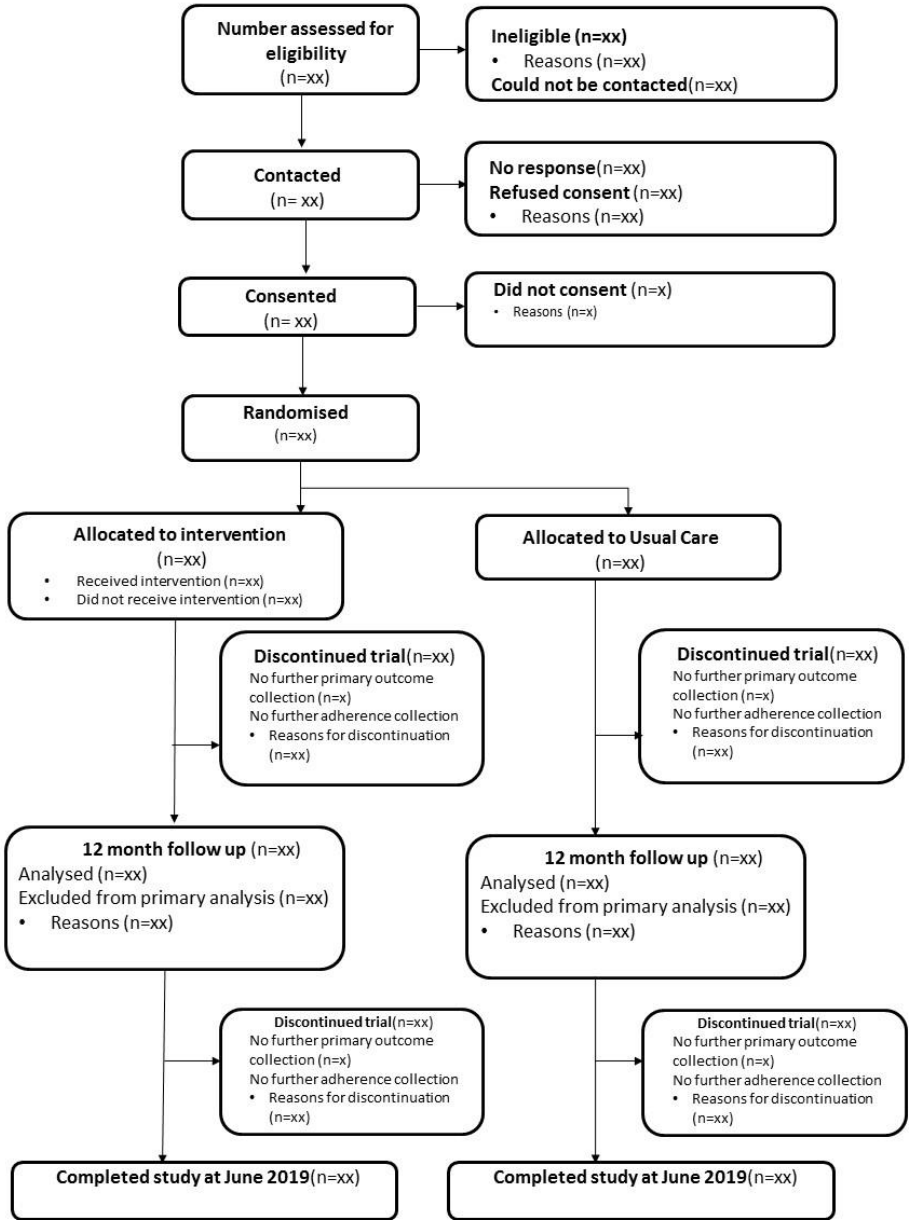
Title	Version	Date	Location
ST001 The Statistical Analysis Plan	5	9 Jan 2018	M:\Junctions\DFS_ScHARR\projects\CTRU\Quality Assurance\SOPs\Current SOPs
ST003 Data Evaluation	5		
ST006 Undertaking a Statistical Analysis	2	11 May 2017	
ST007 Randomisation			
DM005 Central Data Validation	5	21 Jun 2018	
DM012 Study database lock and retention	4	28 Mar 2017	

14 Appendix

14.1 Dummy tables

14.1.1 CONSORT flow diagram

Figure 1: CONSORT flow diagram


Number assessed for eligibility (n=xx)
Ineligible (n=xx)
• Reasons (n=xx)
Could not be contacted(n=xx)
Contacted (n= xx)
No response(n=xx)
Refused consent (n=xx)
• Reasons (n=xx)
Consented (n= xx)
Did not consent (n=x)
• Reasons (n=x)
Randomised (n=xx)
Allocated to intervention (n=xx)
• Received intervention (n=xx)
• Did not receive intervention (n=xx)
Allocated to Usual Care (n=xx)
Discontinued trial(n=xx)
No further primary outcome collection (n=x)
No further adherence collection
• Reasons for discontinuation (n=xx)
Discontinued trial(n=xx)
No further primary outcome collection (n=x)
No further adherence collection
• Reasons for discontinuation (n=xx)
12 month follow up (n=xx)
Analysed (n=xx)
Excluded from primary analysis (n=xx)
• Reasons (n=xx)
12 month follow up (n=xx)
Analysed (n=xx)
Excluded from primary analysis (n=xx)
• Reasons (n=xx)
Discontinued trial(n=xx)
No further primary outcome collection (n=x)
No further adherence collection
• Reasons for discontinuation (n=xx)
Discontinued trial(n=xx)
No further primary outcome collection (n=x)
No further adherence collection
• Reasons for discontinuation (n=xx)
Completed study at June 2019(n=xx)
Completed study at June 2019(n=xx)

14.1.2 Attrition

Table 4: Summary of study discontinuation during the 12 month follow up period

Type of discontinuation or completion	Months 1-3 Intervention	Control	Months 4-6 Intervention	Control	Months 7-9 Intervention	Control	Months 10-12 Intervention	Control	Overall Intervention	Control
Withdrew from the intervention	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from study	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from primary outcome collection	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from adherence data collection	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Lost to follow up	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Death	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Completed									xx(xx.x%)	xx(xx.x%)

This table may be adapted to include participants who have more than one type of withdrawal

Table 5: Summary of study discontinuation during the optional post 12 month follow up period

Type of discontinuation	Post 12 months Intervention	Control	Overall
Withdrew from the intervention	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from study	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from primary outcome collection	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from adherence data collection	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

14.1.3 Baseline characteristics

Table 6: Summary of participant characteristics at baseline by treatment arm

Variable		**Control (n=xx)**	**Intervention (n=xx)**	**All (n=xx)**
Gender	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Age (years)	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Weight	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Height	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
BMI	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Socioeconomic status (IMD)	IMD 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	IMD 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	IMD 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 7: Summary of participant clinical measures at baseline by treatment arm

Variable		Control (n=xx)	Intervention (n=xx)	All (n=xx)
No. of IV days in previous 12 months*	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
No. of participants requiring IV days in previous 12 months*		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FEV1 % predicted (using GLI equation)	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Pseudomonas status				
	None	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Intermittent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Chronic	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adherence to CF medication (in first 2 weeks)	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Adherence to CF medication				
	Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Medium	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subjective adherence	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
Medication				
	Single	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Multiple	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Treatment burden				
	Low (TBC)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Medium (TBC)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	High (TBC)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No. of days since last IV antibiotic start date	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx

Table 8: Summary of questionnaire scores at baseline by treatment arm

Variable		**Control (n=xx)**	**Intervention (n=xx)**	**All (n=xx)**
EQ-5D-5L score	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
PAM-13	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)

	Min., Max.	xx,xx	xx,xx	xx,xx
CHAOS	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
MAD-3	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
SRBAI	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
GAD-7	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
PHQ-8	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx

NB: baseline tables will also be completed by those analysed (participants with primary outcome data)

14.1.4 Primary analysis including sensitivity analyses

Table 9: Primary analysis results

Model	Intervention				Control				Treatment effect	
	n	No. of person years	No. of exacerbations	Rate of exacerbations per year	n	No. of person years	No. of exacerbations	Rate of exacerbations per year	IRR (95% CI)	p-value
Unadjusted	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
Adjusted*	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
Sensitivity analyses										
All exacerbations**	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
Multiple imputation	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
Imputation best case	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
CACE analysis	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
Per protocol	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
									HR (95% CI)	
Multiple event analysis (Anderson-Gill model)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xx.xx	x.xxxx

*adjusted for IV days in previous 12 months (fixed effect) and centre (random effect) ** includes treated and untreated exacerbations

Figure 2: Forest plot showing the results of primary analysis including sensitivity analyses

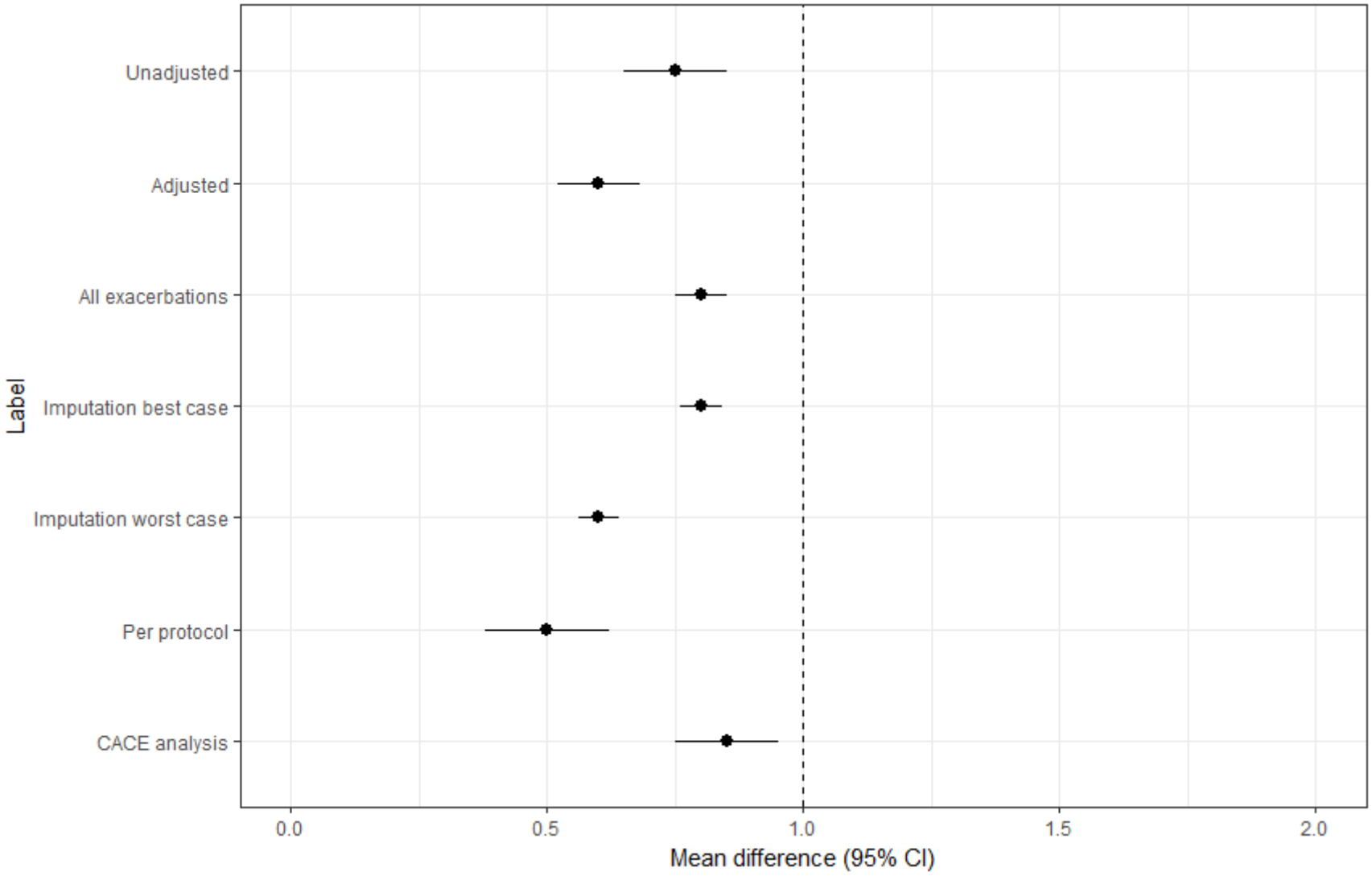


Table 10: Summary of number of exacerbations by intervention arm

Number of exacerbations	Intervention (n=xxx)	Control (n=xxx)	Total (n=xxx)
0	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
1	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
2	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
3	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
…			

14.1.5 Adherence to CF medication

Table 11 Mean adherence at baseline, over 6 months and over 12 months

	n	Intervention	n	Control
Time	xxx	Mean (SD)	xxx	Mean (SD
Baseline (first 2 weeks)	xxx	xx.x(xx.x)	xxx	xx.x(xx.x)
6 months	xxx	xx.x(xx.x)	xxx	xx.x(xx.x)
12 months	xxx	xx.x(xx.x)	xxx	xx.x(xx.x)

Table 12 Treatment effect on normative adherence

	Estimate (95% CI)	p-value
Intervention	xx.x(xx.x-xx.x)	0.xxxx
Time (weeks)	xx.x(xx.x-xx.x)	0.xxxx
Intervention*Time (weeks)	xx.x(xx.x-xx.x)	0.xxxx

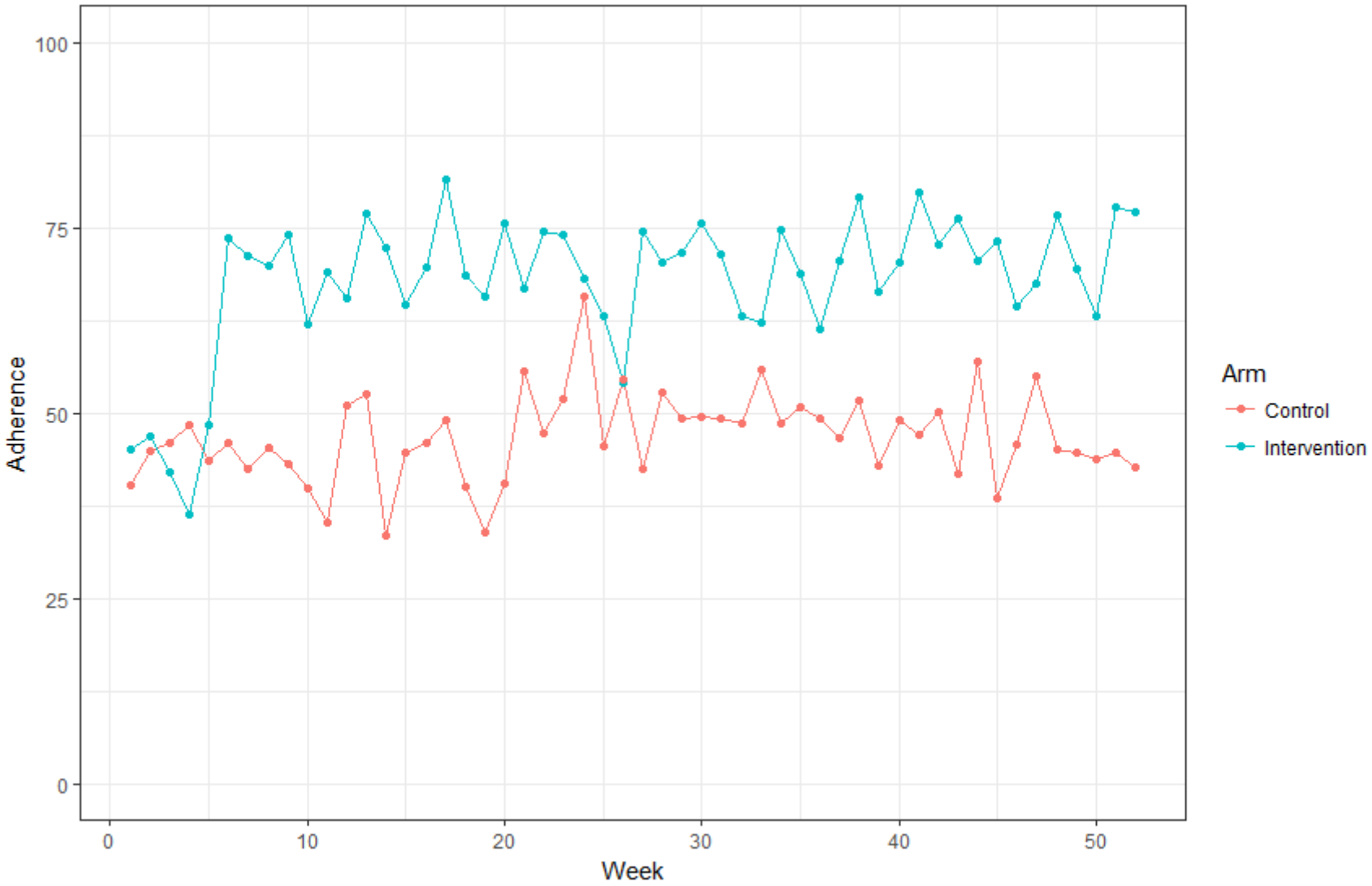


Figure 3: Line graph showing mean weekly adherence by treatment arm for the 12 month study period (repeated for each adherence measure)

14.1.6 Secondary analyses

Table 13: Secondary analysis

Outcome measure	n	Mean (SD) Intervention	n	Mean (SD) Control	n	Mean Difference (95%CI)	p-value	Adjusted mean Difference (95%CI)*	p-value
FEV percent predicted	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
BMI	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
EQ-5D-5L	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
PAM-13	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
CHAOS	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
MAD-3	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
SRBAI	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
CFQ-R	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
…									
GAD-7	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
COM-BMQ	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx
…									
PHQ-8	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx	xx.x(xx.x-xx.x)	0.xxxx

*Adjusted for baseline measure, previous 12 months IV days (fixed effects) and centre (random effect)

14.1.7 Intervention adherence

Table 14: Summary of face to face intervention sessions

Variable		**(n=xx)**
Number of face to face interventionist sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Participants who attended at least 1 session		xx (xx.x%)

Participants who attended at least 3 session		xx (xx.x%)
Participants who attended at least 5 session		xx (xx.x%)

Table 15: Summary of participant interaction with CHH

Variable		(n=xx)
Number CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Number of days with CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Total duration in CFHH (minutes)	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Mean duration of CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Number CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Participants who attended at least 1 session		xx (xx.x%)
Participants who attended at least 5 session		xx (xx.x%)
Participants who attended at least 10 session		xx (xx.x%)
Participants who attended at least 15 session		xx (xx.x%)

Table 16: Summary of interactions with CFHH modules

Variable	Number of participants (n=xx)	Number of clicks across all participants	Number of CFHH sessions with at least 1 click
Module name 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Module name 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 17: Summary of interventionist interaction with CFHH

Variable		(n=xx)
Number interventionist CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Number of days with interventionist CFHH sessions	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx
Total duration in interventionist CFHH (minutes)	N	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)
	Min., Max.	xx,xx

14.1.8 Safety analysis

Table 18: Summary of adverse events

Event	Intervention group (n=xxx)	Control group (n=xxx)	Overall
All AEs	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
Participants with at least 1 AE	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
AE category	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
…	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
All SAEs	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
Participants with at least 1 SAE	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
SAE category	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)
…	xx (xx.x%)	xx(xx.x%)	xx(xx.x%)

14.1.9 Subgroup analyses

Table 19: Subgroup analysis results

Model	Intervention				Control				Treatment effect	
	n	No. of person years	No. of exacerbations	Rate of exacerbations per year	n	No. of person years	No. of exacerbations per year	Rate of exacerbations	IRR (95% CI)	p-value
Subgroup 1	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx
	xxx	xxxx	xxx	xx.xx	xxx	xxxx	xxx	xx.xx	xx.xx	x.xxxx

14.2 Detailed description of questionnaire scoring

14.2.1 COM-BMQ

The COM-BMQ consists of 21 items- 7 items make up the necessities (N) scale and 14 items make up the concerns (C) scale. Each item is scored from 1-5 with 3 items being reverse scored.

Item no.	Question	Necessities or concerns
1	My health, at present, depends on this nebuliser treatment	N
2	Having to use this nebulised treatment worries me	C
3	My life would be impossible without this nebuliser treatment	N
4	Without this nebuliser treatment I would be very ill	N
5	I sometimes worry about the long-term effects of this nebuliser treatment	C
6	This nebuliser treatment is a mystery to me	C
7	My health in the future will depend on this nebuliser treatment	N
8	This nebuliser treatment disrupts my life	
9	I sometimes worry about becoming too dependent on this nebuliser	C
10	This nebuliser treatment protects me from becoming worse	N
11	This nebuliser treatment does more harm than good	C
12	People who are on preventer treatments should stop their treatment every now and again	C
13	This nebuliser treatment is the most important part of my CF treatment	N
14	I have been given enough information about my preventer treatment	C
15	I am concerned that this nebuliser treatment might become less effective if I use it regularly	C
16	This nebuliser treatment is harmless	C
17	This nebuliser treatment gives me unpleasant side-effects	C
18	Having to use this nebuliser treatment is embarrassing	C

19	This nebuliser treatment is difficult to use	C
20	I CANNOT feel this nebuliser treatment working	N
21	Using this nebuliser treatment is an unwelcome reminder that I have CF	C

Items 14, 16, 20 are reverse scored. A mean of the of the necessities and concerns items are calculated separately to produce an overall score. At least 60% of items must be completed to produce a score.