a new journey
CF START

The cystic fibrosis (CF) anti-staphylococcal antibiotic prophylaxis trial (CF START); a randomised registry trial to assess the safety and efficacy of flucloxacillin as a longterm prophylaxis agent for infants with CF

CF START Protocol v3.0. 25/05/2017

Trial Sponsor:
Alder Hey Children's NHS Foundation Trust
Eaton Road
West Derby
Liverpool
L12 2AP

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Cystic Fibrosis strength in numbers

CTRC
Clinical Trials Research Centre

Alder Hey Children's NHS
NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

NHS
National Institute for Health Research

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical trial protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

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Authorised on behalf of the Trial Statistician:

Signature: _____ **Date:** _____

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General Information
This document describes the CF START trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering participants for the first time are advised to contact the coordinating centre (Clinical Trials Research Centre; CTRC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Professor Kevin Southern, via the CTRC.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 12.

Relationship Statements
Roles and responsibilities are fully described in section 15.

The Alder Hey Children's NHS Foundation Trust is the Sponsoring organisation and will formally delegate specific sponsoring roles to the Chief Investigator and Clinical Trials Unit, but remains legally responsible for the trial.

Clinical Trials Unit: The CTRC at the University of Liverpool in collaboration with the chief investigator, Professor Kevin Southern, have overall management responsibility for the trial from a CTU perspective and will be responsible for the co-ordination of centres.

CTRC as part of the Liverpool Trials Collaborative has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The CTRC has a diverse trial portfolio underpinned by methodological rigour, a data management system in compliance with the principles of GCP, and core standard operating procedures.

Contact Details: Institutions

Sponsor:	**Trial Management, Monitoring and Analysis:**	**Clinical Laboratory:**
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Contact Details: Individuals

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Additional Contacts:

The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File:

Contact	**Document Title**
Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	CF START Committee Membership
Principal Investigators	CF START Participating Centres

1 TABLE OF CONTENTS

Glossary

AE	Adverse Event
AR	Adverse Reaction
ASAP	Anti-staphylococcal antibiotic prophylaxis
CI	Chief Investigator
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
EUDRACT	European Clinical Trials Database
GP	General Practitioner
HRA	Health Research Authority
IDSMC	Independent Data and Safety and Monitoring Committee
IWRS	Interactive Web Response System
IMP	Investigational Medicinal Product
MC CTU	Medicines for Children Clinical Trials Unit
MHRA	Medicines and Health Care Products Regulatory Agency
PsA	*Pseudomonas aeruginosa*
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
SA	*Staphylococcus aureus*
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

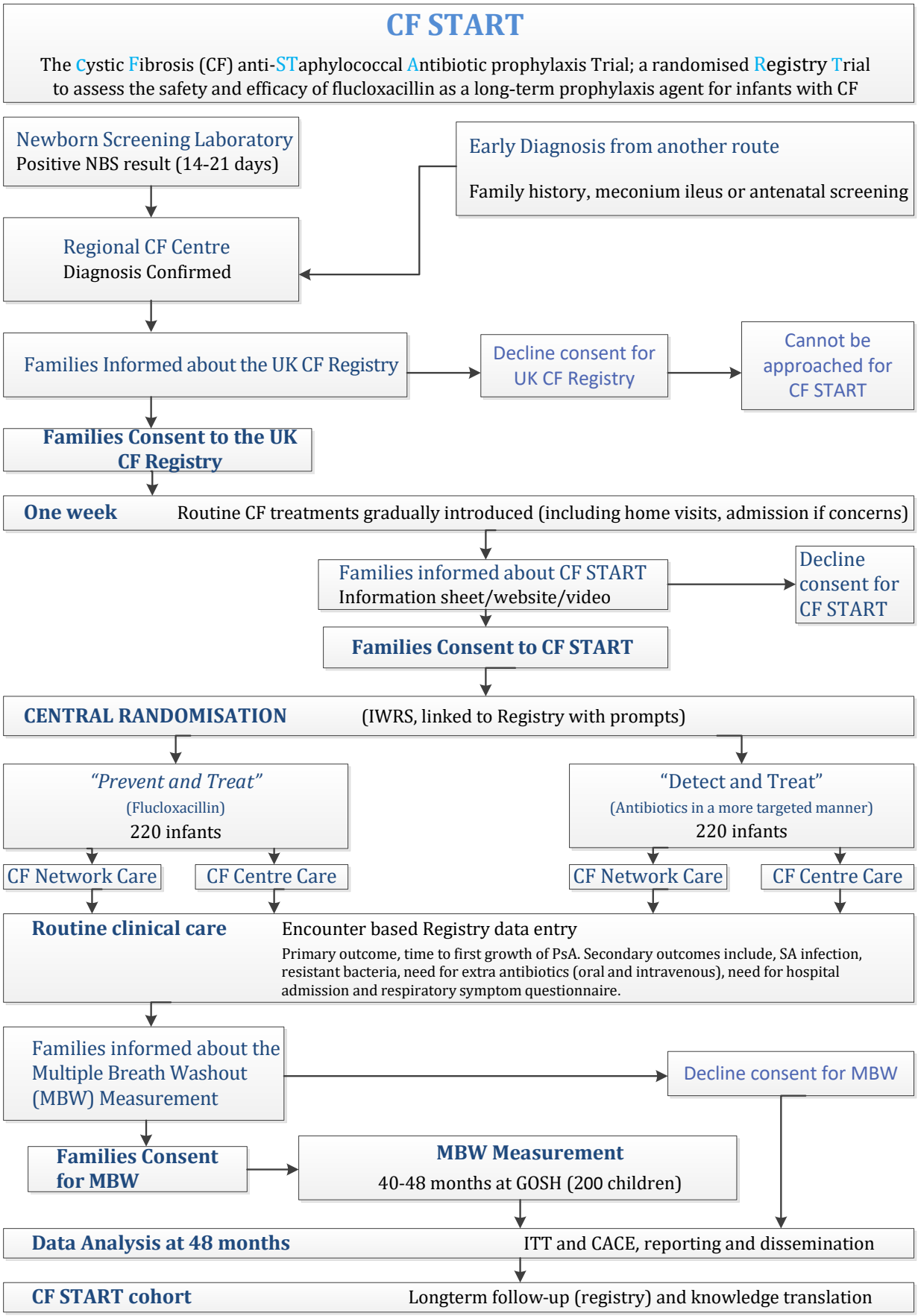
2 PROTOCOL SUMMARY

Full Title:	The cystic fibrosis (CF) anti-staphylococcal antibiotic prophylaxis trial (CF START); a randomised registry trial to assess the safety and efficacy of flucloxacillin as a longterm prophylaxis agent for infants with CF
Acronym	CF START
Phase:	Phase IV A comparative trial of two antibiotic treatment strategies for infants with CF. Anti-staphylococcal antibiotic prophylaxis (ASAP) versus antibiotics given in a more targeted manner. The two arms will be called "*Prevent and Treat*" and "*Detect and Treat*" respectively.
Target Condition:	Cystic fibrosis
Main Inclusion Criteria :	• A confirmed diagnosis of cystic fibrosis through one of the following two routes: - Two CF-causing mutations are identified. **OR** - One or no CF- causing mutations identified and a sweat chloride test result greater than 59 mmol/L. • Age 70 days or less. • Consent for inclusion on the national UK CF Registry. • Consent for inclusion in the CF START trial.
Main Exclusion Criteria :	• An inconclusive diagnosis after newborn screening (NBS). • A condition (non-CF) that, in the opinion of the recruiting investigator will impact on the long-term management and outcome of a participant with CF. • Previous growth of PsA from respiratory culture. • Infants with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillins) or to any of the excipients in the product. • Infants with a history of flucloxacillin associated jaundice/hepatic dysfunction.
Trial Centres and Distribution:	Regional CF centres and shared care centres (network clinics) throughout the UK
Participant Trial Duration:	Duration **per participant is** to age 48 months.
Sample Size	480 participants

Overall Trial duration	State start: 01/08/2016 End date: 31/07/2025	
Agent/ Intervention:	**Intervention:** "*Prevent and Treat*" : Infants will be prescribed prophylactic flucloxacillin suspension, 125 mg (<3 years old) or 250mg (≥3 years old) twice per day, by mouth **Control:** "*Detect and Treat*" : Infants will not be prescribed prophylactic antibiotics. Infants will receive standard CF care as per national guidelines for the following clinical indications; 1) respiratory symptoms (cough), 2) growth of recognised CF pathogen on routine respiratory culture sample (even if asymptomatic) and 3) in preparation for a procedure requiring general anaesthesia.	
	Objectives	**Outcome Measures**
Primary	To demonstrate that infants on ASAP ("*Prevent and Treat*") are not predisposed to earlier airway infection with *PsA*	Age at first growth of *PsA* from respiratory culture collected as part of routine care
Secondary	To determine if ASAP improves respiratory function in pre-school children with CF	Lung clearance index measured by the multiple breath washout technique
	To determine the need for extra antibiotic treatment	Number of courses and total number of days of extra antibiotics (oral, intravenous and aerosolised)
	To determine the number and type of respiratory culture taken during the trial period	Number and type of respiratory culture
	To determine the number and proportion of respiratory cultures positive for *SA*	Positive respiratory cultures for *SA*
	To determine the number and proportion of respiratory cultures positive for *PsA*	Positive respiratory cultures for *PsA*
	To determine the number and proportion of respiratory cultures positive for other significant CF pathogens	Positive respiratory cultures for other significant CF pathogens
	To determine if there is evidence of chronic airway infection	More than 50% of respiratory cultures are positive for the same pathogen during any 12 month period during the trial
	To determine the frequency of hospital admission	Number of inpatient stays and number of days
	To identify any adverse events	Annual blood test results (including liver function tests) Annual ultrasound scan of liver, if

		available Reports of complications (ABPA, CFRD, CFRLD)
	To determine nutritional status	Weight, height and weight for height percentile
	To indentify method of participant feeding	Feeding by: • Breast • Bottle • Combination of breast and bottle Participants breast fed for >3 months will be considered exclusively breast fed in the final analysis.
	To determine the costs to the NHS	CF banding and treatment costs

Schematic of Trial Design:


CF START
The Cystic Fibrosis (CF) anti-STaphylococcal Antibiotic prophylaxis Trial; a randomised Registry Trial to assess the safety and efficacy of flucloxacillin as a long-term prophylaxis agent for infants with CF
Newborn Screening Laboratory
Positive NBS result (14-21 days)
Early Diagnosis from another route
Family history, meconium ileus or antenatal screening
Regional CF Centre
Diagnosis Confirmed
Families Informed about the UK CF Registry
Decline consent for UK CF Registry
Cannot be approached for CF START
Families Consent to the UK CF Registry
One week
Routine CF treatments gradually introduced (including home visits, admission if concerns)
Families informed about CF START
Information sheet/website/video
Decline consent for CF START
Families Consent to CF START
CENTRAL RANDOMISATION
(IWRS, linked to Registry with prompts)
"Prevent and Treat"
(Flucloxacillin)
220 infants
"Detect and Treat"
(Antibiotics in a more targeted manner)
220 infants
CF Network Care
CF Centre Care
CF Network Care
CF Centre Care
Routine clinical care
Encounter based Registry data entry
Primary outcome, time to first growth of PsA. Secondary outcomes include, SA infection, resistant bacteria, need for extra antibiotics (oral and intravenous), need for hospital admission and respiratory symptom questionnaire.
Families informed about the Multiple Breath Washout (MBW) Measurement
Decline consent for MBW
Families Consent for MBW
MBW Measurement
40-48 months at GOSH (200 children)
Data Analysis at 48 months
ITT and CACE, reporting and dissemination
CF START cohort
Longterm follow-up (registry) and knowledge translation

3 INTRODUCTION

3.1 Background

For people with CF, chronic airway infection is the primary cause of poor health and early death. Paediatricians in the UK follow the logic model established over 40 years ago, that using ASAP prevents early *Staphylococcus aureus* (SA) airway infection and delays the development of chronic airway infection with other pathogens, notably *Pseudomonas aeruginosa* (*PsA)*.(1)

3.2 Rationale

Epidemiological studies support ASAP rationale by demonstrating a clear pattern of infection in people with CF, with early *SA* infection followed by later airway infection with gram negative bacteria, most commonly *PsA*.(1) Cystic fibrosis management strategies aim to optimise respiratory condition through prevention of chronic airway infection. (2)

Systematic review of ASAP for CF concludes that this strategy does reduce *SA* airway infection in infants with CF, but with less clear evidence regarding positive impact on well-being.(3)
One US trial showed some evidence that use of ASAP (cefalexin) resulted in increased recognition of *PsA* from respiratory cultures and in light of these findings, US guidelines advocate against the use of routine ASAP for infants.(4, 5)

Recent analysis of UK CF Registry data from the UK has shown that children with CF who are taking ASAP have earlier airway infection with *PsA* compared to children not taking ASAP. (A.Smyth personal communication) This raises the possibility that, compared to a more targeted antibiotic strategy, the routine use of ASAP may predispose infants with CF to earlier chronic airway infection.

The CF START trial will examine ASAP to determine whether this regimen predisposes infants with CF to earlier airways infection with *PsA*, the commonest cause of chronic airway infection in people with CF.

3.2.1 Rationale for the choice of primary outcome

Most adults with CF have chronic airway infection with PsA and the first growth of *PsA* from a respiratory culture is a seminal moment for all people with CF (demonstrated by our work with people with CF and their families (A.Smyth personal communication)). In a series of stakeholder events with CF Health Professionals we have explored numerous outcomes with the aim of determining the result that would most impact on their practice. Overwhelming there was support for a microbiological endpoint for this trial, reflecting the importance of that endpoint not just to families, but also to the teams involved in the care of children with CF. It is the concern over predisposing infants to earlier *PsA* airway infection that has influenced US practice, where national guidelines recommend against the use of routine ASAP.

3.2.2 The rationale for an open label trial comparing two strategies

CF START will compare two treatment strategies; "*Prevent and Treat"* (flucloxacillin prophylaxis) and "*Detect and Treat"* (antibiotics given in a more targeted manner). The second arm is representative of the approach adopted by countries other than the UK. In this way, CF START is reflective of current treatment approaches and results will be translatable to practice. PPI

consultation supported this approach and raised significant concerns about using a placebo. These concerns related to the length of trial and the fact that infants on the placebo may be denied necessary treatment. The two treatment arms in CF START both adopt a pro-active approach to treatment consistent with current standards of care for people with CF.

3.2.3 The rationale for the trial design (non-inferiority)

For the results of CF START to translate to a change in practice, we need to be able to deliver confidence that ASAP does not result in a significant increase in earlier *PsA* growth and this has been the rationale underpinning our trial design and power calculations. Although the non-inferiority design was considered optimal to provide confidence in our result, this was a challenging concept to explain to PPI groups, who felt any increase in the potential to grow *PsA* from respiratory cultures would be a concern. A survey of all Paediatric CF Physicians in the UK supported a power calculation based on UK CF Registry data that would provide confidence that if a difference exists between the two treatment arms, this would be no more than 12 months earlier.

3.3 Risk:Benefit

CF START will assess the withdrawal of an intervention (flucloxacillin prophylaxis) that has been a routine component of UK CF care for over 40 years.

Flucloxacillin is licensed for this age group, has a clear safety profile and is used widely in the UK as a specific therapy for acute infection with *SA*. Use of flucloxacillin as a prophylactic antibiotic is standard care for infants with CF, but is unusual outside of this indication.

Flucloxacillin treatment is very rarely associated with an increased risk of hepatic disorders, namely, hepatitis and cholestatic jaundice. (6). These reactions are related neither to the dose nor to the route of administration of flucloxacillin, and reported cases were mainly in those >50 years of age. There are no reports in infants or children with CF despite being a routine component of UK CF care for over 40 years.

For infants randomised to "*Prevent and Treat*", the risk relates to earlier acquisition of infection with *PsA*, an outcome that the trial is designed to assess.

For infants randomised to "*Detect and Treat*", the risks relate to earlier infection with *SA* and the potential impact of this on respiratory condition. Again we will be collecting important secondary outcomes assessing the impact on respiratory condition, including the measurement of lung clearance index at 40-48 months. As such we aim to provide a clear result that assesses the safety and efficacy of both of these strategies.

Infants randomised to "*Detect and Treat*" may receive less antibiotic therapy than is appropriate for standards of care. This will be addressed through the training of site staff and by working in partnership with families. Parent/carers will be provided with multi-media resources to support understanding of the trial and be empowered to provide appropriate care working with their CF team. Empowering and working in partnership with parent/carers is standard CF practice, but will be reinforced for the trial, in light of the potential risk to infants in the "*Detect and Treat*" arm.

CF START is a Type A CTIMP, reflecting the low risk nature of the trial.

3.4 Objectives

We hypothesise that the use of ASAP (flucloxacillin) predisposes infants with CF to earlier airway infection with *PsA* compared to infants treated with antibiotics in more targeted manner. CF START is a Randomised open label registry trial to assess the safety and efficacy of flucloxacillin as a long term prophylaxis agent for infants with CF.

4 Trial design

CF START is an open label randomised controlled trial employing a parallel group design to compare two treatment strategies. The non-inferiority design is aimed to provide confidence to stakeholders that the currently employed treatment strategy ("*Prevent and Treat"*) does not predispose infants with CF to significantly earlier airway infection with *PsA* compared to infants treated with antibiotics in a more targeted manner ("*Detect and Treat"*).

In addition, CF START will provide valuable data on the effectiveness of this intervention. To achieve this we will collect data over a relatively long time period (up to 48 months of age) and to facilitate this trial design, we are employing an innovative approach, namely the collection of outcome from a national Registry.

Table 1: Summary of Objective, Outcomes and Timepoints

Primary Objective	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
To demonstrate that infants on ASAP ("*Prevent and Treat"*) are not predisposed to earlier airway infection with *PsA*	Age at first growth of *PsA* from respiratory culture collected as part of routine care	All encounters to trial completion (age, 48 months)
Secondary Objective	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
To determine if ASAP improves respiratory function in pre-school children with CF	Lung clearance index measured by the multiple breath washout technique	One trial visit between age 40-48 months
To determine the need for extra antibiotic treatment	Number of courses and total number of days of extra antibiotics (oral, intravenous and aerosolised)	All encounters to trial completion (age, 48 months)
To determine the number and type of respiratory culture taken during the trial period	Number and type of respiratory culture	All encounters to trial completion (age, 48 months)
To determine the number and proportion of respiratory cultures positive for *SA*	Positive respiratory cultures for *SA*	All encounters to trial completion (age 48 months)
To determine the number and proportion of respiratory cultures positive for *PsA*	Positive respiratory cultures for *PsA*	All encounters to trial completion (age, 48 months)
To determine the number and proportion of respiratory cultures positive for other significant CF pathogens	Positive respiratory cultures for other significant CF pathogens	All encounters to trial completion (age, 48 months)
To determine if there is evidence of chronic airway infection	More than 50% of respiratory cultures are positive for the same pathogen during any 12 month period during the trial	All encounters to trial completion (age, 48 months)
To determine the frequency of hospital admission	Number of inpatient stays and number of days	All encounters to trial completion (age, 48 months)

To identify any adverse events	-Annual blood test results (including liver function tests) -Annual ultrasound scan of liver, if available -Reports of complications (ABPA, CFRD, CFRLD)	All encounters to trial completion (age, 48 months)
To determine nutritional status	Weight, height and weight for height percentile	At 48 months (or as near to study end as possible)
To identify method of participant feeding	Feeding by: • Breast • Bottle • Combination of breast and bottle Participants breast fed for >3 months will be considered exclusively breast fed in the final analysis.	At 6 months (or as near to 6 months as possible)
To determine the costs to the NHS	CF banding* and treatment costs	All encounters to trial completion (age, 48 months)

* Banding data will be collected separately

5 TRIAL SETTING AND SELECTION OF CENTRES / CLINICIANS

CF START will be a national UK trial. The aim is that all infants diagnosed with CF in the UK will have opportunity to be enrolled in this trial. In most cases these infants will be diagnosed through the national newborn bloodspot screening (NBS) programme. CF START will recruit from regional CF centres and network clinics (clinics that share the care of participants with a regional centre).

5.1 Selection of Centres/Clinicians

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in the supplementary document 'CF START Site Suitability Assessment'.

Initiation of centres will be undertaken in compliance with SOP[1]; Centres fulfilling the criteria will be selected to be recruitment centres for the CF START trial and will be opened to recruitment upon successful completion of all global (e.g. MREC and MHRA) and trial-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTU as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'CF START Participating Centres' log, maintained separately to the protocol.

5.2 Pilot sites

Eight-twelve sites will be approached for the pilot trial. The sites will include regional and network clinics, both from different models of network care and with different track records in recruiting to clinical trials. Once all pilot sites are set up this will not prevent set up and recruitment at additional sites.

STOP/GO criteria 2 will assess the ability of the CF teams to enter high quality data during the pilot study. The criterion for success will be >90% completion of microbiological data, as these reflect both the primary and important secondary outcomes. STOP/GO criterion 3 will assess recruitment rates during the pilot study. The criterion for success will be that 50% or more of the parent/ legal representative approached will agree to participate. Once successful completion of STOP/GO criterion 2&3 is demonstrated national recruitment will continue. These criteria will be assessed by the TSC and the HTA.

[1] CTRC SOPs TM017 Study Initiation in CTRC and TM018 Study Initiation at Sites

6 TRIAL POPULATION

6.1 Inclusion Criteria

1. A confirmed diagnosis of cystic fibrosis through one of the following three routes:
   - Two *CF-causing* mutations are identified.
   OR
   - One or no *CF- causing* mutations identified and a sweat chloride test result greater than 59 mmol/L.
2. Age 70 days or less.
3. Consent for inclusion on the national UK CF Registry.
4. Consent for inclusion in the CF START trial.

Mutations are listed on the CFTR2 website (cftr2.org). If access to www.cftr2.org is not available (i.e. loss of internet connection), sites should endeavour to confirm eligibility as soon as possible once access to the website becomes available again.

6.2 Exclusion Criteria

1. An inconclusive diagnosis after newborn screening (NBS).*
2. A condition (non-CF) that, in the opinion of the recruiting investigator will impact on the long-term management and outcome of a participant with CF.**
3. Previous growth of *PsA* from respiratory culture.
4. Infants with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillins) or to any of the excipients in the product.
5. Infants with a history of flucloxacillin associated jaundice/hepatic dysfunction.

*Infants with an inconclusive diagnosis after NBS (termed 'CF Screen Positive Inconclusive Diagnosis (CFSPID)') should not receive standard CF care and should not be recruited into CF START (Munck et al 2015).
The two situations that result in a diagnosis of CFSPID after NBS are;

- Two CFTR mutations recognised, one or both of which are not characterised as *CF-causing* and the sweat chloride is less than 30 mmol/L
- The sweat chloride is repeatedly between 30-59 mmol/L and only one or no CFTR mutations are recognised

**Significant non-CF conditions might include chromosomal abnormality (for example, Down syndrome), cerebral palsy, chronic lung disease (oxygen requirement) following pre-term birth and other significant congenital anomalies (for example, severe cardiac disease, tracheo-oesophageal fistula, diaphragmatic hernia).

***NOTE**; previous or current use of antibiotics is not an exclusion criteria*.

6.3 Co-enrolment Guidelines

Infants who are participating in a trial testing a medicinal product will be ineligible for the CF START trial. Where recruitment into another trial is considered to be appropriate (for example, an observational trial) and without having any confounding impact on the CF START trial this must first be discussed with the CTU who will contact the Chief Investigator (Professor Kevin Southern).

7 RECRUITMENT AND RANDOMISATION

7.1 Participant Identification and Screening

A screening log of participants who are assessed for eligibility but not randomised will be maintained in the UK CF Registry and this will provide important information for monitoring purposes.

The majority of potentially eligible infants will be identified by Regional CF Centres after a positive newborn screening (NBS) result from the laboratory. Positive NBS results are processed through Regional CF Centres in the UK. This will facilitate the identification of eligible infants and recruitment. A small number of infants will be identified after a clinical diagnosis (for example, a previous sibling with CF or meconium ileus).

As per standard practice, the CF Centre will organise a diagnostic assessment visit for the family. The diagnostic assessment will involve a clinical examination and sweat test. The parents will receive a definitive result later in the day.

In some cases a presumptive diagnosis is made after NBS; when an infant has clinical features and two CF causing mutations but a confirmatory sweat test is not possible. In these infants, treatment will commence and they may be enrolled for CF START if two CF causing mutations have been recognised (see eligibility criteria).

At the first visit, if the diagnosis is confirmed (or a presumptive diagnosis is made after NBS, see section 6.1), the parent or legal representative will be informed of the national UK CF Registry and provide consent for their infant's data to be included.

Initiation of CF therapies varies across the country, but generally treatments are commenced in a step-wise manner and families are often visited at home to support these interventions. At this point, during the week after diagnosis, CF START will be introduced and consent for this trial obtained once the family have had opportunity to consider (see below).

The family will be informed of CF START by the local CF team at a time they feel it is suitable, also taking into consideration the maximum age of 70 days for eligibility.

For those infants for whom it is not possible to confirm a CF diagnosis at the first visit, inclusion on the UK CF Registry, initiation of treatment and enrolment into CF START will be delayed. The infants will be classified as pending on the Screening Log until resolution.

7.2 Informed Consent

After the diagnostic assessment visit the parent or legal representative will be provided with information about the trial as well as access to other resources (trial website, CF Trust website and trial podcast).

Pre-trial Patient and Public Involvement (PPI) exercises informed that approaching families about CF START may not be appropriate during the initial diagnostic visit, as they are assimilating the diagnosis, however subsequent to this families will usually have multiple visits with CF specialists and other allied health professionals (AHP) e.g. physiotherapy, dietetics. It was considered appropriate for CF START to be introduced during these appointments and parents provided with information (multi-media information package).

When deemed appropriate (generally at the second hospital visit) the Principal Investigator (PI) or designated researcher will review eligibility criteria and obtain consent for CF START. Prior to consent the PI or designated researcher will review the information provided to the family, check for understanding and answer any questions the family have.

7.3 Prospective Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all participants participating in CTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to parent/legal representative by staff with experience in obtaining informed consent. Information sheets and consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the parent/legal representative will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research trial to the parent/legal representative. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All parents/legal representatives will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the trial with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

The parent or legal representative will then sign and date the informed consent document. Both the person obtaining consent and the parent/legal representative must personally sign and date the form. A copy of the informed consent document will be given to participant's legally acceptable representative for their records. The original will be filed in the Investigator Site File (ISF). A copy should be uploaded to the UK CF Registry platform.

The parent or legal representative of the potential participant will have approximately 1-2 weeks to decide whether or not to join the trial.

The parent/legal representative may, without being subject to any resulting detriment, withdraw their child from the trial at any time by revoking the informed consent. The rights and welfare of the participants will be protected by emphasising that the quality of medical care will not be adversely affected if they decline to participate in the trial.

Proxy consent from the parent or legally acceptable representative should be obtained prior to each participant participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The right of the parent/ legal representative to refuse consent for the minor to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis. Similarly, the parent/legal representative of the participant remains free to withdraw the participant at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment of the minor.

7.4 Enrolment/Baseline

Participant enrolment onto CF START will be placed on hold until the inclusion and exclusion criteria as detailed in section 6 is met. The following data will be collected as part of the UK CF Registry prior to enrolment. Once the participant is enrolled onto the trial the data will be recorded as CF START baseline data:

1. Gender
2. Date of birth
3. CFTR genotype
4. Postcode
5. Birth weight
6. Gestation
7. Height and weight
8. Microbiology data
9. Concomitant medications

7.5 Registration/Randomisation Procedures

If eligibility criteria are met and informed written consent obtained, infants will be randomised to receive either

- "*Prevent and Treat"*; Prophylactic flucloxacillin suspension, 125mg (<3 years old) or 250mg (≥3 years old) twice per day, by mouth
  OR
- "*Detect and Treat"*; No antibiotic prophylaxis

Twins or Subsequent siblings with CF:
In the event that twins (and other multiple birth siblings), or subsequent siblings are eligible for inclusion, the first randomised treatment will be given to both/all siblings.

Participants will be randomised in a ratio of 1:1, using a secure (24-hour) web based randomisation programme embedded within the UK CF Registry and monitored by the Registry team with CTRC oversight. .

When the system requirements (consent and eligibility) are confirmed the participant treatment allocation will be displayed on the UK CF Registry, available for the PI and CTRC to review. It is the responsibility of the PI to work in partnership with the parents/legal representative to ensure that prescribed treatments are available from community or hospital pharmacies.

Randomisation: https://www.cfregistry.org.uk

If there are any problems with the randomisation systems contact the coordinating CTU on 0151 794 9764 or via email on cfstart@liverpool.ac.uk

(Note that the coordinating CTU is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Provision for back up randomisation:
In the event of a randomisation system failure, the centre should contact the coordinating team in CTU (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved the participant may be randomised at their next encounter providing they are still eligible to take part.

8 PARTICIPANT TIME LINE, ASSESSMENTS AND PROCEDURES

CF START will collect outcome data from the UK CF Registry and infants in the trial will be managed as per national standards of CF care.

8.1 Schedule for Follow-up

Participants will be followed up for CF START from randomisation until age 48 months.

Table 2: Schedule of Assessments

Procedures	Age (Days)		Post randomisation		Age (Months)		
	≤70	≤70			40-48	48	
	Screening	Randomisation/ Baseline	First Encounter	Subsequent Encounters	Optional GOSH Visit	Trial Completion	Premature Discontinuation
Screening - identified on the UK CF Registry when diagnosed with CF	X						
Appointment with CF Specialist who commences standard CF treatment and provides families with the parent/ legal representative information sheet	X						
Pancreatic Function test			X	X		X	
Assessment of Eligibility Criteria		X					
Informed consent		X					
Review of Medical History		X					
Review of concomitant medications		X	X	X		X	X
Randomisation		X					
Prevent and treat - prophylactic antibiotic prescribed		X	X	X			
Participant feeding assessment (0-6months)			X	X			
Compliance with trial allocation		X	X	X		X	X
Height and weight				X		X	
Microbiology data from any respiratory cultures		X	X	X		X	
Serum liver function tests (if done)			X	X		X	
Multiple breath washout					(X)		
Assessment of Adverse Events			X	X		X	X

(X) – As applicable.

8.2 Procedures for assessing Efficacy

Efficacy will be measured throughout the period of the study using the below measures.

8.2.1 Lung clearance index

See section 8.4.2.1.

8.2.2 Review of concomitant medication

In order to determine the need for extra antibiotic all medication taken during the course of the study will be recorded on the UK CF Registry at each encounter, if applicable, as per standard care. Extra antibiotics are defined as any additional antibiotics (type and dose) to those prescribed on the randomised trial arm. Data recorded will include total number of courses of extra antibiotics and total number of days. The antibiotics will be divided into oral, aerosolised (nebulised) and intravenous.

8.2.3 Respiratory cultures

Participants will provide a cough swab at each encounter as a routine component of CF care. The laboratory assessments will determine the number and type of culture which will be recorded on the UK CF Registry, as will the outcome of those tests. Data on the total number and type of culture will be analysed, and the proportion of those cultures positive for *Staphylococcus aureus*, *Pseuduomonas aeruginosa* and other CF pathogens Respiratory cultures will also provide evidence of chronic airway infection if more than 50% of respiratory cultures are positive during any 12 month period of the trial.

8.2.4 Weight and Height measurement

Weight and height are measured and recorded at each clinic visit. Entry of these data on the Registry is mandatory to complete an encounter. Weight and height data will be collected throughout the trial but the analysis will focus on this outcome in the last 8 months of the trial (age 40-48 months). Weight and height will be recorded as SD for age. In addition the weight for height percentile will be calculated

Weight for height percentile will be calculated using age appropriate formulae.

8.3 Procedures for Assessing Safety

Safety will be measured throughout the period of the study using the below measures.

8.3.1 First growth of PsA from a respiratory culture

This is the primary outcome for the trial and these data will be recorded as for section 8.2.3. When the first isolation of PsA is recorded on the UK CF Registry and transposed to the CF START module, the data enterer will be asked to verify that this is the first growth of PsA. First growth of PsA is a key clinical event for people with CF. (7-10)

8.3.2 Liver function blood test

As part of standard CF care, infants will have annual liver function blood tests taken (most importantly Alanine transferase, ALT) the outcome of which will be recorded on the UK CF Registry. This procedure will provide evidence of any CF related liver disease. In addition liver ultrasound findings will be recorded if undertaken.

8.3.3 Complications

A wide variety of CF complications may be recorded in the UK CF Registry from each encounter.. Examples of these include Allergic Bronchopulmonary Aspergillosis (ABPA), CF related diabetes (CFRD) and CF related liver disease (section 8.3.2). Participants will be monitored for adverse event data (complications) that meet the criteria of serious and possibly, probably or almost certainly related to flucloxacillin (section 10).

8.3.4 Pancreatic Function test

A Pancreatic Function Test may be carried out during the participants time on the trial and therefore recorded in the UK CF Registry.

8.3.5 Participant Feeding Assessment

Participant feeding (breast, bottle or mixed) in the first six months will be recorded in the CF START Module.

8.4 Other Assessments

8.4.1 Health Economics

The economic evaluation will adopt a secondary care NHS costing perspective. Total costs of care will be taken directly from the CF currency, which is a complexity-adjusted yearly banding system with seven bands of increasing complexity. The bandings are derived from UK CF Registry clinical information considering CF complications and drug requirements. Health outcomes will be based on clinical measures, and presented in cost-consequence and cost-effectiveness analyses of a "*Detect and Treat"* (targeted antibiotic therapy) strategy versus *"Prevent and Treat"* (flucloxacillin as per UK guidelines). Costs and benefits will be discounted at 3.5% per annum. Uncertainties will be accounted for in univariate sensitivity analyses and the joint uncertainty in costs and benefits considered through the application of bootstrapping to generate cost effectiveness acceptability curves.

8.4.2 Special Assays or Procedures

8.4.2.1 Multiple Breath Washout (MBW) measurement

The MBW measurement will require a visit to a central laboratory in London when children are aged 40-48 months. All families in CF START will be invited to participate, but it is not compulsory component of CF START and families are able to opt out.
The test takes around 1-2 hours and the test will be performed according to the local and international standards applying at the time. In summary, during this assessment the child will be asked to breathe inert gas via a facemask. As the child is breathing comfortably (tidal breathing) the gas entering the system will be changed and an analyser will then measure how long it takes - i.e. how many breaths, and how big those breaths are - to clear the inert gas from the lungs. This measure is the lung clearance index.

8.5 Participant Transfer and Withdrawal

In consenting to the trial, participants are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the parent/legal representative should be asked to allow continuation of scheduled evaluations, complete an end-of-trial evaluation if appropriate, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable. Follow-up of these participants will be continued through the trial Research Nurses, the lead investigator at each centre and, where these are unsuccessful, through the child's GP, unless the participant explicitly also withdraws consent for follow-up.

8.5.1 Participant Transfers

For participants moving from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via GP.
The parent/legal representative will have to sign a new consent form at the new site, and until this occurs, the participant remains the responsibility of the original centre. The CTU should be notified in writing of participant transfers.

8.5.2 Stopping Trial Intervention

Participants may no longer adhere to their allocated arm for any of the following reasons:

a. Unacceptable toxicity.
b. Intercurrent illness preventing further treatment.
c. Any change in the participant's condition that justifies the discontinuation of allocation in the clinician's opinion (for example, changing from *"Detect and Treat"* to *"Prevent and Treat"*).

If a participant's parent/ legal representative wishes to withdraw their infant/child from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the participant explicitly also withdraws consent for follow-up (see section 8.5.3).

8.5.3 Complete withdrawal of consent ly

The parent/ legal representative for a participant is free to withdraw their child/ infants consent at any time without providing a reason. Parent/ legal representatives who wish to withdraw their child/ infants consent for the trial will have data collected up to the point of that withdrawal of consent included in the analyses.

The participant will not contribute further data to the trial and the CTU should be informed in writing and details of the withdrawal should be recorded within the CF START tab in the UK CF Registry. Data up to the time of withdrawal will be included in the analyses unless the parent/ legal representative explicitly states that this is not their wish.

Consent for being enrolled in the UK CF Registry is a prerequisite for participation in CF START, should participant consent be withdrawn for data to be collected in the UK CF Registry this will result in the participant being withdrawn from CF START. No further data can be collected from the point of consent withdrawal.

8.6 Loss to Follow-up

If any of the trial participants are lost to follow up contact will initially be attempted through the PI or delegated research staff at each centre. If the lead investigator at the trial centre is not the participant's usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the participants' family to provide follow up information to the recruiting centre. Wherever possible, information on the reason for loss to follow up will be recorded.

8.7 Trial Closure

The end of the trial is defined below. However, the trial will be assessed regularly by the Independent Data and Safety Monitoring Committee. They will report any concerns on the interim annual analysis of the trial to the Trial Steering Committee and together they will decide if the trial should be prematurely stopped. Circumstances that may lead to early trial termination include:

a. Evidence of earlier PsA acquisition
b. Evidence of significant difference in a secondary outcome
    i. Increased hospital days
    ii. Increased IV antibiotics

Increased use of oral antibiotics or increased isolation of *SA* will not be criteria for early trial termination as these are anticipated outcomes for the *"Detect and Treat"* arm.

8.7.1 Definition of End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database.

9 TRIAL TREATMENT/INTERVENTIONS

9.1 Introduction

The two arms in this trial are:

- *"Prevent and Treat"*

Flucloxacillin suspension 125 milligrams twice per day (as per UK national CF prescribing guidelines) until the participant is three years of age. At three years of age the dose of flucloxacillin will be increased to 250 milligrams twice per day. Additional antibiotics will be prescribed as per local CF guidelines and depending on clinical indication

- *"Detect and Treat"*

Infants will not be prescribed antibiotics for the purposes of this protocol. The "*Detect and Treat"* group will be prescribed antibiotics as per local CF guidelines for the following clinical indications; 1) respiratory symptoms (cough), 2) growth of recognised CF pathogen on routine respiratory culture sample (even if asymptomatic) and 3) in preparation for a procedure requiring general anaesthesia.

9.2 **"*Prevent and Treat*"**

9.2.1 Formulation, Packaging, Labelling, Storage and Stability

ATC Code – J01CF05

Pharmacotherapeutic group – Beta-lactamase resistant penicillins

Properties: Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β-lactamases.

Table 3: Summary of Flucloxacillin

Active ingredient	Flucloxacillin
Excipients	Refer to SPC
Pack Size(s)	Refer to local supply chain (local pharmacy)
Route of Administration	Oral
Storage temperature / time	Refer to SPC
Supplier's name	Local supply chain (local pharmacy)

The acceptance of the Clinical Trial Notification associated with this protocol by the MHRA means that Annex 13 labelling exemption for this trial has been accepted and confirmed to meet the requirements for Regulation 46(2) of SI 2004/1031:

- The product concerned is an authorised medicinal product within the European Economic Area.
- The product does not require particular manufacturing or packaging processes.
- The participants in the trial have the same characteristics as those covered by the indication specified in the marketing authorisation. While the use of prophylactic flucloxacillin in children with CF is considered off-label, such use is an established practice and supported by published evidence. This is in line with the information provided in the risk adapted approach guidance.

- The product will be dispensed to a participant in accordance with a prescription given by a healthcare professional and a standard dispensing label will be applied to the product at the point of dispensing.

9.2.2 Preparation, Dosage and Administration of Trial Treatment

Flucloxacillin should be administered orally at a dose of 125 milligrams twice per day until the participant is three years of age. At three years of age the dose of flucloxacillin will be increased to 250 milligrams twice per day. Sites should refer to the current SPC, which can be accessed via https://www.medicines.org.uk/emc/, for all treatment decisions.

9.2.3 Dose Modifications

Flucloxacillin should be administered at the above dose.

9.2.4 Specific Restrictions

The participant may not tolerate flucloxacillin. Most commonly this relates to palatability and the families will be provided with a support package to support them with this. In some rare cases the participant may have a mild adverse drug reaction (ADR), such as loose stools or a rash. In these cases the ADR usually settles but if it is persistent the CF team may opt for an alternative antibiotic prophylaxis.

9.2.5 Overdose

The occurrence of an overdose which has resulted in an AR/AE should be reported via the complication tab on the UK CF Registry. Overdose with high doses (mainly parenteral) neurotoxicity may develop. Gastrointestinal effects such as nausea, vomiting and diarrhea may be evident and should be treated symptomatically. Flucloxacillin is not removed from the circulation by haemodialysis.

9.2.6 Accountability Procedures for Trial Treatment/s

Flucloxacillin will be prescribed according to the local practice and dispensed by hospital and community pharmacies as they would be normally in clinical practice. The CF team will correspond regularly (after each encounter) with the family and the General Practitioner to ensure that the supply of all CF medicines, including flucloxacillin, is reliable. As CF START is a low risk pragmatic trial, they will be no formal recording of accountability.

9.3 "*Detect and Treat*"

Participants randomised to this arm will not receive prophylactic antibiotic treatment. They will be followed up for purposes of CF START and any antibiotics prescribed during their trial participation will be recorded.

9.3.1 Accountability Procedures for Trial Treatment/s

Not applicable; there is no prophylactic antibiotic therapy in the "*Detect and Treat"* arm.

9.4 Assessment of Compliance with Trial Treatment/s

As a standard component of CF care and as part of the national guidance, parent/carers are asked about adherence to treatments at each clinic visit. The UK CF Registry will present the treatment arm to which the participant is randomised ("*Prevent and Treat"* or "*Detect and Treat"*) and data will be entered into the UK CF Registry following each encounter to confirm that the participant continues to adhere to their randomised treatment arm.

9.5 Concomitant Medications/Treatments

9.5.1 Medications Permitted

Refer to SPC guidance.

9.5.2 Medications Not Permitted/ Precautions Required

Refer to SPC guidance.

9.5.3 Data on Concomitant Medication

The dose and name of all chronic concomitant medications will be documented on the UK CF Registry. The PI or delegated research member should reassess concomitant medications at each clinic visit. Any medications introduced/discontinued or any changes to current medications should be documented on the UK CF Registry.

At each encounter the CF team will record (name, dose and duration) any additional antibiotics (oral/ IV) prescribed since the last encounter.

10 SAFETY REPORTING

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- the case of a product with a marketing authorization, in the summary of product characteristics for that product
- the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

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

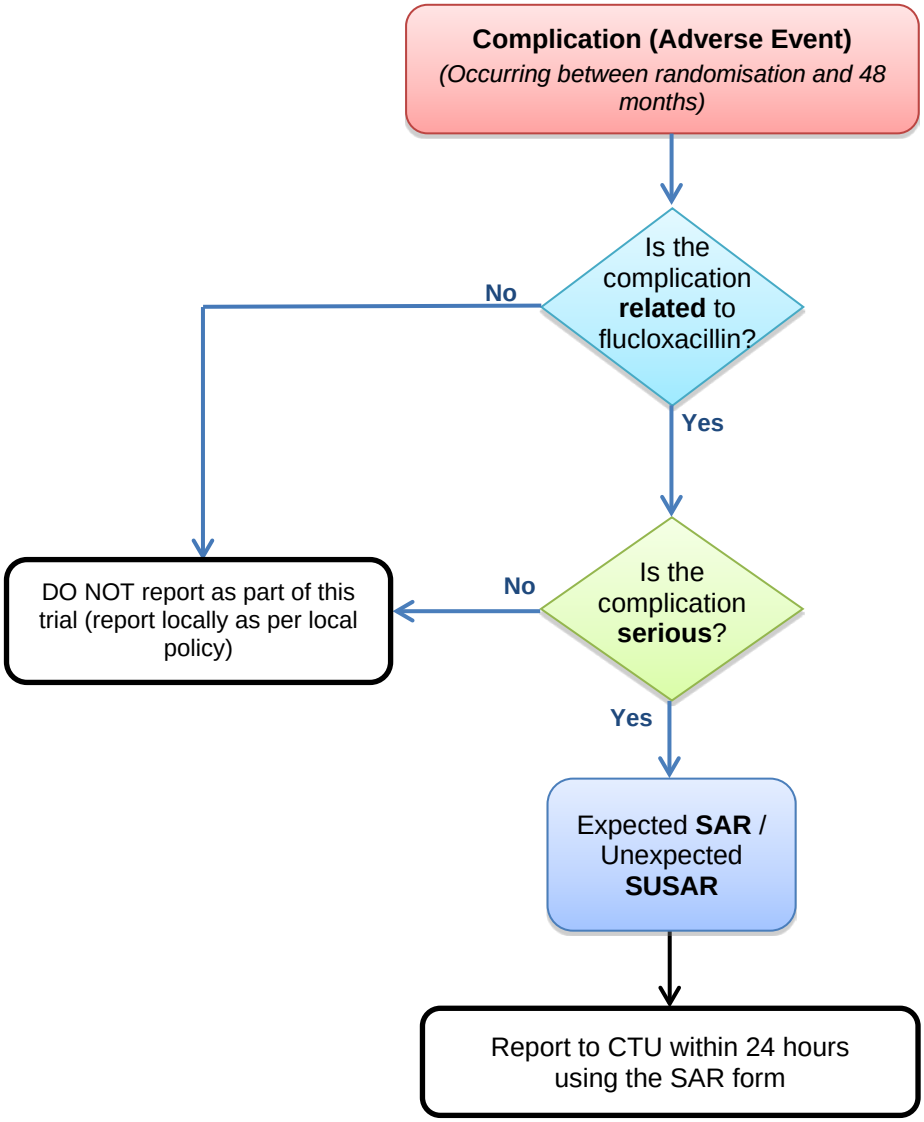
*'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Time Period for Safety Reporting

Safety reporting of Serious Adverse Reactions will be reported during the clinical trial from the date of randomisation until 48 months.

10.2.1 Flowchart for Reporting Requirements of Adverse Events

For the purposes of CF START, adverse event data is drawn from the 'complications' tab of the UK CF Registry. This requires that encounter data be documented promptly on the UK CF Registry.
Only complications that meet the criteria of serious and possibly, probably or almost certainly related to flucloxacillin will be expedited. Potential SARs should therefore be recorded on the UK CF Registry as soon as the centre becomes aware (within 24 hours).



10.3 Notes on Adverse Event Inclusions and Exclusions

10.3.1 Reference Safety Information

The Reference Safety Information (RSI) for the assessment by the CI of expectedness of SARs occurring in participants allocated to prophylactic antibiotics in CF START is Section 4.8 Undesirable effects of SPC Flucloxacillin 250mg/5ml Powder for Oral Solution.

10.3.2 Notification of deaths

Any deaths which have been assessed and judged by the investigator to be possibly, probably or almost certainly related to flucloxacillin must be reported to the CTU and Chief Investigator within 24 hours using the SAR form generated through the UK CF Registry. The withdrawal form should also be completed on the CF START Module (within 7 days of becoming aware).

Any deaths which have not been assessed and judged by the investigator to be possibly, probably or almost certainly related to flucloxacillin must be reported to the CTU (within 7 days of becoming aware) using the withdrawal form on the CF START Module.

10.4 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.5 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 4: Definitions of Causality.
If any doubt about the causality exists the local investigator should inform the trial coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 4: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the

	influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.6 Expectedness

All events judged by the Chief Investigator or delegate to be possibly, probably, or almost certainly related to the flucloxacillin, graded as serious and **unexpected** (see Reference Safety Information described in section 10.3.1) for list of Expected Adverse Events) should be reported as a SUSAR.
The assessment of expectedness will not be assessed by the reporting investigator; this will be determined by the chief investigator or their delegate.

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.
When reporting SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

Regardless of treatment arm, complications (AEs) will be reported for participants where the event is deemed serious and the causal relationship to flucloxacillin is assessed and judged by the investigator to be possibly, probably or almost certainly related to flucloxacillin. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning reporting should be directed to the coordinating centre in the first instance. If the trial treatment ends prematurely, participants will be followed up until trial end.

10.8.1 Non serious ARs/AEs (Complications)

All such events, whether related to flucloxacin or not, should be recorded as a complication on the UK CF Registry.

10.8.2 Serious ARs/SUSARs

SARs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAR form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be submitted within 5 days if the reaction has not resolved at the time of reporting. Multiple events occurring at the same time should be recorded separately i.e. one SAR form per diagnosis.
The CTU will notify the MHRA and main REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the trial. Local investigators should report any SUSARs as required locally. Responsibilities – Investigator
The Investigator is responsible for reporting all AEs that are observed or reported during the trial, regardless of their relationship to trial product.

All SARs must be reported immediately by the investigator to the CTU via a SAR form on the UK CF Registry.

i. The minimum information required for reporting will appear as mandatory fields on the UK CF Registry.
ii. The SAR form should be authorised by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SARs and making trial related medical decisions. In the absence of the designated investigator the form should be completed and submitted by an alternative member of the research site trial team. As soon as possible thereafter the responsible investigator should check the SAR form, make amendments as appropriate, authorise and resubmit the form. The initial report shall be followed by detailed reports as appropriate.
iii. Submit the SAR form though the registry (immediately, within 24 hours) to the CTU.
iv. The UK CF Registry will send an email alert to the TC and CI to **notify** that a SAR form has been uploaded.
v. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).
vi. In the case of a SAR the participant must be followed up until clinical recovery is complete and laboratory results have returned to normal or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
vii. Follow-up information should be entered onto the UK CF Registry and submitted within 5 days if the reaction has not resolved at the time of initial report.
viii. The participant **must** be identified by trial number, date of birth and initials only. The participant's name **should not** be used on any correspondence.

10.8.3 Maintenance of Blinding

This is an unblinded trial.

10.9 Responsibilities – CTU

The CTU is undertaking duties delegated by the trial co-sponsor, Alder Hey Children's NHS Foundation Trust, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-trial SUSARs that occur after the participant has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial and likely to affect the safety of the participants, such as:

a. A SAR which could be associated with the trial procedures and which could modify the conduct of the trial;
b. A significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
c. A major safety finding from a newly completed animal trial (such as carcinogenicity).
d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the participants.

Staff at the CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SARs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report. The PIs at all institutions participating in the trial will be notified of any SUSARs.
Participant safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

10.9.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAR reporting rates across sites. The CTU will send Developmental Safety Update Reports (DSURs) containing a list of all SARs to regulatory authorities and main REC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTU to carry out site visits if there is suspicion of unreported AEs in participant case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

10.9.2 Urgent Safety Measures

An urgent safety measure (USM) is a procedure not defined by the protocol, which is put in place prior to authorisation by the MHRA and REC in order to protect clinical trial participants from any immediate hazard to their health and safety.

The sponsor or delegate will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the MHRA and REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

If the study is temporarily halted it may not recommence until authorised to do so by the MHRA and REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to MHRA and REC), the sponsor should notify the MHRA and MREC within 15 days of the date of termination by submitting the formal End of Trial Notification.

10.10 Contact Details and Out-of-hours Medical Cover

Parents will be directed to contact the research team at their CF centre or shared care centres should medical advice be required during office hours. 24 hour access to specialist medical advice is not considered necessary due to the studies low risk level. If medical advice is required outside of office hours then the parent of the participant will be advised to seek usual medical advice.

11 STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation

Participants will be randomised using a secure (24-hour) web based randomisation programme monitored by the Registry team with CTRC oversight to ensure allocation concealment. Randomisation lists will be generated in a 1:1 ratio using simple block randomisation with random variable block length. Factors within this protocol that are being used to stratify randomisation will not be disclosed to prevent prediction in this open trial.

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11.2 Sample Size calculation

The sample size is based on "time to first identification of PsA on respiratory culture (any type) following randomisation and treatment allocation". Data on this outcome have become available from the UK and US Registries. Combined data on 9250 infants with CF demonstrate a median age of acquisition of approximately 40 months (unpublished data from Smyth's group, available on request). A reduction in the age of acquisition by 12 months (to 28 months) was considered clinically significant by stakeholders (Physicians survey) and PPI representatives and both confirmed that any longer than 12 months would be a concern to them. The trial was therefore powered to provide confidence that "*Prevent and Treat*" would not be considered inferior as long as the median age to acquisition of PsA was no more than 12 months shorter than "*Detect and Treat*".
Assuming approximately 10% attrition, we will recruit 480 infants, with the aim of comparing 220 in each arm, per protocol analysis. With 220 in each arm, a test of non-inferiority of the intervention group (*"Prevent and Treat"*) compared to the standard group (*"Detect and Treat"*) with a 2.5% one-sided significance level will have 80% power to reject the null hypothesis of non-inferiority (a hazard ratio of 1.54 or greater) when the *"Detect and Treat" exponential* parameter (λs) is 0.0173 and the true hazard ratio is 1.0.

11.3 Interim Monitoring and Analyses

No formal interim analyses of primary or secondary outcomes will be performed but analyses of the accumulating data (recruitment, protocol deviations, baseline characteristics, compliance, withdrawals, missing data and safety data) will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed by the CTU trial statistician. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further participants or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. All closed results (results split by treatment) will be confidential to the IDSMC members and will not be for review by the trial management group (except the statistical team preparing the IDSMC report). The IDSMC members will make formal recommendations to the trial working group and TSC (see section 15.4.2) regarding the continuation of recruitment of participants into the trial and will comply with a trial-specific IDSMC charter according to ICH GCP guidelines. The IDSMC will be asked to consider participant safety, particularly any Sudden Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial.

A report shell will be discussed with the IDSMC at its first meeting before recruitment starts and circulated prior to the first report being produced. Analysis Plan

The primary end-point will be analysed on an intention to treat basis and the analysis of time to first growth of PsA will be summarised by Kaplan-Meier curves for each treatment group and compared overall using the logrank test and survival regression methods. Non-inferiority of the "*Prevent and Treat*" group will be accepted in a 0.025 level test, if the upper boundary of the 97.5% confidence interval around the hazard ratio lies below 1.54.

Given that ITT analysis is likely to be anticonservative when testing for non-inferiority, secondary analysis will be undertaken to estimate efficacy of treatment, factoring out deviation from randomised treatment. In order to prevent selection bias associated with standard per protocol analysis (whereby participants are censored at the time of treatment deviation), a complier average causal effect (CACE) will be estimated using a rank-preserving structural failure time model (RPSFTM) as described by Robins (11). The RPSFTM retains the balance afforded by randomisation while adjusting for direct switches between trial treatments, providing an estimate of treatment effect in the absence of such switches. However given the difficulties associated with data capture of daily fluctuations in dose, this RPSFTM estimate will not adjust for everyday variation in treatment receipt, thus providing an estimate that is generalisable to usual conditions of use.

Characteristics of continuous data will be expressed as the mean (+/-SD) and median (interquartile range). Differences will be examined using the Student's t test or the Mann-Whitney rank sum test, depending on the distribution of the data and will include the appropriate confidence interval.

For binary data, proportions will be reported for both treatment groups and the relative risk and corresponding 95% confidence interval will also be reported.

Missing data will be monitored and strategies developed to minimise its occurrence. Missing data will be handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions; however these will be informed by data collected on the reasons for missing data.

A full statistical analysis plan will be written prior to any data being analysed that will describe in detail the methodology that is described above.

12 REGULATORY AND ETHICAL APPROVALS

12.1 Statement of Compliance

Statement of compliance: The trial will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (1996),
- CTRC Clinical Trials Research Centre Standard Operating Procedures
- International Conference on Harmonisation Good Clinical Practice (ICH GCP) http://www.ich.org/ (accessed 11/2014)
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- Research Governance Framework 2005.

Table 5: Summary of SI/EU Regulation Impact/ Scope:

SI /EU Regulation	Title	Main impact/scope
2001/20/EC	The EU Clinical Trials Directive	National Competent Authority Ethics Framework GCP legal requirement Good Manufacturing Practice Protocol/Amendments/safety Protection of Vulnerable Groups Consent / Data protection
2004/1031	Medicines for Human use Clinical Trials Regulation	Transposed EU CT Directive in UK
2005/28/EC	EU Good Clinical Practice (GCP) Directive	Investigator brochure Archiving Mandatory training for trial teams
2006/1928	Amends 2004/1031	Investigator brochure /essential documents Serious Breach Declaration of Helsinki 1996 version for CTIMP
2006/2984	Amends 2004/1031	Consent for incapacitated adult by legal representative or emergency deferred consent
2008/941	Amends 2004/1031	Blood safety and quality Emergency Deferred consent for children
2009/1164	Miscellaneous Amendment	Urgent Safety measures
2009/3063	Amends 2004/1031	Nurse and pharmacists to prescribe unlicensed medicines

12.2 Regulatory Approval

This trial fall within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA).

12.3 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

1/ Informed consent of parents - a continuous consent approach will be used to ensure families have ample time to consider participation and the opportunity to discuss the trial with their clinical team or others. The consent process and information will be in line with clinical discussions on antibiotic administration. Valuable PPI input from families recently in this situation has assist in the design of the process &information sheets.
2/ Use of multi-media information - informing parents/ legal representative about the trial. The TMG will work with the HRA to ensure that these resources are informative but not coercive. The same will apply to the planned support strategy of the CF Trust, to increase awareness of the CF START without applying inappropriate pressure on parent/carers to participate.

12.4 Ethical Approval

HRA approval includes assessment of governance and legal compliance with the independent REC opinion provided through the UK research ethics service. HRA Approval applies only to the NHS in England. Sites in Northern Ireland, Scotland or Wales will be supported through existing UK-wide compatibility systems, by which each country accepts the centralised assurances, as far as they apply, from national coordinating functions without unnecessary duplication. Local Research & Development (R&D) will be notified of the HRA Approval and confirmation of capacity and capability will be should be forwarded to CTU before the site is initiated and participants recruited.

12.5 Protocol Deviation and Serious Breaches

Incidence of protocol non-compliance are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

A breach of the protocol or GCP is ‘serious’ if it meets the regulatory definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. All serious breaches of GCP or protocol will be reported to the MHRA and REC in an expedited manner by the sponsor or delegate.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the CTRC who will in turn notify the sponsor. The sponsor will assess the breach and determine if is meets the criteria of a ‘serious’ breach of GCP or protocol and therefore requires expedited reporting to the MHRA and REC.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC). In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice form the Trial Statistician. However, the sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to the MHRA and REC within 7 days by the sponsor or delegate and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the sponsor, TMG, TSC, IDSMC, REC or MHRA, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

12.6 Trial Discontinuation

In the event that the trial is discontinued, participants will be treated according to usual standard clinical care.

13 DATA MANAGEMENT AND TRIAL MONITORING

Details of the monitoring to be carried out for the CF START trial are included in the CF START Trial Monitoring Plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 15.4.

13.1 Risk Assessment

A risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The type of trial monitoring should be specific to the individual trial and can take the form of on-site visits or central monitoring.

In accordance with the CTRC SOP TM005 will undergo a risk assessment, completed in partnership between:

- Representatives of the Trial Sponsor;
- Chief Investigator;
- Trial Coordinator and supervising Senior Trial Manager;
- Trial Statistician and Supervising Statistician;
- MC CTU Director.

13.2 Source Documents

In order to resolve possible discrepancies between information appearing in the UK CF Registry and any other participant related documents, it is important to know what constitutes the source document and therefore the source data for all information in the UK CF Registry.

The UK CF Registry will be considered the source document for data where no prior record exists and which is recorded directly in the UK CF Registry. A CF START source document checklist will be produced for each site.

Date(s) of conducting informed consent process including date of provision of participant information, randomisation number and the fact that the participant is participating in a clinical trial (including possible treatment arms) should be added to the participant's medical record chronologically.

13.3 Data Capture Methods

The UK CF Registry is the primary data collection instrument for the trial. Data entered routinely in the UK CF Registry will be used alongside CF Start specific data fields in order to collect the data required for CF Start. The UK CF Registry is a web based remote data entry system that captures information for each CF visit (encounter). Data should be entered on an encounter basis, clinics should aim to enter data on the UK CF Registry within three weeks of an encounter and certainly no later than six weeks after the encounter. Where centre staff are aware of a serious adverse reaction (SAR), data should be entered more promptly in line with the SAR reporting timelines specified in section 10.2 of the protocol.

13.4 Monitoring

13.4.1 Central Monitoring

CF Start data collected via the UK CF Registry will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. The CTU will monitor the data being entered. Any data issues arising from data recorded in the CF Start section of the UK CF Registry will be flagged to participating centres via the annotation system functionality. This will allow centres to identify where there are issues with data submitted. Responses to the annotation system and any amendments to data will be saved within an audit trail for transparency of why data was changed. There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.4.2 Clinical Site Monitoring

In order to perform their role effectively, members of the CF Start team and persons involved in Quality Assurance and Inspection may need direct access to primary data collected at participating centres - e.g. participant records, laboratory reports, the UK CF Registry etc. Since this affects the participant's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.5 Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
The data extracted from the UK CF Registry by CTU personnel for the purposes of CF START will not contain any personal data that will enable the CTU staff to identify them.
Verification that appropriate informed consent is obtained will be enabled through CTU access to copies of parent/ legal representative signed informed consent forms uploaded onto the UK CF Registry.
This access to identifiable data is disclosed in the Parent/ legal representative Information Sheet. The CTU will preserve the confidentiality of participants taking part in the trial and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.6 Quality Assurance and Control

The following activities will be implemented to assure protocol compliance, ethical standards, regulatory compliance and data quality:

- The Trial Coordinator at the CTU will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at CTU and the individual site.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- Data will be evaluated for compliance with protocol and accuracy in relation to source documents
- The trial will be conducted in accordance with procedures identified in the protocol.
- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.
- The types of materials to be reviewed, who is responsible, and the schedule for reviews may be specified or referenced in other documents.

- Types and mechanisms of training of staff for the trial should be specified.
- The PI and other key staff from each centre will attend site initiation training, coordinated by the CTU, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol;
- The Trial Management Group is to monitor screening, randomisation and consent rates between centres.
- The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the Trial Monitoring Plan.
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.7 Records Retention

The principal investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the ISF, until the CTU informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

The PI is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The PI is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTU will archive essential documents in compliance with regulatory requirements. All electronic trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

CF START is sponsored by Alder Hey Children's NHS Foundation Trust and co-ordinated by the CTU in the University of Liverpool. The Alder Hey Children's NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated trial, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to participants treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Equivalent cover to that provided by the Clinical Negligence Scheme for Trusts should be in place for non-UK sites; this will be checked as part of the site set-up process.

Alder Hey Children's NHS Foundation Trust holds insurance against claims from participants for harm caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that Alder Hey Children's NHS Foundation Trust has been negligent. However, if this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. Sponsor, Alder Hey Children's NHS Foundation Trust, does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 ROLES AND RESPONSIBILITIES

15.1 Role of Trial Sponsor and Trial Funder

The Alder Hey Children's NHS Foundation Trust is the Sponsoring organisation and is legally responsible for the trial.
The Alder Hey Children's NHS Foundation Trust delegates specific roles to the Chief Investigator and Clinical Trials Unit with regards to trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. Delegations are described in contracts.

15.2 Funding and Support in Kind

Funder(s)	Financial and Non-financial Support Given	Role
NIHR HTA	Financial Support: NIHR HTA provides on-going help and support to the CI to ensure that the project progresses smoothly. Trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results are the responsibility of sponsor and their delegates, though the funder will monitor progress against key milestones via the submission of regular progress reports. The funder requires to approve the initial protocol and amendments prior to submission for ethical/regulatory approval. The funder requires to be provided with copies of project outputs at least 28 days before publication or presentation.	Funder
UK Cystic Fibrosis Trust	Financial Support: The Cystic Fibrosis Trust sponsors and manages the UK CF Registry. The Cystic Fibrosis Trust provides the technical infrastructure to enable trial sites to transfer relevant UK CF Registry data for consented patients into a dedicated CF START Module.	Data support and collection service

15.3 Protocol Contributors

Name	Affiliations	Contribution to protocol
Kevin Southern	Alder Hey Children's NHS Foundation Trust, Eaton Road, West Derby, Liverpool.	Clinical aspects, trial design and conduct
Paula Williamson	Medicines for Children Clinical Trials Unit, Clinical Trials Research Centre, University of Liverpool	Statistical arrangements, trial design and conduct
Ashley Jones	Medicines for Children Clinical Trials Unit, Clinical Trials Research Centre, University of	Statistical arrangements, trial design and conduct

	Liverpool	
Helen Hickey	Medicines for Children Clinical Trials Unit, Clinical Trials Research Centre, University of Liverpool	Governance arrangements and trial conduct
Abigail Bennett	Medicines for Children Clinical Trials Unit, Clinical Trials Research Centre, University of Liverpool	Governance arrangements and trial conduct
Mandy Wan	Evelina London Children's Hospital St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH	IMP arrangements
Alan Smyth	Division of Child Health, School of Clinical Sciences, Queens Medical Centre, Nottingham.	Clinical aspects, trial design and conduct
Siobhán Carr	Royal Brompton and Harefield Hospital, Sydney Street, London	Clinical aspects, trial design and conduct
Paul Aurora	Great Ormond St Hospital, Great Ormond St, London	Clinical aspects, trial design and conduct
Dyfrig Hughes	Bangor University, Bangor, Gwynedd	Health economics aspects
Rebecca Cosgriff	UK CF Trust, One Aldgate, Second floor, London.	Arrangements in relation to CF registry
Jess Nickless	UK CF Trust (PPI), One Aldgate, Second floor, London.	Aspects relevant to patients and the public

15.4 Trial Committees

15.4.1 Trial Management Group (TMG)

A TMG will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet frequently (at least three times a year). Refer to the TMG terms of reference and trial oversight committee membership document for further details.

15.4.2 Trial Steering Committee (TSC)

The TSC will consist of an independent chairperson, two/three independent experts in the field of CF and a statistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

15.4.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent chairperson in the field of paediatric clinical trials, plus two independent members: one who is an expert in the field of CF and one who is an expert in medical statistics.
The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 11.3.
The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial. Refer to the IDSMC charter and trial oversight committee membership document for further details.

16 PUBLICATION AND DISSEMINATION

16.1 Publication Policy

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s), Health Economist(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/ Appendix of the main publication.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Version 1.0 (29/07/2016)

Original Approved version.

17.2 Version 2.0 (29/09/2016)

Section	Amendments
2, 7.5, 9.1, 9.2.2	At three years of age the participants twice daily dose of flucloxacillin will be increased to 250 mg. The applicable sections of the protocol have been amended to reflect this.
11.2	Typo correction to hazard ratio, 1.429 has been changed to 1.54.
15.3	Jo Eatock's contact details removed.

17.3 Version 3.0 (25/05/2017)

Section	Amendments
All	Minor typographical corrections made throughout.
Contact details	Fax number amendment for the Medicines for Children Clinical Trials Unit.
Glossary	Addition of Interactive Web Response System.
2.	Removal of the following inclusion criteria: 'Two CFTR mutations (not known CF-causing mutations) and a sweat chloride test result greater than 29 mmol/L.' Addition of sample size. Clarification of timepoint for nutritional status. Addition of secondary outcome; to identify method of infant feeding.
Schematic of Trial Design	Replaced with new schematic for clarity.
5.2.	Description of STOP/GO Criteria included.
6.1.	Removal of the following inclusion criteria: 'Two CFTR mutations (not known CF-causing mutations) and a sweat chloride test result greater than 29 mmol/L'.
7.4.	Removal of the following assessments at enrolment/ baseline: 9. Pancreatic function (defined as sufficient or insufficient, if PERT is prescribed). 10. Participant feeding in first six months (breast or bottle or mixed).
7.5.	Minor detail changes.
8.1.	Minor corrections to the schedule of assessments.
8.3.4. & 8.3.5	Detail in relation to 'Pancreatic function test' and 'Participant feeding assessment' added.
8.5.2. & 8.5.3.	Detail changed to ensure differentiation between stopping trial intervention alone and complete withdrawal of consent.
9.2.5.	Additional instructions regarding overdose reporting.
10.3.2.	Additional detail regarding death reporting.
10.9.2.	Re-written for clarity.
11.3.	Removal of 'Sign off of the report shell will be formally documented.'

12.5.	Re-written for clarity.
15.2.	UK Cystic Fibrosis Trust details included.
15.3.	Details for Paula Williamson included.

18 REFERENCES

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19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Parent/ legal representative information sheet and consent form
GP Letter
Participating sites
Guidance for SAR Completion