CF STORM
CLEARING THE AIR

A randomised open label trial to assess change in respiratory function for people with cystic fibrosis (pwCF) established on triple combination therapy (Kaftrio™) after rationalisation of nebulised mucoactive therapies (the CF STORM trial)

CF STORM Protocol
V6.0, 13/02/2025

Study Sponsor:
Alder Hey Children's NHS Foundation Trust
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LIVERPOOL CLINICAL TRIALS CENTRE LCTC

UCL

UK Clinical Trials Accelerator Platform Supported Study – Cystic Fibrosis Trust

Alder Hey Children's NHS
NHS Foundation Trust

In partnership
Cystic Fibrosis Trust

UNIVERSITY OF LIVERPOOL

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Protocol Approval

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

Authorised by Co- Chief Investigator*:

Signature: Kevin W Southern
boxSIGN 46786WL8-4Y22WVVJ

Date: 13 Feb 2025

Professor Kevin Southern
Professor of Child Health

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

Authorised by Co- Chief Investigator*:

Signature: Gwyneth Davies
boxSIGN 17J3LV96-4Y22WVVJ

Date: 13 Feb 2025

Dr Gwyneth Davies

Clinical Associate Professor (UKRI Future Leaders Fellow)

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

Authorised on behalf of Sponsor*:

Signature: 

Date: 4 Mar 2025

Kelly Davies
Research Governance Manager.

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

Authorised on behalf of the Lead Statistician*:

Signature: AP Jones
boxSIGN 42YWJYX1-4Y22WVVJ

Date: 13 Feb 2025

Dr Ashley Jones
Head of Statistics

General Information

This document describes the CF STORM 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. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre; LCTC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant co-Chief Investigators, Professor Kevin Southern or Dr Gwyneth Davies, via LCTC.

This protocol defines the participant characteristics required for study 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. 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. These 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 15.

The Liverpool Clinical Trials Centre 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 Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Outcome data for the trial will be collected from the national UK Cystic Fibrosis (CF) Registry. This patient registry was established and is maintained by the UK CF Trust, a disease-specific charity based in the UK. The UK CF Trust registry team have worked closely with the LCTC and Chief Investigators to develop a research module on which data are collected securely and anonymously. The LCTC and research team are responsible for the quality of data and governance of the study. As well as answering the primary research question, these data will inform the Health Economic Analysis.

In light of the challenges of the COVID-19 pandemic, the trial has been designed to facilitate remote enrolment and data collection.

Contact Details: Institutions

Sponsor:	Trial Management, Monitoring and Analysis:	Health Economics:
Alder Hey Children's Hospital NHS Foundation Trust Sponsorship Team, Clinical Research Division 1st Floor, Institute In The Park Alder Hey Children's Hospital NHS Foundation Trust Eaton Road Liverpool Merseyside L12 2AP 0151 252 5570 research@alderhey.nhs.uk	Liverpool Clinical Trials Centre, 2nd Floor Institute in the Park, Alder Hey Children's NHS Trust, Eaton Road, Liverpool. L12 2AP. 0151 794 9764 cfstorm@liverpool.ac.uk	Norwich Medical School Faculty of Medicine and Health Sciences University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ. 01603 593911 adam.wagner@uea.ac.uk

Other Medical or Technical Departments and/or Institutions:
CF Registry, Cystic Fibrosis Trust, One Aldgate, Second floor, London. EC3N 1RE. 0203 795 2180 registry@cysticfibrosis.org.uk www.cysticfibrosis.org.uk

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	Co- Chief Investigator (Co-CI):	Co- Chief Investigator (Co-CI):
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Contact Details: Individuals

In cases where the Co-CIs are unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:
Professor Stuart Elborn Department of Medicine The Queen's University of Belfast Faculty of Medicine, Health & Life Sciences 90 Lisburn Road, Belfast. BT9 6AG 02890975882 s.elborn@qub.ac.uk

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 Table of Contents

2 Glossary

AE	Adverse Event
AR	Adverse Reaction
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire Revised
CI	Chief Investigator
CIn	Confidence Interval
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
EMEA	European Medicines Agency
EQ-5D-5L	EuroQol five-dimension scale questionnaire, 5-component scale
EU	European Union
EUCTD	European Clinical Trials Directive
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MHRA	Medicines and Health Care Products Regulatory Agency
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
PI	Principal Investigator
ppFVC	Percent predicted Forced Vital Capacity
ppFEF 25-75	Forced Expiratory Flow between 25-75% of vital capacity
ppFEV1	Percent predicted Forced Expiratory Volume in One Second
PSF	Pharmacy Site File
PwCF	People with Cystic Fibrosis
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information

RSO	Research Support Office
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

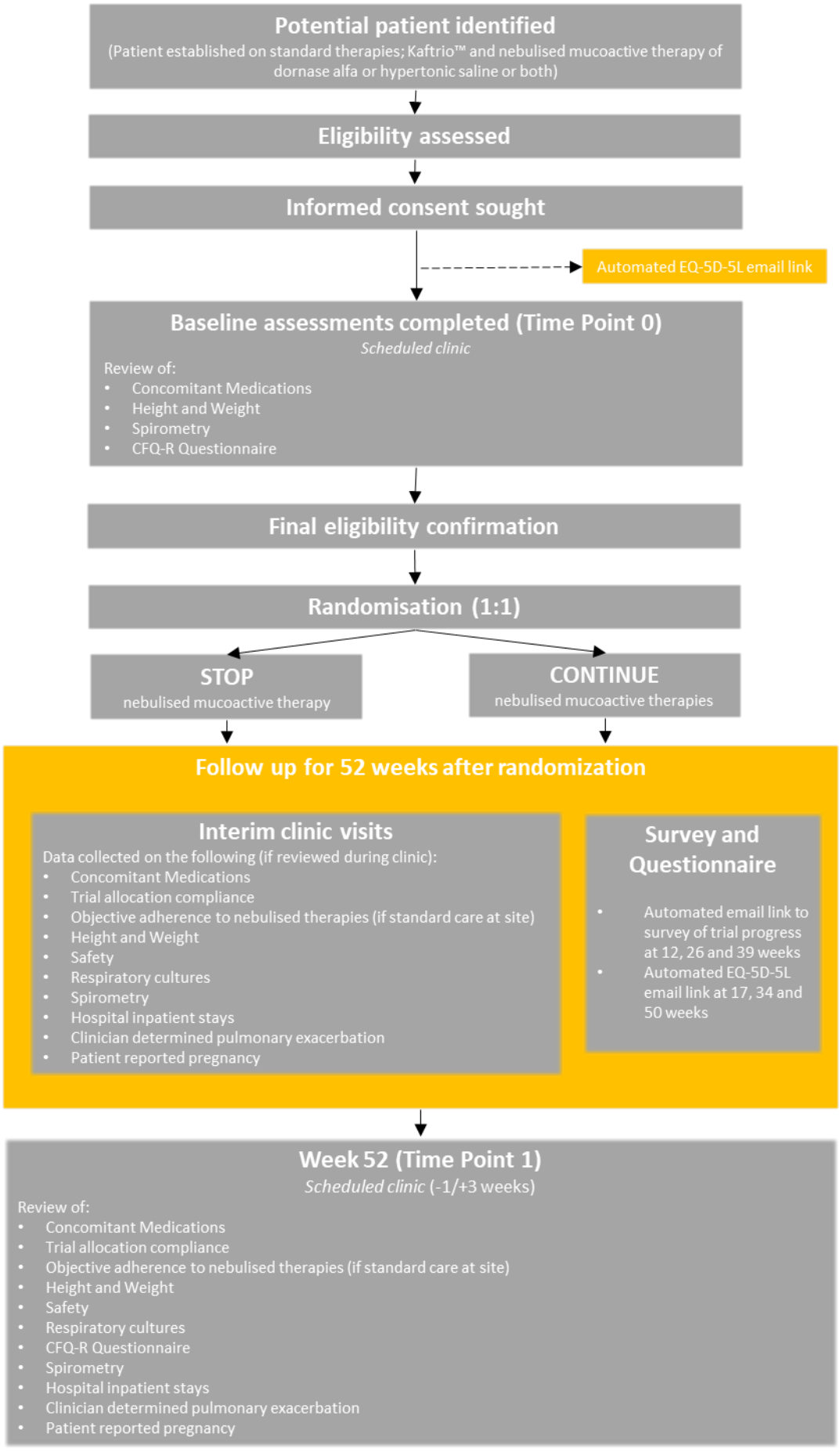
3 Protocol Overview

Full Title:	A randomised open label trial to assess change in respiratory function for people with cystic fibrosis (pwCF) established on triple combination therapy (Kaftrio™) after rationalisation of nebulised mucoactive therapies (the CF STORM trial)
Acronym:	CF STORM
Phase:	IV
Target Population:	Cystic fibrosis 6 years-of-age or older
Sample size:	572 (minimum target)
Inclusion Criteria:	1. Clear diagnosis and clinical features of CF. 2. One or two Phe508del variants. 3. Established on daily mucoactive nebulised therapy (hypertonic saline or dornase alfa or both) for at least 3 months. 4. 6 years-of-age or older. 5. Established on Kaftrio™ for at least 3 months. 6. Enrolled on the UK CF Registry. 7. Able to undertake spirometry. 8. No need for extra antibiotics (oral or intravenous) in previous two weeks. 9. Completed informed consent and assent if applicable obtained from the participant, participant's parent or legal representative and agreement of participant to comply with the requirements of the study
Exclusion Criteria:	1. Significant adverse reaction to Kaftrio™ requiring dose change during the 3 months prior to screening. 2. ppFEV1 below 40% after Kaftrio™ therapy at any point during the 3 months prior to screening. 3. History of solid organ transplant or placed on active transplant waiting list. 4. Other non-CF condition that, in the opinion of the local CF team, significantly impacts on clinical progress. 5. Participation in a CTIMP within the last 3 months (the 3-month period does not apply to open label Kaftrio™ CTIMPs). 6. Prescribed Mannitol dry powder for inhalation as part of usual daily CF care within the last 6 weeks.
Study Centres and Distribution:	Specialist adult and paediatric CF centres in the UK
Patient Study Duration:	Total Duration per participant: 52 weeks

Study Duration	Start date of trial: 01/04/2021 End date of trial: 31/01/2026	
IMP / Intervention:	"CONTINUE": Participants will continue prescribed mucoactive nebulised therapy (dornase alfa, hypertonic saline or both).	
	IMP: Form: Dose: Route: CE Device: Form: Dose: Route:	dornase alfa Nebulised solution 2.5mg 1-2 times daily Inhalation (Nebulised) hypertonic saline Nebulised solution 4ml (3-7%) Sodium Chloride Solution 1-3 times daily Inhalation (Nebulised)
	"STOP": Participants will stop taking prescribed nebulised mucoactive Therapies (dornase alfa, hypertonic saline or both).	
Objectives:		
Primary:	Refer to section 9 for further details on endpoint/outcome measures	The primary outcome is the change in percent predicted Forced Expiratory Volume in One Second (ppFEV1) measured in a clinical encounter at baseline and trial-end at 52 weeks.
Secondary:	Refer to section 9 for further details on endpoint/outcome measures	To assess longitudinal patterns of change in ppFEV1 over the trial period To assess change in respiratory function between baseline and 52 weeks To assess change in respiratory function over the trial period To determine the need for extra antibiotic treatment To determine the need for extra chronic medications To determine the number and proportion of respiratory cultures positive for significant pathogens To determine need for hospital admissions

		To access change in nutritional status between baseline and 52 weeks To compare the number of pulmonary exacerbations between the two arms Assess change in disease specific QoL To identify adverse events relating to large drop in respiratory function or treatment of pulmonary exacerbation with IV antibiotics To determine the costs to the NHS To determine if the 'STOP' intervention represents value for money

3.1 Schematic of Study Design



4 Roles and Responsibilities

4.1 Sponsor

The Alder Hey Children's NHS Foundation is the Sponsoring organisation and is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigators and the Liverpool Clinical Trials Centre (LCTC).

4.2 Funder

This study is funded by NIHR Health Technology Assessment Programme.

Funder(s)	Role
NIHR Health Technology Assessment Programme	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

Chief Investigators: Professor Kevin Southern and Dr Gwyneth Davies are the co-Chief Investigators for the trial and are responsible for the overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the Co-Chief Investigators, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management (related to LCTC activity only), safety reporting, data management, creating randomisation lists, statistical analysis, participating site coordination, user acceptance testing and accepting the functionality of the CF STORM research module..

The UK CF Trust Registry team: will develop the CF STORM research module, which is placed within the UK CF Registry platform and enables the collection of data from the core UK CF Registry. This includes developing and system testing the functionality and accessibility of the research module (including a randomisation system, safety reporting system, e-Consent / e-Assent system, EuroQol five-dimension scale questionnaire, 5-component scale (EQ-5D-5L) and Survey of Trial Progress Questionnaire systems) and software maintenance (change control, version control, back-ups of the software and database). In this process the UK CF Registry team will work closely with the LCTC and study team to provide data and maintain functionality during the trial period.

4.3 Oversight Committees

CF STORM trial is subject to oversight from the following committees:

Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will consist of an independent chairperson, several independent experts in the field of CF, a biostatistician, including both CIs and observers. The role of the TSC is to provide overall oversight for the trial and provide advice through its independent Chairman. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the trial (at least annually). However, the Funder may withdraw funding subject to contract conditions and this may influence the Sponsors decision on whether to continue with the trial.

Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) will consist of an independent chairperson, plus 2 independent members; who are experts in the field of CF, and an independent biostatistician.

The IDSMC will be responsible for reviewing and assessing recruitment, monitoring of safety, trial conduct and external data. Unlike the TSC and TMG the IDSMC will be able to see the results split by treatment group. 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 13.3 and 14.3 respectively.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

4.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Professor Kevin Southern	University of Liverpool and Alder Hey Children's NHS Foundation Trust	Clinical aspects, trial design and conduct
Dr Gwyneth Davies	UCL Great Ormond Street Institute of Child Health and Great Ormond St Hospital, Great Ormond St, London	Clinical aspects, trial design and conduct
Dr Ashley Jones	LCTC, University of Liverpool	Statistical arrangements, trial design and conduct
Helen Hickey	LCTC, University of Liverpool	Governance arrangements and trial conduct
Abigail Williams	LCTC, University of Liverpool	Governance arrangements and trial conduct
Dr Siobhán Carr	Royal Brompton and Harefield Hospital, Sydney Street, London	Clinical aspects, trial design and conduct
Professor Jennifer Whitty	Norwich Medical School, University of East Anglia	Health economics aspects (until September 2021)
Rebecca Cosgriff	UK CF Trust, One Aldgate, London	Arrangements in relation to UK CF Registry (until July 2022)
Professor Stuart Elborn	The Queen's University of Belfast	Clinical aspects, trial design and conduct

Name	Affiliations	Contribution to protocol
Dr Damian G Downey	Wellcome-Wolfson Institute for Experimental Medicine, The Queen's University of Belfast	Clinical aspects, trial design and conduct
Professor Paula Williamson	Biostatistics, University of Liverpool	Statistical arrangements, trial design and conduct
Professor Andrew Jones	Respiratory Medicine, The University of Manchester	Liaison with CRG and commissioners. Clinical aspects, trial design and conduct.
Dr William Flight	Respiratory Medicine, Oxford University Hospitals NHS Foundation Trust	Lead Adult Clinician. Clinical aspects, trial design and conduct (until August 2022)
Professor Alan Smyth	Division of Child Health, University of Nottingham	Clinical aspects, trial design and conduct
Dr Charles Haworth	Respiratory Medicine, Royal Papworth Hospital NHS Foundation Trust	Clinical aspects, trial design and conduct
Professor Jane Davies	Paediatrics, Imperial College of Science, Technology and Medicine	Liaison with CTAP. Clinical aspects, trial design and conduct
Lorna Allen	Cystic Fibrosis Trust	Aspects relevant to patients and the public
Dr Sarah Clarke	Cystic Fibrosis Trust	Arrangements in relation to UK CF Registry
Mary Yip	Cystic Fibrosis Trust	Arrangements in relation to UK CF Registry (until November 2021)
Dr Adam Wagner	Norwich Medical School, University of East Anglia	Health economics aspects (From October 2021)

5 INTRODUCTION

5.1 Background

CF STORM will be a non-inferiority randomised open-label trial to evaluate whether pwCF can rationalise their daily treatment without a significant reduction in their respiratory function. Patients established on Kaftrio™, for more than three months will be enrolled and randomly allocated to either 'STOP' or 'CONTINUE' their existing mucoactive nebulised treatment (dornase alfa, hypertonic saline or both). The primary outcome will be change in Forced Expiratory Volume in One Second (percent predicted FEV_1 ($ppFEV_1$)) at 52 weeks. This and other secondary outcomes (including need for extra antibiotic treatment and weight) will be collected on the UK CF Registry. In addition, eligibility will be assessed, e-Consent recorded, and randomisation will be undertaken on the CF STORM Module as will collection of quality of life (QoL) data. This provides opportunity for pwCF to be recruited remotely, in line with delivery of care during the COVID-19 pandemic. The results of CF STORM, together with data from the SIMPLIFY trial (a shorter non-pragmatic trial being undertaken in the US) will inform the knowledge transfer exercise that will be undertaken by the CF STORM team at the end of the trial, co-ordinated by the PPI leads.

5.2 Rationale

In partnership with the James Lind Alliance (JLA), members of the CF STORM team conducted the largest global stakeholder engagement exercise in the field of cystic fibrosis (CF). (1, 2) The project established research priorities for pwCF, their families and healthcare workers in the field. The number one research priority was, "What are the effective ways of simplifying the treatment burden of people with cystic fibrosis?".

This is an exceptional time in the field of CF, with introduction of therapies that address the underlying molecular defect.(3) For pwCF who are eligible (~75% of the UK CF population), Kaftrio™ promises to be a transformative therapy. (4, 5)

Kaftrio™ became available for pwCF in the UK in September 2020, following confirmation of European Medicines Agency authorisation (Kaftrio™ in the UK and Trikafta™ in the US). This represents an ideal opportunity to test the highest priority JLA-derived research question in a robust clinical trial and evaluate the impact of Kaftrio™ on the journey of pwCF. (6)

The CF STORM trial will be undertaken in parallel with the introduction of Kaftrio™ in the UK. This will enable the associated health technology appraisal by the National Institute for Health and Care Excellence (NICE) to evaluate the potential for rationalising existing daily treatments and further improve the lives of pwCF, through clear evidence. Without this trial many pwCF will rationalise their standard treatments in non-systematic manner with potential for harm.

We will be investigating the impact of stopping nebulised mucoactive therapies. The evidence for nebulised mucoactive therapies for pwCF is derived from high quality systematic reviews and has informed NICE guidelines for CF care, however this evidence base is from studies undertaken before highly effective modulator therapies. For dornase alfa, there is good quality evidence that daily treatment with this nebulised therapy leads to a modest and sustained improvement in respiratory function in pwCF with established lung disease.(7) The evidence for hypertonic saline in this age group is less robust with no significant sustained improvement in respiratory function from this intervention.(8) Patients on hypertonic saline had fewer pulmonary exacerbations. Nebulised dornase alfa is a standard of care for pwCF (NICE guideline 78 (1.6.17), published 25th October 2017).(9) Hypertonic saline is also in the guideline and is regularly used by pwCF, often in addition to dornase alfa, and sometimes alone, despite the lower quality evidence. Both therapies require nebulisation, which is time consuming and considered a significant burden by pwCF. (6)

Data from the UK CF Registry demonstrate that most pwCF in the UK are on mucoactive nebulised therapy, most commonly dornase alfa +/- hypertonic saline (Table 1). A smaller proportion of patients are on

hypertonic saline alone. Extensive patient engagement has driven the concept and design of this trial. People with CF felt strongly that the trial should include patients taking both mucoactive therapies, rather than just dornase alfa, to be inclusive and reflect current practice in the UK (Table 1).

Table 1; UK CF Registry data (2019) reviewing the number of pwCF eligible for Kaftrio™ following initial licencing in those aged 12 years and above, and the proportion of those patients on mucoactive nebulised therapy.

	Adult	Paediatric	Overall
Number of centres/clinics*	35	99	134
Total number of patients	5670	4177	9847
Number of patients eligible for Kaftrio™ (%)	4309 (76)	1640 (39)	5949 (60)
Number on dornase alfa (DA) only (%)	1775 (41)	696 (42)	2471 (42)
Number on hypertonic saline (HS) only (%)	283 (7)	47 (3)	330 (6)
Number on DA and HS (%)	1096 (25)	670 (41)	1766 (30)

*Adult sites are all centres (>100 patients), many Paediatric sites are smaller (clinics)

In 2022, Kaftrio™ was additionally licensed for children 6 to 11 years of age in the UK. Similar to people with CF aged 12 years and above, daily mucoactive therapies are commonly prescribed in this age group. In the 2021 UK CF Registry, 79.6% of children aged 8-11 years, and 53.1% of children aged 4-7 years were prescribed dornase alfa (2021 UK CF Registry Annual Report, published Sept 2022).

CF STORM extended its recruitment to participants aged 6 years and over in 2023. This reflected the challenge of recruiting sufficient adults with CF and the opportunity to recruit younger patients (6-11 years), for whom Kaftrio™ had now become licensed and available in routine care.

5.3 Risk and Benefits

5.3.1 Potential Risks

This trial is categorised as Type A (No higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the Trial Master File.

5.3.2 Potential Benefits

We anticipate that discontinuation of mucoactive therapy to be a dominant strategy with reduced cost from reduced mucoactive therapy use, no change in ppFEV$_1$, and improved benefits through reduced treatment burden and potentially improved quality adjusted life years (QALYs).

Data from the Cystic Fibrosis Questionnaire Revised (CFQ-R) Treatment Burden domain, together with data from the subset of patients recording adherence will inform the treatment burden aspect of this work. Using a societal perspective, these outcomes will be included in an additional evaluation that considers the wider costs of treatment burden to the patient and society.

5.4 Objectives

5.4.1 Primary Objective

The primary objective is to determine if people with CF, established on Kaftrio™, can stop their daily nebulised mucoactive drugs without a significant fall in respiratory function after 52 weeks in comparison to those continuing on nebulised mucoactive drugs.

5.4.2 Secondary Objective(s)

The secondary objectives are:

- What is the impact of stopping nebulised muco-active therapies on the following secondary outcomes, disease specific quality of life, number of physician-defined pulmonary exacerbations, nutrition (BMI), longitudinal changes in ppFEV1, need for extra antibiotics, need for hospital admission and changes in respiratory culture microbiology.
- To determine the health economic impact of stopping nebulised muco-active therapies.

6 STUDY DESIGN

CF STORM is designed as a randomised, open-label, non-inferiority trial with 1:1 allocation ratio.

Through extensive PPI consultation we constructed a trial design that is pragmatic and reflects the lived experience of pwCF. The trial will randomly allocate patients 1:1 to either 'STOP' or 'CONTINUE' their existing daily nebulised mucoactive therapies (stratified by clinical site and nebulised mucoactive treatment(s) at enrolment; with data from the UK CF Registry we have modelled stratification of randomisation for different number and sizes of sites). Non-inferiority margins, will provide confidence that stopping mucoactive therapies is not associated with a significant decrease in ppFEV$_1$ over the 12-month trial period.

6.1 Blinding

This is an open label study with no blinding requirements.

6.2 Who is blinded

All researchers and participants know whether an intervention has been stopped or will be continued.

6.3 Study Setting

Participants will be identified and recruited from adult and paediatric CF centres in the UK. With the COVID-19 pandemic there has been a significant move to remote specialist clinic consultations for pwCF. Patients and parents now have regular email correspondence with their CF team. This has become a more established process for providing information and one that will be utilised by CF STORM for patient engagement and trial management, if available. In addition, national commissioners have provided funding for handheld spirometers during the COVID-19 pandemic to support home measurement of respiratory function. The CF STORM trial will utilise these developments in digital communication and remote monitoring to facilitate participation in this trial through electronic consent/randomisation and collection of home spirometry data, when face-to-face clinic visits are not possible.

6.3.1 Selection of Participating Sites

This trial has received full Clinical Trials Accelerator Platform (CTAP) badging status. CTAP is a national CF clinical trials network managed by the UK Cystic Fibrosis Trust. A team of CTAP Trial Coordinators support clinical teams across the UK in delivering trials. A short survey was circulated to CTAP centres across the UK to request their expression of interest in the trial. Following this the CTAP circulated a feasibility survey to all interested sites in the UK. This feasibility survey will form the basis of site selection.

Sites will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

6.3.2 Selection of Principal Investigators

Principal Investigators will require relevant research experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct

research as such will be obtained prior to site initiation. A suitable co-investigator should be identified at each site to deputise in case of PI absence.

6.3.3 **Pilot study**

During the six months internal pilot we aim to recruit 20% of the total participant number (153) and this will be the primary target.

We will employ the following additional traffic-light criteria with regards proceeding to the full trial (Table 2):

- RED: Average recruitment rate falls below 1.275 patients per site per month, or the number of sites opened is less than 10, or the number of participants who have received the intervention they were randomised to is below 80% – unless there are mitigating circumstances, determine that recruitment is not feasible and decide not to proceed;

- AMBER: Average recruitment rate per site per month is between 1.275 and 2.55*, or the number of sites opened is between 10 and 15, or the number of participants who have received the intervention they were randomised to is between 80% and 99% – review recruitment strategies, report to TSC and NIHR HTA and continue with a modified recruitment strategy.

- GREEN: The primary target for this metric will be recruiting 153 patients. Other metrics will include average recruitment rate per site per month exceeding 2.55* (100% target rate) and 16 or more sites opened and the number of participants who have received the intervention they were randomised to is equal to 100%– proceed with trial.

Following the pilot phase, the main phase will be completed within 12 months. In addition, the IDSMC will monitor and report on all aspects of trial performance during the pilot phase, most notably compliance to trial intervention and secure recording of the primary outcome measure.

Table 2; Revised internal pilot grade scoring system

	Red	**Amber**	**Green**
Average recruitment rate (patient/centre/month)	<1.1.275	1.275-2.55*	>2.55*
Number of sites open	<10	10-15	>15
Percentage of those randomised that agree to comply with the allocated intervention	<80%	80-99%	100%

*153/60 (number of patients recruited/number of recruitment months across open sites).

7 ELIGIBILITY CRITERIA

The CF STORM trial aims to recruit a minimum of 572 patients based on revised sample size calculations described in Section 13.1.1. All participants and participant's Legal Representative if applicable must provide written, informed consent / assent before any study procedures occur (see Section 10.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

7.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1. Clear diagnosis and clinical features of CF.
2. One or two Phe508del variants.
3. Established on daily mucoactive nebulised therapy (hypertonic saline or dornase alfa or both) for at least 3 months.
4. 6 years-of-age or older.
5. Established on Kaftrio™ for at least 3 months.
6. Enrolled on the UK CF Registry.
7. Able to undertake spirometry.
8. No need for extra antibiotics (oral or intravenous) in previous two weeks.
9. Completed informed consent and assent if applicable obtained from the participant, participant 's parent or legal representative and agreement of participant to comply with the requirements of the study

7.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Significant adverse reaction to Kaftrio™ requiring dose change during the 3 months prior to screening.
2. ppFEV$_1$ below 40% after Kaftrio™ therapy at any point during the 3 months prior to screening.
3. History of solid organ transplant or placed on active transplant waiting list.
4. Other non-CF condition that, in the opinion of the local CF team, significantly impacts on clinical progress.
5. Participation in a CTIMP within the last 3 months (the 3-month period does not apply to open label Kaftrio™ CTIMPs).
6. Prescribed Mannitol dry powder for inhalation as part of usual daily CF care within the last 6 weeks.

7.3 Co-enrolment Guidelines

Co-enrolment in another interventional CTIMP is not considered acceptable because it will introduce biases and negatively impact trial integrity. Only co-enrolment to a non-CTIMP trial is acceptable.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

Eligible patients will be randomised to either 'STOP' or 'CONTINUE' daily nebulised mucoactive therapies. Patients in the 'CONTINUE' arm of the trial will continue to receive daily dornase alfa, hypertonic saline or both (as per the guidance of their local CF team) and patients in the 'STOP' arm will no longer receive daily dornase alfa, hypertonic saline or both.

8.2 Treatment Name / Description

8.2.1 'CONTINUE' arm - Dornase alfa

Active ingredient:	Dornase alfa
Formulation:	Nebuliser solution
Manufacturer:	Local pharmacy stock
Packaging, storage and stability:	Refer to SPC
Supplier's name:	Local pharmacy stock
Regulatory Status:	Market Authorised

8.2.2 'CONTINUE' arm - Hypertonic saline

Active ingredient:	Hypertonic saline
Formulation:	Nebuliser solution
Manufacturer:	Local pharmacy stock
Packaging, storage and stability:	Refer to Patient Information Leaflet (PIL)
Supplier's name:	Local pharmacy stock
Regulatory Status:	CE Device

8.3 Manufacturing and Distribution

Intervention supplies are sourced from usual NHS stock.

8.4 Preparation, Dosage and Administration

8.4.1 Dornase alfa

One ampoule (2.5mg) of Dornase alfa should be inhaled using a nebuliser once or 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.

8.4.2 Hypertonic saline

One ampoule (4ml (3-7%) sodium chloride solution) of hypertonic saline should be inhaled using a nebuliser two to three times per day. Sites should refer to the current PIL for all treatment decisions.

8.5 Treatment Modifications

After the patient has entered the trial, the clinician is free to consider alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient. However, the reason for

doing so should be recorded in the CF STORM Module and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant/Legal Representative remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing further treatment.

8.6 Assessment of Compliance to trial allocation

CF STORM is an open label pragmatic trial and compliance to the trial intervention is a key factor when considering the non-inferiority design. We have established a four-point plan to support and monitor compliance with the trial intervention. This will be evaluated by the IDSMC in the pilot phase of the trial.

The four distinct processes to support and monitor compliance with the trial allocation;

- When introduced to the trial, patients will be able to access the trial website, which will include the ethics-approved patient information sheets and videos explaining the trial, in particular the importance of adhering to treatment allocation. Prior to recruitment physicians will be trained to ensure that patients are fully informed and willing to enter into the study and to comply with either the 'STOP' or 'CONTINUE' allocation.
- At each encounter, investigators will be trained to discuss compliance with the allocation with the patient. This will be recorded in the CF STORM trial module.
- In addition, patients will receive an automated email every three months. This will thank them for their support for the trial and include a short survey to assess their compliance with trial allocation, to ask them if they are happy to continue and whether they have complied with their allocation. The data from this survey will be stored on the CF STORM study module.
- More detailed objective monitoring of adherence data will be collected throughout the study. These data will be recorded from patients who have the capacity to provide electronic data capture from their nebuliser device and do this as part of their standard clinical care. For these patients, we will record data 3 months prior to randomisation, baseline data, encounter data and trial-end data. For patients in the pilot phase, we will collect baseline data and at the three-month time point. The adherence to nebulised therapies will be calculated as the proportion of taken doses compared to the expected number of doses agreed with and prescribed by the CF team (unadjusted adherence). These data will be reviewed by the IDSMC and inform the evaluation of the pilot phase. To optimise data collection, we will be opening pilot sites that regularly undertake electronic data capture as part of clinical practice, however patients not routinely collecting these data will not be excluded from the pilot as this would disadvantage patients with less severe lung condition, who may only be taking dornase alfa (and therefore not using a device that enables data capture).

8.7 Concomitant Medications/Treatments and Specific Restrictions

8.7.1 Medications Permitted

Refer to SPC / PIL guidance.

The COVID-19 vaccination can be administered where appropriate without any consideration for timing etc. in relation to the trial intervention.

8.7.2 Medications Not Permitted/ Precautions Required

Refer to SPC / PIL guidance.

8.7.3 Data on Concomitant Medication

The name and duration of all chronic concomitant medications and additional antibiotics will be documented in the UK CF Registry / CF STORM Module. The dosage will also be recorded for dornase alfa and hypertonic saline. The researcher should reassess all concomitant medications at each encounter with the participant. Any medications introduced/discontinued should be documented.

8.8 Overdose

The occurrence of an overdose which has resulted in an AR should be reported via the complication tab on the UK CF Registry. The effect of dornase alfa overdose has not been established. Systemic toxicity of dornase alfa has not been observed and is not expected due to the poor absorption and short serum half-life. Systemic treatment of overdose is therefore unlikely to be necessary. Overdose of hypertonic saline through substantial oral ingestion may require the use of a diuretic to remove excess sodium.

Specific information on reporting adverse events can be found in Section 11.

9 OUTCOMES

9.1 Primary Outcome

The primary outcome is the change in percent predicted Forced Expiratory Volume in One Second ($ppFEV_1$) measured in a clinical encounter at baseline and trial-end at 52 weeks.

Respiratory function, as determined by spirometry, is a key outcome for pwCF in determining the efficacy or safety of an intervention.

In response to the COVID-19 pandemic, funding has been secured to provide pwCF with devices that enable home spirometry. These have been rolled out successfully in the UK and have facilitated home monitoring of pwCF during this period. Centres have provided patients with clear guidance on how to perform spirometry and the newer devices enable central monitoring of quality.

Studies suggest that home spirometry results in consistent values over time in an individual. To avoid any systematic bias between home and hospital spirometry values, baseline and trial-end spirometry measurements must be undertaken on the same device in the same location.

The preferred option for collecting the primary outcome is for $ppFEV_1$ to be measured by spirometry performed in hospital, however if this is not possible then the home spirometry should be undertaken using an established standard operating procedure for the clinic and with central monitoring by the CF team and/or respiratory physiologist of the quality of the technique (see researcher manual for further guidance).

For patients undertaking home spirometry, at baseline participants will be asked to collect three measures at least one day apart before starting the intervention (over a maximum period of 5 days). Similarly, three home spirometry measures will also be requested for the final study visit (again over a maximum period of 5 days which incorporates the final visit date) prior to reverting to standard care. Each should be recorded on the registry.

To ensure uniform calculation of $ppFEV_1$ across all trial sites, the raw spirometry values for FEV_1 (ml) will be recorded on the UK CF Registry and these will be converted to $ppFEV_1$ through an internationally accepted formula embedded in the UK CF Registry database. (10) This will require a reliable height measurement and for patients who are still growing, a stadiometer will be used for accurate height measurement at home.

Baseline $ppFEV_1$ should be recorded on the day of randomisation (no earlier than 14 days before randomisation). The trial-end $ppFEV_1$ should be recorded at the final trial visit at 52 weeks (time point 1; range 51-55 weeks).

9.2 Secondary Outcome(s)

Objectives	Outcome Measures	Timepoint(s) of evaluation
Efficacy:		
To assess longitudinal patterns of change in $ppFEV_1$ over the trial period	$ppFEV_1$	Time points 0 and 1, and any time points between (encounters during trial period)
To assess change in respiratory function between baseline and 52 weeks	Percent predicted Forced Vital Capacity (ppFVC)	Time points 0 and 1
To assess change in respiratory function over the trial period	Forced Expiratory Flow between 25-75% of vital capacity ($ppFEF_{25-75}$)	Time points 0 and 1
To determine the need for extra antibiotic treatment	Number of courses and total number of days of extra antibiotics (oral, intravenous and nebulised)	Time points 0 and 1
To determine the need for extra chronic medications	Number of courses and total number of days of chronic medications (oral and nebulised)	Time points 0 and 1
To determine the number and proportion of respiratory cultures positive for significant pathogens	Positive respiratory culture for new significant pathogens	Time points 0 and 1, and any encounters between
To determine need for hospital admissions	Number of separate hospital inpatient stays. In addition, total number of inpatient days (subdivided into total IV days and total non-IV days)	Time point 1 and any encounters between
To assess change in nutritional status between baseline and 52 weeks	Weight (kg) Height (cm) Body Mass Index	Time point 0 and 1
To compare the number of pulmonary exacerbations between the two arms	Clinician determined pulmonary exacerbation	Time point 1 and any encounters between
Assess change in disease specific QoL	CFQ-R (total and domain scores)	Time point 0 and 1
Adverse events and pregnancy		
To identify adverse events relating to large drop in respiratory function or treatment of pulmonary exacerbation with IV antibiotics	$ppFEV_1$ and intravenous antibiotics (dates and drug name)	Throughout trial period within 4 weeks of event, and Time 1.
Health Economics		
To determine the costs to the NHS	Treatment costs and compliance to allocation	Time point 1 (and any encounters between)
To determine if the 'STOP' intervention represents value for money	Incremental cost per QALY gained compared to 'CONTINUE' arm, estimated using the EQ-5D-5L QoL measure	Time points 0 and 1 (and also 17, 34 and 50 weeks)

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

An anonymised screening record of patients who are assessed for eligibility but not randomised will be maintained in the CF STORM Module and this will provide important information for monitoring purposes.

Access to the UK CF Registry if not already acquired can be gained from the UK CF Registry Site Administrator. Access to the CF STORM Module will be issued to the Site PI upon site initiation. The PI will then be able to provide access to other site personnel who are already UK CF Registry users. No login details will be required for the CF STORM Module. Training for the CF STORM Module will be coordinated by the LCTC as part of the site initiation visit, with support throughout the study from the Registry Support Manager.

The researcher should ensure that the patient is participating in the UK CF Registry. If not already registered the parent/legal representative will be informed of the national UK CF Registry and consent for the UK CF Registry must be gained before the CF STORM consent.

The screened patient must be identified within the UK CF Registry, once identified the screener may access the 'CF STORM Screening and Enrolment Form' through the CF STORM button. Once the patient is deemed potentially eligible the researcher should send a standardised email to the potential participant with a link to the study website (www.cfstorm.org.uk) which will contain a copy on the ethically approved patient information sheet. All screened patients should be recorded in the CF STORM Module with reason for ineligibility if applicable.

The majority of potentially eligible participants will be identified during their routine remote or face-to-face CF consultations. The site study team and CTAP Trial Coordinators will assist in this identification process.

10.2 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log. Eligibility criteria are described in detail in Section 07.

Eligibility confirmation must be documented in the participant's medical notes and then on the 'CF STORM Screening and Enrolment Form'. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation).

10.3 Informed Consent

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 patients participating in CF STORM. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team 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. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

10.3.1 Prospective Informed Consent/Assent Process

Informed consent will be sought from patients / Legal Representatives (for minors) who will be approached by the study team and invited to consider participation.

Patients / Legal Representatives will be approached by a member of the local research team, this may be face-to-face or remote. A copy of the ethically approved written information sheet will be available on the study website. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the patient / Legal Representative has fully understood all the information and will ask if they are happy to consent to participate in the trial. Where this is the case, the clinician will enter the patient / Legal Representative's email address into the CF STORM Module and the module will reveal a unique code to the researcher. The module will send an email to the patient / Legal Representative which will contain a link to the e-Consent and the clinician will verbally provide the patient / Legal Representative with a unique code to access their e-Consent link. e-Consent will be obtained by the patients / Legal Representatives by confirming agreement to a number of statements using the radio buttons with options 'yes' or 'no' and typing their first name and second name into the e-Consent webpage. If 'no' is selected for any of the statements e-Consent will not be obtained.

Minors (aged under 16) will be approached for e-Assent. A Young Person Information Sheet describing (in simplified terms) the details of the trial intervention, trial procedures and risks will be available on the trial website. If the site team and parent/carers, consider the minor to be of insufficient developmental capacity to complete the e-Assent then they will not be able to participate in the trial. Where a minor is approached for e-Assent, they will not be entered into the trial until assent (in addition to legal consent from their Legal Representative) is provided. If a Legal Representative is consenting for a minor, they will receive an e-Consent link and an e-Assent link. The clinician will verbally provide the minor with their own unique access code to their e-Assent link. The minor should personally access the link and type their first and second name into the e-Assent webpage.

Following completion of the e-Consent (and e-Assent for minors) the clinician who has been delegated to take consent will indicate they have obtained informed consent (and assent) by entering their name onto the Module. The clinician must then download a copy of the completed e-Consent (and e-Assent for minors) from the Module to file in the ISF and the patient's medical records. The Module will automatically send a copy of the completed e-Consent (and completed e-Assent for minors) to the patient / Legal Representative for their records. They will also receive a second automated email inviting them to complete an online EQ-5D-5L Questionnaire. A reminder email will automatically be sent on day 7 and 10 if the questionnaires have not been completed by the patient.

> N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

If a minor turns 16 years of age during their participation on the trial, they should be directed to read the adult information sheet on the study website. The clinician should then ideally re-consent the patient by replacing the Legal Representative's email address with the patients email address and move through the consent process as they would for an adult as described above.

10.4 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.7) in order to accurately complete the CF STORM baseline data and collect the necessary information for the trial analyses. The following data are collected routinely on the UK CF Registry and after enrolment will be transferred to the CF STORM Module. Once the participant has consented to the trial the following data will be recorded as CF STORM baseline data:

- Routine data entry (encounter) including FEV_1*, Weight, Height and CFQ-R measurement
- Additional CF STORM measures CFQ-R (if not routinely captured) and EQ-5D-5L**

**Patients should have their FEV_1 assessed no earlier than 14 days before randomisation.*
***Patients should complete the EQ-5D-5L as soon as possible following receipt to ensure there is no significant change in patient status. Those patients who have not completed the EQ-5D-5L within two weeks of consenting to the trial may still be randomised.*

The patient can proceed to randomisation once baseline assessments have been completed (see Section 10.7 for details).

10.5 Randomisation

10.5.1 Randomisation Process

Participants will be randomised within the 'CF STORM Screening and Enrolment form', this is a secure (24-hour) web-based randomisation system embedded within the form. The system is monitored by the UK CF Registry team. Participants will be randomly allocated in a ratio of 1:1 to either 'STOP' or 'CONTINUE' nebulised mucoactive therapies.

Randomisation should occur as soon as possible after e-Consent (and e-Assent for minors) has been provided. This will ensure that the participant status has not changed significantly between the eligibility assessment and the participant being randomised. The CF STORM Module will automatically request for eligibility to be reconfirmed if more than 14 days have passed since eligibility was last confirmed.

When the system requirements (i.e. consent/assent and eligibility) are confirmed the participant treatment allocation will be displayed on the CF STORM Module. An automated email confirmation will be sent to the Participant / Legal Representative to inform them of the allocated treatment arm. The LCTC Trial Manager will receive an automated email confirming that a randomisation has taken place. It is the responsibility of the PI or delegated research staff to work in partnership with the participants / Legal Representatives to ensure that they are contacted and understand the allocation and that if randomised to 'CONTINUE', the prescribed treatments will continue to be available from their community or hospital pharmacies.

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

If there are any problems with the randomisation systems contact LCTC on 0151 795 8785 or via email on cfstorm@liverpool.ac.uk

(Note that LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and university closure days)

10.5.2 Randomisation System Failure

In the event of a randomisation system failure, the centre should contact the coordinating team at LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays and university closure days) 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.

10.6 Intervention

Once the research team are aware of the treatment allocation they should attempt to verbally inform the participant immediately (within 24 hours or next working day) and the participant should either 'STOP' or 'CONTINUE' nebulised mucoactive therapies straight away, as described in Section 8.4.

10.7 Schedule for Assessments and Follow-up

All assessments at baseline and study completion are to be conducted in line with the Schedule of Assessments below. All follow up encounters until 52 weeks will be conducted in line with standard consultations.

Schedule of Assessments:

Procedures/ Assessments	Screening	Baseline/ Randomisation (Time Point:0 (0 weeks) *	12 weeks	17 weeks	26 weeks	34 weeks	39 weeks	50 weeks	Any interim encounters (Time Point 0-1)	Study Completion (Time Point:1 (52 weeks (-1/+3 weeks))	Premature Discontinuation
Signed e-Consent/ e-Assent Form		X									
Assessment and confirmation of Eligibility Criteria	X	X									
Review of Medical History	X	X									
Review of any clinician defined pulmonary exacerbation									X	X	X
Review of Concomitant Medications	X	X							X	X	X
Randomisation		X									
Study Intervention**		X	X	X	X	X	X	X	X	X	
3-month pre-randomisation data collection of nebuliser data from electronic devices		(X)									
Compliance with trial allocation		X							X	X	X
Survey of trial progress (email)			X		X		X				
Objective adherence to nebulised therapies (if collected routinely)									(X)	(X)	(X)
Height and weight		X							(X)	X	X
Assessment of Adverse Events		X							(X)	X	X
Spirometry	X	X							(X)	X	(X)
Respiratory cultures		(X)							(X)	(X)	(X)
Hospital inpatient stays									(X)	X	(X)

Procedures/ Assessments	Screening	Baseline/ Randomisation (Time Point:0 (0 weeks) *	12 weeks	17 weeks	26 weeks	34 weeks	39 weeks	50 weeks	Any interim encounters (Time Point 0-1)	Study Completion (Time Point:1 (52 weeks (-1/+3 weeks))	Premature Discontinuation
Pregnancy assessment		(X)							(X)	(X)	(X)
EQ-5D-5L generic QoL measure (email)		X		X		X		X			(X)
CFQ-R disease specific QoL measure		X						X	(X)		(X)
Airway clearance techniques recorded on the UK CF Registry		X								X	

(X) – As indicated/appropriate.
**At baseline, all procedures should be done before study intervention.*
*** Re-prescription of intervention as required (only applicable to 'CONTINUE' arm).*

Baseline / Randomisation Visit (0 Weeks)

The following data should be collected and assessments/activities performed:

- Assessment of Eligibility Criteria
- Signed Consent Form (& Assent Form for minors)
- Review of Concomitant Medications (will determine number of courses and total number of days of extra antibiotics and chronic medications)
- Study allocation recorded in patient notes
- Review of medical history
- Height and weight
- Spirometry for assessment of percent predicted Forced Expiratory Volume in 1 second (ppFEV$_1$)
- Percent predicted Forced Vital Capacity (ppFVC) and percent predicted Forced Expiratory Flow between 25-75% of vital capacity (ppFEF 25-75) should be recorded if available
- 3-month pre-randomisation data collection of nebuliser data from electronic devices
- CFQ-R; recorded by the researcher in the UK CF Registry. The disease-specific questionnaire measures the impact on overall health, daily life, perceived well-being and symptoms
- Airway clearance techniques
- Assessment for patient reported pregnancy (female of a childbearing age only)

Interim encounters

Interim encounters are all clinics which occur after randomisation and before the Study completion. The following data should be collected if the assessments/activities are performed:

- Review of Concomitant Medications (will determine number of courses and total number of days of extra antibiotics and chronic medications)
- Review of any clinician defined pulmonary exacerbation
- Assessment of compliance with trial allocation
- Objective adherence to nebulised therapies (if collected routinely)
- Height and weight
- Assessment of Adverse Events (complications)

- Spirometry for assessment of percent predicted Forced Expiratory Volume in 1 second (ppFEV$_1$)
- Percent predicted Forced Vital Capacity (ppFVC), percent predicted Forced Expiratory Flow between 25-75% of vital capacity (ppFEF 25-75)
- Respiratory cultures (laboratory assessment will determine number and type of culture)
- Review hospital in-patient stays
- Assessment for patient reported pregnancy (female of a childbearing age only)

Emails sent directly to the patient or the Participant/ Parent/ Legal Representative

The email address provided at the enrolment stage for e-Consent will be used to contact the Participant / Legal Representative during the trial for information trial progress (compliance with trial allocation and information around airway clearance techniques) and the EQ-5D-5L measure.

- Email with link to Survey of trial progress (sent at 12, 26 and 39 weeks)
- Email with link to EQ-5D-5L questionnaire (sent at 17, 34 and 50 weeks)

50 Weeks

- CFQ-R; completed as per routine care and recorded by the researcher in the UK CF Registry.

Study Completion (52 weeks *(-1/+3weeks)*)

The following data should be collected, and assessments/activities performed:

- Review of Concomitant Medications (will determine number of courses and total number of days of extra antibiotics and chronic medications)
- Assessment of compliance with trial allocation
- Objective adherence to nebulised therapies (if collected routinely)
- Height and weight
- Assessment of Adverse Events (complications)
- Respiratory cultures (laboratory assessment will determine number and type of culture)
- Spirometry for assessment of percent predicted Forced Vital Capacity (ppFVC), percent predicted Forced Expiratory Flow between 25-75% of vital capacity (ppFEF 25-75) and percent predicted Forced Expiratory Volume in 1 second (ppFEV$_1$)
- Review hospital in-patient stays
- Clinician determined pulmonary exacerbation
- Assessment for patient reported pregnancy (female of a childbearing age only)
- Airway clearance techniques

10.8 Intervention Discontinuation and Participant Discontinuation / Withdrawal

In consenting to the trial, participants / Legal Representatives agree to all trial activities including administration of trial intervention and treatment and follow-up assessments and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.8.1 Premature Discontinuation of Trial Intervention

Participants may not comply with the trial allocation for reasons including, but not limited to:

- Participant-led, i.e. request by the participant / Legal Representative
- Unacceptable toxicity (see Section 11 for Adverse Event reporting)
- Intercurrent illness preventing further treatment of allocated intervention
- Death
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of the treatment allocation in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment allocation or other trial procedures.
    - Participant meets an exclusion criterion (either newly developed or not previously recognised). This includes discontinuation of Kaftrio™, but not a reduction in FEV_1 below 40%. If there is a transient fall in FEV_1 below 40% this should be managed as appropriate by the local team.
    - Participant unable to follow allocated treatment arm for 4 weeks.

Discontinuation from study intervention does not mean discontinuation of the study altogether, and the remaining follow up assessment and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see section 10.8). Every follow-up encounter at and after the participant's premature discontinuation of trial intervention should record that the participant is no longer on the allocated treatment arm.

10.8.2 Participant Withdrawal from Follow Up

Participants / Legal Representatives are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study (unless required by law, e.g. safety events) and LCTC should be informed via email and via completion of the Withdrawal tab on the CF STORM Module.

In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any Serious Adverse Reactions (SARs) will be notifiable to LCTC via processes detailed in Section 11 even if a participant has withdrawn from follow up.

10.8.3 Participant Transfer

If a participant moves 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.

The participant remains the responsibility of the original site until s/he is transferred to the new site on the UK CF Registry. LCTC should be notified by email in the event of a participant being transferred to another site.

10.8.4 Loss to Follow-up

A participant will be considered lost to follow up if s/he fails to attend the study completion visit and is not contactable by the site research team after this.

If a participant fails to attend a routine clinic appointment the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed appointment and advise the participant on the importance of the appointment.

- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. telephone calls, emails and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable, they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the CF STORM Module, Withdrawal tab.

10.9 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. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA
- All site data entered onto the CF STORM Module, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

10.9.1 Study Discontinuation

In the event that the trial is discontinued, participants will return to their local standard care.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

On CF-STORM, safety events will be collected relating to both the dornase alfa (trial IMP) and hypertonic saline (a CE-marked medical device). Only events related to an IMP are legally required to be expedited to the regulator and ethics – separate definitions are provided below to distinguish between events and their different expedited reporting requirements.

11.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered.

An AE which is assessed to be “probably”, “possibly” or “almost certainly” related to the trial IMP dornase alfa will be classed as an AR.

Serious Adverse Event (SAE)
Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR)
An AR which meets the definition of serious (see Section 11.2) is a Serious Adverse Reaction (SAR). A SAR that has been assessed as “expected” (see Section 11.5 Expectedness) according to the Reference Safety Information (see below) will remain classified as a SAR only, however some SARs that are considered ‘unexpected’ will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An AR that is classed in nature as serious and “unexpected” (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Related Adverse Event (Related AE)
An AE which is assessed to be “probably”, “possibly” or “almost certainly” related to the hypertonic saline is classed as a Related AE.

N.B. this definition does not include events related to the trial’s IMP dornase alfa – such events are classed as ARs (see above).

Related Serious Adverse Event (Related SAE)

An SAE which is assessed to be “probably”, “possibly” or “almost certainly” related to the hypertonic saline is classed as a Related SAE.
N.B. this definition does not include events related to the trial’s IMP dornase alfa – such events are classed as SARs (see above).

Related Unexpected Serious Adverse Event (RUSAE)
A Related SAE which is not expected, i.e. not consistent with the known effects of hypertonic saline as described in the product information (see section 11.5.1) is classed as a RUSAE.

N.B. this definition does not include events related to the trial’s investigational medicinal product – such events are classed as SUSARs (see above).

Reference Safety Information (RSI)
The information used for assessing whether an adverse reaction (or a Related SAE) is expected (see section 11.5). This is contained in the Summary of Product Characteristics (SmPC) (or equivalent document) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR (or Related SAE) must be the current approved version at the time of onset of the event. The RSI for this trial IMP and other trial procedures is defined in section 11.5.1.

11.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event is assessed as serious if it:

- Results in death;
- Is life threatening, i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an in-patient 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, or hospitalisations for pulmonary exacerbations, including prolonged existing hospitalisation for pulmonary exacerbation, do not constitute a SAE);
- Results in persistent or significant disability or incapacity (substantial disruption of one’s ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the product regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.3 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 1: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.

N.B. 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 11.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.4 Assessment of "Causality" – Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 2: 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.

Events that are assessed as being "possibly", "probably" or "almost certainly" related will be reported as having a reasonable possibility of being related, and events assessed as "unrelated" or "unlikely" will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of the product (dornase alfa / hypertonic saline) or SmPC/PIL and known risk profiles of other drugs in the same class. If any doubt about the causality exists, the local investigator should inform the LCTC who will notify the Chief Investigators. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA will be informed of both points of view.

11.5 Assessment of "Expectedness"

The Chief Investigators for the CF STORM trial are responsible for determining whether a safety event is expected or unexpected, however a Chief Investigator will not assess their own patients, these patients will be assessed by the other Chief Investigator. There is no requirement for a reporting investigator to assess expectedness.

An event will be considered unexpected if it is not listed within the current and approved RSI for the product at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this

is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

11.5.1 **Reference Safety Information (RSI)**

Dornase alfa is the CF STORM IMP. The following document will be used as its RSI and used to assess expectedness of SARs:

- Dornase alfa – Summary of Product Characteristics – Pulmozyme 2500 U/ 2.5 ml, nebuliser solution- Section 4.8.

Hypertonic Saline is a CE-marked medical device (not an IMP) being used for its intended purpose in CF STORM. The following document will be used as its RSI and used to assess expectedness of Related SAEs:

- Hypertonic saline – Patient Information Leaflet – PulmoClear Sterile 7% Hypertonic Sodium Chloride Solution, 'Side effects' section.

11.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below described "active monitoring" period which meet the definition of serious (see section 11.2) and are recorded for this study must continue to be reported by sites to LCTC in accordance with the timeframes and procedures described in section 12. The same processes established for SARs and Related SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until the study completion visit.

Pregnant women will be followed up until the study completion visit with the patient (see Section 11.8 for more information on reporting pregnancy).

11.7 Notes on Safety Event Recording

CF STORM is a low-risk CTIMP trial. Expedited safety reporting will be limited to death and related safety event (SAR for dornase alfa / Related SAE for hypertonic saline) reporting, however adverse event data (complications) will be collected and specifically monitoring by the IDSMC for:

- A pulmonary exacerbation managed with intravenous (IV) antibiotics (in hospital or home)
- An absolute fall in percent predicted forced expiratory volume in one second ($ppFEV_1$) >10% predicted between consecutive encounters

In the case of pulmonary exacerbation managed with IV antibiotics, or a drop in $ppFEV_1$ >10%, the encounter will need to be recorded on the UK CF Registry within 4 weeks of the event date (site investigators will be encouraged to enter in a timely manner). Note, pulmonary exacerbation managed with IV antibiotics (in hospital or home) or a drop in $ppFEV_1$ >10% do not constitute a SAE/R, see Section 11.2 Assessment of Seriousness.

- The following events will not be captured during the study as adverse events Acute courses of oral antibiotics
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after randomisation
- Laboratory abnormalities in liver function tests that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).

- Injury or accidents
- Pregnancy (See section 11.8 for more details)

Hypertonic saline is categorised as a CE marked medical device and therefore any event which meets the definition of “serious” and is “probably”, “possibly” or “almost certainly” related to the hypertonic saline (Related SAE) will be recorded and reported to the LCTC in the same way as a SAR for the purposes of this protocol. If the event is deemed to be related but not expected this will be recorded at LCTC as a Related Unexpected Serious Adverse Event (RUSAE). LCTC will inform the site of any new RUSAEs and the site should report the RUSAE in line with their internal procedures.

11.8 Reporting of Pregnancy

Women entering the CF STORM will not be required to take a pregnancy test. Being pregnant is not an exclusion criteria per se, although it may be considered a non-CF condition that impacts on progress by the trial investigator and the patient.

If a woman becomes pregnant during the trial it should be recorded along with the outcome of the pregnancy (if applicable) on the CF STORM Module at each encounter and their annual review. However, if the pregnancy extends beyond the end of the follow-up period, then the pregnancy outcome will not be followed up.

11.9 Notification of Deaths

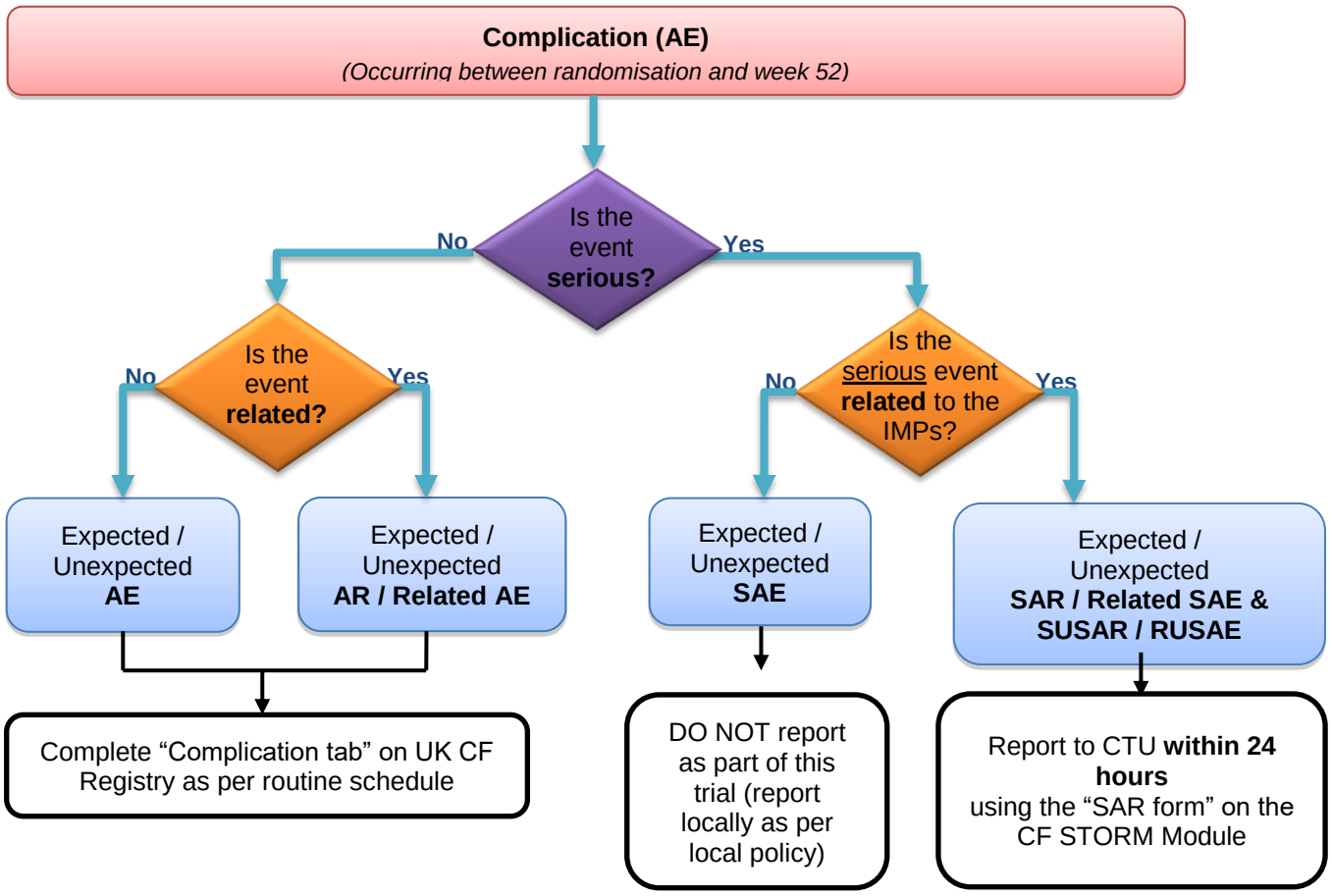
Any deaths which have been assessed and judged by the investigator to be “possibly”, “probably” or “almost certainly” related to the dornase alfa (SARs) or hypertonic saline (Related SAEs) must be reported to the LCTC and the Chief Investigators within 24 hours of becoming aware using the “SAR Form” generated within the CF STORM Module. The death should also be reported within the Demographics section on tab ‘3. Diagnosis’ within the UK CF Registry and manually transferred over to the CF STORM Module The patient should also be reported as withdrawn by completing the D8 tab in the CF STORM Module.
Any deaths which have not been assessed and judged by the investigator to be “possibly”, “probably” or “almost certainly” related to the dornase alfa or hypertonic saline must be reported to the LCTC (within 7 days of becoming aware) via the Demographics section tab ‘3. Diagnosis within UK CF Registry and manually transferred over to the CF STORM Module. The patient should also be reported as withdrawn by completing the D8 tab in the CF STORM Module.

12 REPORTING REQUIREMENTS

12.1 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

12.1.1 Flowchart for Site Reporting Requirements of Adverse Events



12.1.2 Reporting Safety Events to the LCTC

All safety events (whether or not assessed as "serious" / "related" / "expected") should be recorded on the UK CF Registry under the "Complications tab". Intravenous antibiotics (dates and duration) and decline >10% in ppFEV$_1$ between consecutive encounters will be recorded on the UK CF Registry within 4 weeks of the event.

Safety events which are assessed as "serious" and "related" must **also** be recorded in more detail on the "SAR form" which can be found within the CF STORM Module; a single form is used for each individual event

(i.e. a single diagnosis), though multiple symptoms can be recorded. *N.B. this includes events assessed as either "related" to the dornase alfa IMP (i.e. SARs) and events assessed as "related" to the hypertonic saline trial procedure (i.e. Related SAE).*

Where additional information is received by site after initial submission to LCTC, this should be updated on the "SAR form" within 5 days. The "SAR form" collects data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by a Co-Chief Investigator and assessed for causality and expectedness.

12.1.3 **Follow-up After Adverse Events**

All reportable 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 patient to be stable.

When reporting "serious" safety reactions 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.

12.2 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 12.1) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-I as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events, the correct medical terminology **must** be used in accordance with MedDRA.

All safety events must be recorded on the "Complications tab" **within seven days of the site team becoming aware of the event**.

Safety events which meet the definition of "serious" and "related" must be reported in more detail to the LCTC on the "SAR form" and reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The "SAR form" should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information* must be provided in initial reports for all studies.

The minimum information* required for reporting is as follows:

- Valid EudraCT number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One safety event
- One suspect product (including active substance name)
- A causality assessment.

Safety events should also be reported to the site R&D team in accordance with local policy.

REPORTING AN INITIAL OR FOLLOW-UP SAR / Related SAE

The investigator should ensure the actions below are completed for all reportable SARs / Related SAEs:

1) The complication (AE) should be marked as 'serious' on the CF STORM Module.
2) The LCTC will receive an alert email to alert them that the SAR criteria has been met (only for AEs assessed as "serious" and "related").
3) The responsible investigator will then complete the "SAR form" within the CF STORM Module and provide sign off (immediately, within 24 hours).
4) The LCTC will receive an alert email to notify them that a "SAR form" has been completed.
5) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
6) The patient must be identified by trial number **only**. The patient's name **should not** be used on any correspondence.
7) SARs / Related SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised (see Section 11.7.4). N.B. Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information should be entered onto the CF STORM Module and submitted as soon as more information becomes available if the event has not resolved at the time of initial report.

In the event of a problem with the CF STORM Module (power failure, server failure etc.) please contact the LCTC.

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.

12.3 LCTC Responsibilities

The trial Sponsor, Alder Hey Children's NHS Foundation Trust have delegated to LCTC the duty of onward reporting of safety events to REC and MHRA. SOPs will be followed to ensure appropriate reporting as detailed below.

The LCTC Central Safety Team will alert the Chief Investigators (or Medical Reviewers) within 24 hours of receiving the minimum information of a SAR / Related SAE from site. One of the Co-CIs will review information provided by site and will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" to the trial IMP dornase alfa and "unexpected" (i.e. SUSARs) will be expedited to the REC and the MHRA within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC receives the legal minimum information. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC receiving the legal minimum information.

Additionally, SUSARs will be reported to the trial Sponsor and Principal Investigators of participating sites within the agreed timelines. The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

Safety events which are assessed as "serious", "related" to the trial device procedure hypertonic saline and "unexpected" (i.e. RUSAEs) will be reported to the originating site within 7 days in order for them to perform applicable local reporting requirements. RUSAEs will not be expedited to MHRA or REC by LCTC.

New events related to the conduct of the trial and likely to affect the safety of the participants, such as the below statement should be reported in an expedited fashion:

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

The PIs at all institutions participating in the trial will be notified of any SUSARs/RUSAEs within a reasonable timeline. Any concerns raised by the TSC/IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

12.3.1 **Safety Reports**

Safety reports will be generated during the course of the trial which allows for monitoring of safety event including reporting rates and safety events by site / arm. The LCTC will send annual reports containing a list of all SARs to the MHRA and REC, the IDSMC will receive both SARs and Related SAEs. 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.

12.3.2 **Urgent Safety Measures (USMs)**

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

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 REC and 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 REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

12.4 Contact Details and Out-of-hours Medical Cover

As IMP is used as standard NHS practice emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for CF STORM participants. All participants will be provided with a copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

13.1.1 Sample Size Calculation

For the power calculation, we have used published UK CF Registry data that map the change in $ppFEV_1$ in a smaller population of pwCF established on a similar highly effective mutation specific therapy (ivacaftor), a significant proportion of whom were on dornase alfa.(11)

We have used the larger Standard Deviations for $ppFEV_1$ from the results of the post-market surveillance UK CF Registry trial, as these data better represent our patient population, longer duration of follow-up and registry-based data collection. (11)

The non-inferiority margin was determined using the approach recommended by Food and Drug Administration (FDA) guidelines (https://www.fda.gov/media/78504/download), referred to as the fixed margin method, which involves a combination of statistical and clinical considerations. The percentage is conventionally set at 50%, i.e. the non-inferiority margin is half the lower Confidence Interval (CIn) limit of the established (ivacaftor-comparator) rate. (12) The difference in mean change (95% CIn) of $ppFEV_1$, based on data (presented at 2016 North American CF Conference) from Volkova et al. was 8.1 (6.51, 9.69), and therefore half of the lower limit of the 95% CIn is just over three.(11) This is consistent with the limit difference determined for the CF SIMPLIFY trial.

Finally, we triangulated these calculations with PPI and stakeholder input to confirm the acceptability of the limit difference of 3%.

A sample size of 343 in each arm (with a one-sided 0.025 significance level) will have a 90% power to reject the null hypothesis that removing nebulised mucoactive therapy (“STOP”) is worse than continuing nebulised mucoactive therapy (“CONTINUE”) by a mean difference of more than 3 or farther from zero in the same direction in favour of the alternative hypothesis that removing nebulised mucoactive therapy (“STOP”) is not worse than continuing nebulised mucoactive therapy (“CONTINUE”) by a mean difference of more than 3 or farther from zero in the same direction i.e. the means are non-inferior, assuming that the expected difference in means is 0 and the common standard deviation is 12.1.

Based on information from previous trials in the field of CF, we do not anticipate that missing data will be above 10%. We have inflated the sample size by 10% and a total of 382 participants will be randomised to each treatment group (764 participants in total).

13.1.2 Sample Size Revision

Following significant challenges to recruitment, it was agreed with the trial funder to reduce the statistical power from 90% to 80% to ensure that the trial is delivered in a reasonable time frame. The reduced power was considered acceptable by the TMG and independent oversight committees, and in conjunction with new trial data (13) would provide strong evidence to inform clinical practice.

To reach 80% power, a sample size of 257 in each group is required. Allowing for 10% dropout requires 286 patients in each group, giving a total of 572 participants. 90% power requires 343 patients to be recruited in each group, giving a total of 686 participants overall. Allowing for 10% dropout requires 382 in each group, giving a total of 764 overall. We aim to recruit a minimum of 80% power.

13.1.3 Feasibility of Sample Size

Sites will open remotely with support and training from the CF STORM team. The trial has been badged by CTAP and the CTAP trial co-ordinators support site opening, recruitment and trial management in each of

their centres. In addition, we will include centres outside the CTAP network, who meet site suitability criteria (see section 6).

13.2 Method of Randomisation

13.2.1 Allocation Sequence Generation

The allocation sequence will be generated by a statistician who is independent to the trial team. 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.

13.2.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

13.3 Interim 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 LCTC 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 TMG and TSC (see section 4.3) regarding the continuation of recruitment of participants into the trial and will comply with a trial-specific IDSMC charter.

The IDSMC will be asked to consider participant safety, particularly any Suspected Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial.

13.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Analyses will be conducted using the intention to treat principle with a 2.5% level of statistical significance and one sided 97.5% CIns. The primary outcome, and other continuous outcomes (including quality of life scores) will be analysed using analysis of covariance adjusted for baseline score. The primary analysis will also be adjusted for the stratification factors used in randomisation.

Non-inferiority of the “stop nebulised therapy” group will be accepted in a 0.025 level test, if the lower bound of the one sided 97.5% CIns in means in the primary outcome lies above -3.

Given that poor study conduct quality (including eligibility violations, poor adherence, treatment crossovers and missing data) typically leads to a dilution of the treatment effect, and thus an increased probability of falsely concluding non-inferiority, we will supplement intention to treat analyses with appropriate causal methods to adjust for treatment crossovers rather than rely on per protocol or as treated analyses (which are typically subject to selection biases).

Missing data will be handled by considering the robustness of the complete case analysis to sensitivity using various imputation assumptions. These assumptions will be informed by data collected on the reasons for missing data.

13.4.1 **Health Economic Analysis Plan**

A comprehensive health economic evaluation plan will be developed in line with recent MRC-approved consensus guidance. (14) The aim of the economic evaluation is to address the question "What is the cost-effectiveness, from an NHS perspective over a period of 12 months, of stopping nebulised mucoactive drugs for people with cystic fibrosis established on Kaftrio™, compared to remaining on their standard mucoactive therapy?" It is hypothesised that discontinuation of mucoactive therapy will be a dominant strategy, with reduced cost from reduced mucolytic use, and no change in FEV_1, with reduced treatment time potentially improving QALYs.

<u>Overview of economic analysis</u>

The Base case within-trial economic analysis will use individual participant level data collected over 12 months from the CF-STORM trial. The Base case analysis will undertake a cost utility analysis from an NHS and PSS perspective, in keeping with the NICE reference case. (15) The evaluation will adhere to published guidelines for the economic evaluation of health care interventions as appropriate. (16-18) The within-trial base case economic analysis will compare costs and consequences of each arm over the first 12 months after randomisation. As the trial is only for one year of follow-up, costs and outcomes will not be subject to discounting. It is expected that the majority of costs and benefits associated with the intervention will be captured in this period, and therefore it is not considered necessary to develop a decision-analytic model.

<u>Costs and outcomes</u>

Resource use will be drawn from the UK CF Registry, and valued in monetary terms, with costs per unit estimated using appropriate UK unit costs for the most up to date cost year at the time of analysis. The primary outcome measure for the economic evaluation will be QALYs, estimated using the adult EQ-5D-5L quality of life measure for all participants. Participants aged 12 years and above will self-complete the measure. In participants <12 years, their parent/ legal representative, will be asked to complete the EQ-5D-5L as a proxy for the child. For consistency, where a parent/legal representative completes the baseline EQ-5D-5L, they will be asked to continue doing so, even if during the study their child/adolescent becomes 12 years of age. Utility will be calculated using methods recommended by NICE at the time of analysis, currently NICE recommend the use of the interim scoring system proposed by van Hout and colleagues. (19, 20)

<u>Interpretation</u>

If cost effectiveness analysis reveals that discontinuation of mucoactive therapy results in reduced costs and superior outcomes compared to standard care as hypothesised, discontinuation will be described as 'dominant' and cost effective based on the available evidence. If it is not immediately clear which pathway should be preferred, cost effectiveness will be expressed in the form of an incremental cost effectiveness ratio (ICER), estimated by taking the ratio of the difference in the mean costs and mean outcomes. The economic CF STORM trial HTA 19/160 – NIHR13188916 analysis will use a cost-effectiveness threshold (ƛ) of £20,000 per QALY, with an ICER below this level indicating that discontinuation of mucoactive therapy is cost effective.

Analysis of uncertainty

Sensitivity analyses will be undertaken to explore uncertainties surrounding key parameters in the economic evaluation in order to investigate how robust the findings are. If the results of the evaluation are not clear, non-parametric bootstrapping will be used to determine the level of sampling uncertainty surrounding the ICER. The bootstrap estimates will be plotted on a cost effectiveness plane, and used to generate cost effectiveness acceptability curves, showing the probability that each treatment arm is cost effective across a range of values of willingness to pay. A secondary analysis of health state utility will be undertaken, re-estimating utility using CFQ-R* scores mapped to the EQ-5D-5L measure. (21) This secondary analysis is important as there is some uncertainty regarding the sensitivity and responsiveness of the EQ-5D-5L in cystic fibrosis. (22)

The following additional sensitivity analyses will also be undertaken if appropriate:

1. Dealing with missing data (in line with the statistical analysis plan)
2. The cost of mucoactive therapy will be varied to test the impact this has on the incremental cost per QALY.
3. Costing of resource use in each arm based on the CF Banding tariffs.

Values will be varied to find at what cost, if any, the intervention would switch from being cost ineffective to cost effective or vice versa.

*Participants aged 12 years old and above will complete the adult version of the CFQ-R. Those participants who are aged 6-11 years old will complete the age appropriate version of the CFQ-R.

Secondary analyses

As measures of treatment burden are not included in the EQ-5D-5L, or the domains of CFQ-R that are mapped to EQ-5D-5L using the algorithm developed by Acaster *et al*, we will undertake a secondary cost-consequence evaluation using a partial societal perspective, to present the disaggregated costs and potential benefits of stopping mucoactive therapy. Additional outcomes used in this analysis will include the treatment burden domain scores from the CFQ-R instrument, and the time recorded from nebulisers for the subgroup of patients for whom this data will be available.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the CF STORM trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source Documents

The UK CF Registry and CF STORM Module will be considered the source document for data where no prior record exists and which is recorded directly in the UK CF Registry and CF STORM Module. A CF STORM source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes CF STORM-specific source data.

Date(s) of informed consent (and assent where appropriate) processes, including date of provision of patient information, Study Identifier and the fact that the patient is participating in a clinical trial (including possible treatment arms) must be added to the patient's medical record chronologically.

14.2 Data Collection 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 STORM Module's specific data fields in order to collect the data required. 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 and manually transfer the data over to the CF STORM Module within three weeks of an encounter and certainly no later than six weeks after the encounter. Where centre staff are aware of a SAR/ Related SAE, data should be entered more promptly in line with the SAR reporting timelines specified in section 12.2 of the protocol. Training will be provided to sites for the CF STORM Module prior to any data entry.

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

14.3.1 Central Monitoring

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the Trial Monitoring Plan. Monitoring is risk-adapted, based on the Risk Assessment. CF STORM 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. Other data checks relevant to patient

rights and safety will also be regularly performed as per LCTC processes. Any data issues arising from data recorded in the CF STORM 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.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

14.3.2 **Clinical Site Monitoring**

In order to perform their role effectively, members of the LCTC and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, the UK CF Registry, etc. Since this affects the participant's confidentiality, this fact is included on the e-Consent/ e-Assent. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol
- discussing any emerging problems that may have been identified prior to the visit
- checking query completion practices.

14.4 Risk Assessment

A risk assessment is performed for each trial coordinated by the LCTC 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 LCTC SOPs, CF STORM will undergo a risk assessment, completed in partnership between:

- Representatives of the Trial Sponsor;
- Chief Investigators;
- Trial Coordinator and Supervising Senior Trial Manager;
- Trial Statistician and Supervising Statistician;
- LCTC Director.

14.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CF STORM data will be labelled with the Study Identifier and Case ID number when transferred to the LCTC.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool, Alder Hey Children's Hospital and University of East Anglia are registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor, the University of Liverpool's Data Protection Officer and University of East Anglia and appropriate processes followed.

14.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

14.7 Records Retention

The retention period for the CF STORM data and information is 25 years from the official End of Trial date (defined in section 10.11 above). Core UK CF Registry data will remain accessible through governance pathways as per the regulatory guidance of the UK CF Trust Registry.

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant medical records, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the LCTC.

The PI is also responsible for archiving 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). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. third-party vendors).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All trial data transferred to the LCTC from the CF STORM Module will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

The trial will be carried out in accordance with the applicable regulations and LCTC SOPs.

15.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion. The specific ethical considerations are:

- Recruitment of children
- Obtaining remote consent (e-Consent)

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), the MHRA, the Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical, e.g. MHRA and REC requirements are handled based on their nature and severity.

15.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP, etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

15.4.2 Serious breaches

A breach of the protocol or GCP is ‘serious’ if it meets the 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”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

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 affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. 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 MHRA and REC within 7 days by the LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, 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.

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

16 INDEMNITY

CF STORM is sponsored by Alder Hey Children's NHS Foundation Trust and co-ordinated by LCTC 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.

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".

17 PUBLICATION AND DISSEMINATION

17.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will 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 Investigators, Statistician(s) and Trial Manager(s) involved as a minimum. 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 will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

17.1.1 **Authorship**

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the CF STORM Consortium which will also be named at the manuscript head.

17.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of CF STORM will be published regardless of the magnitude or direction of effect.

There are just over 10,000 children and adults with CF in the UK. Kaftrio™ is now licensed for use in children aged 6-11 in addition to the existing approvals for its use in children 12 years upwards . The impact of this managed access programme will be appraised by the team at NICE and data from CF STORM will provide key information to guide that process.

The knowledge transfer exercise will be undertaken in October 2023 and will immediately inform pwCF of the implications of the results of CF STORM for their individual patient journey. We will produce a resource that outlines the main "take home messages" and this will be distributed through the CF Trust framework, including their social media platforms.

Global translation of results will be achieved through our close links with the European CF Society and through our contacts at the US Cystic Fibrosis Foundation.

17.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be assessed by the Sponsor and Data Controller organisations.

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 6.0 (13/02/2025)

Summary of Amendments from Protocol V5.0 to Protocol V6.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
11.5.1	Reference Safety Information (RSI)	Nebusal 7% has been discontinued and therefore the Patient Information Leaflet for PulmoClear Sterile 7% will now form the RSI for Hypertonic Saline.

18.2 Version 5.0 (14/05/2024)

Summary of Amendments from Protocol V4.0 to Protocol V5.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
3	Protocol Overview	572 ‘minimum target’ added.
13.1.2	Sample Size Revision	Sample size clarification.
10.3.1	Prospective Informed Consent/Assent Process	Added that minors should ‘ideally’ be re-consented on reaching 16 during participation.

18.3 Version 4.0 (25/07/2023)

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
N/A	N/A	Change of sponsor signatory from Jason Taylor to Kelly Davies.
3	Protocol Overview	Study end date changed to 31/01/2026. Sample size reduced to 572 from 764. Target population and Inclusion criteria age reduced from 12 years old to 6 years old.
5.2	Rationale	Updated to add rationale for including 6-11 year olds.
7	Eligibility Criteria	Update to sample size to 572 from 764.

7.1	Inclusion Criteria	Updated inclusion criteria to 6 years-of-age or older.
11.6	Time period for Active Monitoring of Safety Events	Updated section reference error.
13.1.2	Sample Size Revision	New sub-section detailing the sample size change.
13.4.1	Health Economic Analysis Plan	Additional information included regarding questionnaire completion for children.
17.2	Dissemination to Key Stakeholders	Updated to reference 6-11 year olds.

18.4 Version 3.0 (13/01/2023)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
N/A	N/A	Addition of ISRCTN Number.
N/A	N/A	Addition of UK Clinical Trials Accelerator Platform Supported Study logo.
N/A	N/A	Title update for Gwyneth Davies.
N/A	N/A	Typographical errors corrected through-out Protocol.
3	Protocol Overview	Inclusion 8 amended from six weeks antibiotic use to two weeks antibiotic use.
4.3	Oversight Committees	Minor corrections to oversight committee descriptions.
4.4	Protocol Contributors	Health Economist lead Professor Jennifer Whitty has been replaced by Dr Adam Wagner and the Protocol has been updated to reflect this.
7.1	Inclusion Criteria	Inclusion 8 amended from six weeks antibiotic use to two weeks antibiotic use.
8.7.1	Medications Permitted	Addition to confirm that there are no concerns around participants receiving a COVID-19 vaccination.

10.3.1	Prospective Informed Consent/Assent Process	Added re-consent detail for minors who reach 16 during participation.
10.7	Schedule for Assessments and Follow-up	Randomisation and confirmation of eligibility criteria added to the 'Schedule of assessments' for clarity.
11.8	Reporting of Pregnancy	Clarification of pregnancy reporting.
13.4.1	Health Economic Analysis Plan	Additional sensitivity analyses detailed.
14.4	Source Documents	Correction made to participant identifier to change 'Case ID' to 'Study Identifier' on e-Consents/ e-Assent.
14.5	Confidentiality	Addition of 'Study Identifier' in data transfers.
16	Indemnity	Correction made to explain that as sponsor is an NHS Trust they do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity.
17	Data Sharing	Access to the IPD will be assessed by the Sponsor and Data Controller organisations rather than processed in accordance with the LCTC policy on data sharing.

18.5 Version 2.0 (07/01/2021)

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
7.3	Co-enrolment Guidelines	Clarification of co-enrolment guidelines

18.6 Version 1.0 (18/12/2020)

Unapproved version submitted to ethical and regulatory bodies on 18/12/2020.

19 REFERENCES

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version-controlled documents.