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The Cystic Fibrosis Home *Sputum-induction* Trial (CF-HomeSpIT) -
self management for better
microbiology surveillance

CF-HOMESPIT

Full Title: The Cystic Fibrosis Home *Sputum-induction* Trial (CF-HomeSpIT) - self management for better microbiology surveillance.

Short Title: CF-HomeSpIT

Sponsor:

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Funder:

CYARU; The Children's Hospital for Wales; Welsh Paediatric Deanery
American Cystic Fibrosis Foundation Grant [MAHENT20GO]

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R&D ref: 19/NOV/7783

REC ref: 22/WA/0196

IRAS ref: Project ID 281516

Protocol version number and date:

Version 1.1 dated 26/07/2022

This protocol has been authorised by:

Name	Role	Signature	Date
Dr Julian T. Forton	Chief Investigator		



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1. GENERAL INFORMATION

1.1. Study Summary

Study Title	The Cystic Fibrosis Home <i>Sputum-induction</i> Trial (CF-HomeSpIT) - self management for better microbiology surveillance
Internal ref. no. / short title	CF-HomeSpIT
Study Design	Internally controlled interventional trial
Planned Sample Size	80-100
Planned Study Duration	Three years from study opening. This will include recruitment and end of all protocol activities.
Primary Objectives	1) To compare microbiological yield from matched <i>sputum-induction</i> performed at home by parents, with <i>Gold-standard clinic cough swab</i> performed by health-care professionals on the same day, in children with cystic fibrosis.
Secondary Objectives	1) To compare pathogen yield from matched <i>sputum-induction</i> performed at home by parents to <i>clinic sputum-induction</i> performed by health-care professionals on the same day, in children with cystic fibrosis. 2) To identify the role of <i>early morning saliva sampling</i> taken at home and <i>clinic saliva sampling</i> , for microbiological surveillance in children with cystic fibrosis. 3) Patient parent acceptability of home <i>sputum-induction</i> and <i>saliva sampling</i> procedures
Statistical Methodology and Analysis	Matched pairs data will be analysed using the McNemar test. Sample size calculations will be generated using discordant proportions predicted using previous data on sputum induction where available. Potential confounders, including age, the presence of respiratory symptoms, and the ability to expectorate spontaneously before the procedure will be analyzed using binary logistic regression, with generalized estimating equations



	(GEE) to account for correlation between any repeated measurements in the same individual.
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1.2 Funding and Support in kind

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
CVUHB	0.1 WTE consultant (Dr Forton)
American Cystic Fibrosis Foundation Grant [MAHENT20GO]	0.4 WTE specialist physiotherapy £38,128 Overheads £3050
CYPRU	Additional microbiology laboratory costs (PHW) £4500
CYPRU	Consumables and suitable sample storage facilities

1.3 Role of Study Sponsor and Funder

Cardiff and Vale University Health Board is the Sponsor for this research study and assumes overall responsibility for the initiation and management of the study. Neither the sponsor nor any funding body is involved in study design, conduct, data analysis or data interpretation, in manuscript writing, or dissemination of results. Neither the sponsor nor any funders control the final decision regarding any of these aspects of the study.

1.4 Protocol Contributors

Dr Julian Forton, the chief investigator for the study has developed this research and designed the study. Informal advice from patients and their carers has been taken with regard to the acceptability of the intervention proposed in this study and support has been universal.

2. ABBREVIATIONS

CF	Cystic Fibrosis
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CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ISF	Investigator Site File
HCRW	Health and Care Research Wales
HRA	Health Research Authority
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research & Development Office
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
SI	<i>Sputum-induction</i>

3. BACKGROUND AND RATIONALE

Background: detecting lung infection in children with cystic Fibrosis

Longitudinal surveillance studies using repeated bronchoalveolar lavage in children with cystic fibrosis have reported that 30% of these children have *Pseudomonas aeruginosa* detected in the first 6 years of life, and that infection with any significant pathogen occurs in the first 2 years of life in 71% of children. Notably, early infection is identified as the major determinant of lung function deterioration by school age, suggesting that it is an important driver of lung inflammation and has a crucial contribution to the development of cystic fibrosis lung disease. Young children with cystic fibrosis are generally asymptomatic, cough free, and non-productive of mucus. These children are often incapable of expectorating sputum even if actively coughing during an exacerbation. Effective sampling for lower airway microbiology is therefore problematic, yet remains crucial in this age group if infection is to be effectively treated or prevented, and the potential benefits of the CF newborn screening programme properly realised. Cystic Fibrosis standards of care recommend doing regular oropharyngeal cough swabs or throat swabs for bacterial surveillance in young non-expectorating children. However, oropharyngeal cultures are a poor surrogate for cultures from lower airway samples taken at concurrent



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bronchoalveolar lavage. Bronchoscopy and bronchoalveolar lavage is invasive, requires a general anaesthetic and cannot be routinely used for microbiology surveillance.

***Sputum-induction* and the CF-SpIT Research Group, Cardiff**

The CF-SpIT research Group led by Dr Julian Forton (CI) based at the Children's Hospital for Wales in Cardiff performed a definitive large single-centre internally-controlled interventional trial comparing cough swab and bronchoalveolar lavage to *sputum-induction*. *Sputum-induction* is a simple non-invasive, safe and easily repeatable approach to stimulating expectoration of sputum in children. The CF *Sputum-induction* Trial (CF-SpIT) was published in the Lancet Respiratory Medicine in 2018 and demonstrated *sputum-induction* to be well tolerated in all age groups. Pathogen yield was threefold compared to cough swabs and equivalent to the current gold standard bronchoscopy and bronchoalveolar lavage. The Impact of this study has been to transform the care of children with CF across the UK, Australia and North America, with many leaders in the field now advocating annual routine *sputum-induction*, and *sputum-induction* before any consideration of bronchoscopy and bronchoalveolar lavage.

Further studies required

One important consideration in introducing routine *sputum-induction* is that it is currently performed by a health professional and takes approximately 30 minutes to perform. The child receives nebulised hypertonic saline and physiotherapy to loosen secretions which they can then cough out, or which can be suctioned from the oropharynx in younger children who are unable to cough out. Staff resources are therefore a limiting factor to the universal application of the *sputum-induction* procedure.

85% of patients with cystic fibrosis use hypertonic saline as an adjunct to their home physiotherapy. The current application aims to test whether *sputum-induction* can successfully be transferred to the home setting in children already using hypertonic saline and who can expectorate after the procedure without suction. This will have significant cost savings and help health care staff concentrate on younger children who will need a more involved procedure involving suction.

The Cystic Fibrosis Home *Sputum-induction* trial (CF Home-SpIT) will compare the microbiology yield from *sputum-induction* performed at home with cough swab and *sputum-induction* performed in the clinic, in an attempt to establish home *sputum-induction* as a valuable addition to standard care in children with CF.

There is increasing interest in saliva as an easy access approach to microbiology surveillance. In this study we will include two further sample approaches taken in parallel: early morning saliva taken at home, and clinic saliva.

By taking 5 samples in parallel, this study will enable comprehensive comparison of new and relevant approaches to airway sampling at home and in clinic against cough swab gold standard.



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2. Weiser R, Oakley J, Ronchetti K, Tame J, Mahenthalingam E, **Forton JT** (2022). The lower airway microbiota in children with cystic fibrosis captured by induced sputum sampling. *J Cyst Fibros*. 2022 Jan 22:S1569-1993
3. **Forton JT** (2019). Detecting respiratory infection in children with cystic fibrosis: Cough swab, *sputum-induction* or bronchoalveolar lavage (2019) *Paediatr Respir Rev* 31, pp. 28-31
4. Ronchetti K, Tame J, Paisey C, Thia LP, Doull I, Howe R, Mahenthalingam E, **Forton JT** (2018). The CF-*Sputum-induction* Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. *Lancet Respir Med*. 2018 Jun;6(6):461-471
5. **Forton JT** (2015). Induced sputum in young healthy children with Cystic Fibrosis (2015). *Paediatr Respir Rev*. 2015 Oct; 16 Suppl 1:6-8

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Primary objectives:

- 1) To compare microbiological yield from matched *sputum-induction* performed at home by parents, with *Gold-standard clinic cough swab* performed by health-care professionals on the same day, in children with cystic fibrosis.

Secondary objectives:

- 1) To compare pathogen yield from matched *sputum-induction* performed at home by parents to *clinic sputum-induction* performed by health-care professionals on the same day, in children with cystic fibrosis.
- 2) To identify the role of *early morning saliva sampling* taken at home and saliva sampling taken in clinic, in microbiological surveillance for children with cystic fibrosis.
- 3) Patient parent acceptability of home *sputum-induction* and *saliva sampling* procedures.

Objectives	Outcome Measures/Endpoints
Primary Objectives 1) To compare microbiological yield from matched <i>sputum-induction</i> performed at home by parents, with <i>Gold-standard clinic cough swab</i> performed by health-care professionals on the same day, in children with cystic fibrosis.	Microbiology yield from matched <i>home-sputum-induction</i> sample compared with same day <i>Gold-standard clinic cough swab</i> in children with cystic fibrosis
Secondary Objectives 1) To compare pathogen yield from matched <i>sputum-induction</i> performed at	



<p>home by parents to <i>clinic sputum-induction</i> performed by health-care professionals on the same day, in children with cystic fibrosis.</p> <p>2) To identify the role of <i>early morning saliva sampling</i> taken at home and saliva sampling taken in clinic, in microbiological surveillance for children with cystic fibrosis.</p> <p>3) Patient parent acceptability of home <i>sputum-induction</i> and <i>saliva sampling</i> procedures.</p>	<p>Microbiology yield from matched <i>home-sputum-induction</i> sample and same day <i>clinic sputum-induction</i> sample</p> <p>Microbiology yield from <i>matched early morning saliva sample, clinic saliva sample</i> and same day <i>clinic cough swab</i> sample</p> <p>Patient / Parent Questionnaire results. Descriptive qualitative outcomes.</p>
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5. STUDY DESIGN

- The study is a prospective single-centre internally-controlled interventional trial comparing pathogen yield from *home-sputum-induction, early morning home saliva sampling* and *clinic saliva*, to standard *clinic-sputum-induction* and *Gold standard clinic cough swab*. Samples will be matched for within-patient comparisons.
- The participating population are the South Wales Paediatric Cystic Fibrosis Cohort, who are managed by the Paediatric CF MDT at the Children's Hospital for Wales.
- The CF SpIT Research Group are clinical researchers. The patients are very well known to the CI and clinical CO-I, both of whom hold NHS positions and are responsible for CF care in South Wales. 122 patients have already contributed >200 *sputum-induction* samples for the CF-SpIT trial. Mechanisms for collecting adequate samples for this study are in place.

6. STUDY MANAGEMENT

The research will be supervised by the Chief investigator. The project steering group will consist of the CI, Clinical Co-PI and Senior Operations Manager for R&D in the Acute Child Health Directorate. Meetings will be held 6 times a year. R&D and Ethics reports will be produced annually.



7. SCHEDULE OF STUDY PROCEDURES

Procedures	Visits					
	Post 1	Phone call 1	Post 2 -14 days	Phone call 2 -7 days	Phone call 3 -1 day	Study Visit Day 0
Screening and eligibility check	✓	✓		✓	✓	✓
Invitation leaflet, patient information sheet and consent form mailed to parent and patient	✓					
Informed consent		✓				
Demographics		✓				
<i>Home Saliva and Sputum-induction</i> pack provided			✓			
Reminder and information opportunity				✓	✓	
<i>Home Saliva and Sputum-induction</i> procedures completed by patient at home						✓
Safety assessment and adverse event assessment for home <i>sputum-induction</i> and <i>early morning saliva</i> procedure.						✓
Home samples received and processed						✓
Clinic sample collection: <i>cough swabs, clinic saliva & sputum-induction</i>						✓



Patient and parent questionnaire						✓
Physiotherapist questionnaire						✓

N.B. The study will run for three years, so participants may be approached again at subsequent annual reviews to take part again.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

- The participating population are the South Wales Paediatric Cystic Fibrosis Cohort, who are managed by the Paediatric CF MDT at the Children's Hospital for Wales. The patients are very well known to the CI and clinical co-PI, both of whom are clinical researchers with NHS positions. 122 patients have already contributed to previous *sputum-induction* trials.

8.2 Inclusion Criteria

- Children with Cystic Fibrosis cared for by the South Wales Paediatric Cystic Fibrosis Service at The Children's Hospital for Wales.
- Children already using hypertonic saline as part of their home physiotherapy regimen.
- Willing and able to provide informed consent and assent.

8.3 Exclusion criteria

- Children not already using hypertonic saline as part of their home physiotherapy regimen.
- Children thought to be unable to expectorate sputum after hypertonic saline nebuliser
- Children not able to provide assent.

9. STUDY PROCEDURES

9.1. Screening and Eligibility

There are 186 children in South Wales with Cystic Fibrosis. Nearly all patients use hypertonic saline as part of their physiotherapy regimen, and so will be eligible for recruitment. Those that are potentially able to cough up spontaneously after hypertonic saline and physiotherapy will be identified by physiotherapy colleagues and defined as eligible for recruitment. Generally, these children are > 4 years of age.

The Paediatric Cystic Fibrosis Cohort are well known to the research group clinicians, have been followed up by the CF MDT since birth and are extremely well



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known to the team. The South Wales paediatric CF cohort are familiar with clinical trials with >120 having contributed to a clinical trial, run by the same clinical researchers in the last 5 years.

Children who fit inclusion criteria for the research trial will be identified by the direct clinical care team and an invite letter, patient information sheets and consent form will be mailed to their home address by a member of the research team delegated to the task (Post 1 visit) prior to their next routine clinical review at CF clinic. (Information leaflets will be available for parent, for children > 12 years and for children < 12 years of age).

9.2. Recruitment

Recruitment will be managed by a research physiotherapist (a member of the direct clinical care team), employed and overseen through the Children and Young Adult Research Unit (CYARU) at the Children's Hospital for Wales. The project will be closely supervised by the CI and clinical co-PI, who are the clinicians that run the CF clinics.

No patients will be recruited via PICS, publicly, or through disease registers.

9.3. Informed Consent (phone call 1)

- The patients will be contacted by a member of the patient's care team or the research team after at least 24 hours has passed since the patient information sheets would have been received and this information will be discussed and questions answered.
- For all patients written parental consent and patient assent will be sought by a member of the patient's care team or researcher on the delegation log.
- The parent and patient will sign their respective consent/assent forms during the virtual call using the software 'Attend Anywhere' which is widely used within the Health Board for virtual patient appointments. They will then send the consent forms back to the research site in a pre-paid envelope.
- Once the consent form has been received by the site, the *Home Saliva and Sputum-induction* pack can be sent to the participant 14 days prior to their clinic visit (study visit, day 0).

9.4 Phone call 2 and 3

- A *home sputum and saliva pack* with required disposables and universal containers will be provided by post 14 days before the study visit.
- The parent will be contacted by telephone 7 days before the Study Visit by a member of the research team to talk through the procedure.
- The parent will be contacted by telephone the day before the Study Visit by a member of the research team to remind them and talk through the procedure.

9.5 Home sputum induction procedure on the morning of the study visit



On the morning of the study visit, the family will perform the *early-morning-saliva* and *home-sputum-induction* procedures at home using the home instructions outlined in section 9.7

9.6 Study Visit

The Study Visit will be combined with a routine clinic visit and will take place in the outpatient Department at The Children's Hospital for Wales +/- CYARU.

1) *Early-morning-saliva* and *home-sputum-induction* samples.

The parent will deliver the *early-morning-saliva* and *home-sputum-induction* to the clinic staff or research team. This will be processed immediately as described in section 9.8

2) Research history and examination proforma for safety assessment and adverse event assessment for Home *Sputum-induction* procedure

- Does the patient have a wet cough today?
- Was the *early-morning-saliva* procedure attempted?
- *early-morning-saliva* procedure successful??
- Was the *home-sputum-induction* procedure attempted?
- Was the *home-sputum-induction* procedure successful?
- Were there any side effects?
- At what time was the *home-sputum-induction* sample taken?
- How long did the home sputum procedure take?
- The child will have a general physical examination as part of the safety assessment

3) Airway samples

- The child will have 2 cough swabs taken (one for clinical microbiology labs (Public Health Wales) and one for storage at -80C in CYARU). These will be taken using normal clinical protocols.
- The child will have a *clinic-saliva-sample* taken as described in section 9.7
- The child will have a clinic *sputum-induction* procedure as described in section 9.7
- Samples taken will be divided, and handled as described in section 9.8

4) Parent questionnaire

A questionnaire related to acceptability and tolerance of the *early-morning-saliva* and *home-sputum-induction* procedures will be provided for patient and parent at the study visit.

- **Did you manage to get a *home saliva* sample?**
- **How easy was it to fit this in on the morning of clinic?** {Likert scale}



- **How long did it take?**
- **Would you be willing to do this regularly at home before clinic?**
- **If yes, how many times a year would this be reasonable?**

- **Did you manage to get a *home sputum-induction* sample?**
- **How easy was it to fit this in on the morning of clinic? {Likert scale}**
- **How long did it take?**
- **Would you be willing to do this regularly at home before clinic?**
- **If yes, how many times a year would this be reasonable?**
- **Is there anything you would like to mention about the research study**

9.7 Manual: Instructions for sampling

Home based *early morning saliva* and *sputum-induction* sampling protocol

Instructions for parents and patients:

On the morning of your clinic visit

- Wake your child up a little bit earlier than normal.
- Try and perform both the *early-morning-saliva* and *sputum-induction* procedures immediately your child wakes up and before he/she has had anything to eat or drink.
- If your child usually takes DNase in the morning, omit this today.

Doing the *early-morning-saliva* procedure at home

- Wake your child up and ask them to **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT**. Show them the diagram and demonstrate it to them yourself
- Collect spittle in the universal pot labelled *early-morning-saliva*
- Ask them to **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT** a total of three times.
- Collect all saliva produced into the same single collection pot.
- Screw the cap on the pot tightly, write on the pot the time that you took the sample and bring to clinic.

Doing the *sputum-induction* procedure at home



- Administer 2 puffs of salbutamol via metered dose inhaler and spacer if you normally do so before starting physiotherapy.
- Use your home nebuliser to deliver 7% sterile hypertonic saline for a maximum of 15 minutes - do exactly as you would normally do as part of your physiotherapy regimen.
- Apply your normal physiotherapy techniques during and after the procedure. This may include chest percussion, vibration, active cycle of breathing techniques, and positive expiratory pressure (PEP), vibratory PEP (e.g. aerobika, acapella).
- Ask your child to **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT** during and after the procedure whenever they feel anything loose and ask them to spit up directly into the collection pot labelled *home-sputum-induction*.
- Aim that they **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT** at least three times during the procedure.
- Once completed, screw the cap on tightly, write on the pot the time that you took the sample and bring to clinic.

Getting the sample to us

- Seal the 2 pots in the plastic bag that you have been provided with, and bring to clinic.
- Please give the sample to someone in clinic immediately upon arrival.

Hospital based *cough swab, saliva and sputum-induction* sampling*

* Ronchetti K, Tame J, Paisey C, Thia LP, Doull I, Howe R, Mahenthalingam E, Forton JT (2018). The CF-*Sputum-induction* Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. *Lancet Respir Med.* 2018 Jun;6(6):461-471

Instructions for physios:

Cough swabs

- First obtain a 2 cough swabs as per normal clinical protocol for children with CF.

Saliva

- ask the child to **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT**. Show them the diagram and demonstrate it to them yourself
- Collect spittle in the universal pot labelled *clinic-saliva*
- Ask them to **COUGH, HUFF, COUGH, CLEAR THROAT, SPIT** a total of three times.
- Collect all saliva produced into the same single collection pot.
- Screw the cap on the pot tightly, write on the pot the time that you took the sample

Clinic Sputum induction

Protocol version 1.1 dated 26/07/2022 R&D:19/NOV/7783. IRAS PROJECT ID:281516



- Administer 200mcg salbutamol via metered dose inhaler and spacer to prevent bronchospasm.
- Use a jet nebuliser attached to wall oxygen at a flow rate of 5 l/min to deliver 8 ml of 7% sterile hypertonic saline for 15 minutes.
- Assess the chest every 5 minutes.
- Apply physiotherapy techniques during and after procedure, including chest percussion, vibration, active cycle of breathing techniques, positive expiratory pressure (PEP) and assisted autogenic drainage.
- Obtain sputum either by expectoration (in children able to cooperate) or by suctioning through the nasopharynx or oropharynx using a sterile, mucus extractor or suction catheter size 6, 8 or 10.

9.8 Sample Handling

Samples will be collected from 5 procedures

- Home collected *early-morning saliva* sample
- Home collected *sputum-induction* sample
- Clinic *cough swab*
- Clinic *saliva* sample
- Clinic *sputum-induction* sample

Sample processing

Saliva and Sputum-induction samples

The volume of *saliva* and *sputum-induction* samples will vary but will usually be less than 2 mls in total. All *Saliva* and *Sputum-induction* samples will be divided into two. One sample will be sent to the University Hospital of Wales clinical microbiology laboratories for standard CF clinical processing according to National CF Trust guidelines, and the other sample will be frozen and stored at a -80°C facility at the Children and Young Adult Research Unit (CYARU) on site in the Children's Hospital for Wales. They will then be sent in batches to CU labs.

Cough swab samples

Cough swab samples will be taken in duplicate. The first sample will be sent to the C&V clinical microbiology laboratories as routine samples for standard CF clinical processing according to National CF Trust guidelines. The second sample will be processed by clinical research staff. It will be rinsed in 1 ml of normal saline and the resulting solution will be frozen and stored at a -80°C facility at the Children and Young Adult Research Unit (CYARU) on site in the Children's Hospital for Wales. They will then be sent in batches to CU labs.

Research sample storage and processing



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- All stored samples will be designated a research unique identifier and stored at -80c in the CYARU (CVUHB).
- The patient will not be identifiable from the unique identifier
- The code for sample identification will be kept by the CI.
- Participation in this study is voluntary and patients are free to withdraw at any time without giving a reason and without medical care or legal rights being affected.
- If a patient does withdraw consent, research samples will be destroyed according to locally approved practices.
- All samples will be transferred from CYARU in batches to the laboratories of Professor Eshwar Mahenthiralingam in the Department of Biosciences, Cardiff University, under Cardiff and Vale / Cardiff University collaboration agreement ref. SC35274 517322.
- Samples will be included in batch DNA extraction. DNA that is extracted will be stored securely in a DNA archive in the Department of Biosciences and will be used in this project and ongoing research projects.
- In most cases, the entire sample will be processed, and no further human tissue will remain. Some samples however, may be archived as whole material until the end of the trial, and used in future research projects. If they are not used by the end of the trial, then they will be destroyed.
- The trial site will ensure that at all times, samples are appropriately labelled in accordance with the study procedures to comply with the current Data Protection legislation. Biological samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act

9.9 Discontinuation / Withdrawal of Participants from Study

All participants have the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason, in the best interests of the patient. If the participants withdraws all samples that have already been analysed and data collected up until this point will be kept. If the samples have not been analysed they can be destroyed.

9.10 Study Amendments

It is the sponsor's responsibility to classify amendments as being non-substantial or substantial. The CI will seek advice from Cardiff & Vale UHB R&D office prior to submission to the relevant bodies. The CI will seek approval for any substantial amendments to the protocol or other study documents from HCRW and REC. The NHS R&D Office will need to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to these approvals being granted. Non-substantial amendments should be notified to



the REC for information and may also need to be reviewed and accepted by R&D departments before they can be implemented in practice at site.

9.11 Definition of end of study

The end of the study is defined as the date of the study visit of the last patient.

10. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

There are no products, devices or tools that differ from normal clinical practise

- **Medicinal Product note**

Hypertonic saline 7% used in this study is not classed as a medicinal product.

- **Devices**

Nebulisers used in the home-sputum procedure will be the same device as the patient uses every day (PariTurboBoy, PARI GmbH; eFlow®rapid Nebuliser, PARI GmbH; Ineb AAD, Philips Respironics). Clinic *sputum-induction* procedures will be performed using a jet nebuliser set (SideStream disposable kit; Philips Respironics, Murrysville, PA, USA)

- **Patient and parent Questionnaire**

Patient and parent will be provided with a questionnaire at the Study Visit, related to acceptability and tolerability of performing the new intervention (*home early-morning saliva* and *home sputum-induction*). This will involve assessing duration of commitment, and acceptability as a regular home intervention.

11. SAFETY REPORTING

Adverse Events and Serious Adverse Event definitions

Adverse Event (AE): Any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease. Expected AEs with no causal relationship to the trial in this patient group include items such as: respiratory infection, constipation and diarrhoea, abnormal liver function tests.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* Note: The term “life-threatening” in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.



** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.1. Reporting procedures for SAEs

- Any queries concerning adverse event reporting should be directed to the study coordinator, Dr Rhian Thomas Turner at the CYARU at the Children's Hospital for Wales. Contact number: 02921 847848, or to the CI Dr Julian Forton (02920744891)
- An SAE form will be completed by a medically trained member of the Research team and delivered to the study coordinator within 24 hours.
- Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.
- Only reports of Serious Adverse Events (SAEs) that are: **related** to the study (i.e. they resulted from administration of any of the research procedures) and **unexpected** (i.e. not listed in the protocol as an expected occurrence) will be submitted to both the REC that gave a favourable opinion of the study and C&V R&D office by the Chief Investigator (CI) using the Non-CTIMP safety report to REC form which is available on the HRA website.
- These will be sent within 15 days of the chief investigator becoming aware of the event.
- **Unrelated and Expected SAEs** do not require reporting to C&V R&D Office but a copy of the SAE report should be retained in the Investigator Site File for monitoring/audit.
- The risk of related SAEs is low due to the nature of the study and the fact that patients and parents will be collecting a sample from a procedure they are already doing routinely at home.
- AE and SAEs that will not require recording include any episodes related to the underlying diagnosis of cystic fibrosis, not temporally related to the short procedure either at home or in clinic. Temporally related is defined here as within 6 hours of the procedure.
- The CI will send the Annual Progress Report to the main REC and to the sponsor using the HRA template.

11.2. Urgent Safety Measures and Serious Breaches of GCP



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The Chief Investigator and Principal Investigators (PIs) may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However they must alert the sponsor as soon as possible of any such urgent measures by contacting the Cardiff and Vale UHB R&D Office and CI. The Chief Investigator (CI) will notify the REC of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action.

In the event that a serious breach of GCP is suspected, this will be reported to the sponsor and REC immediately and will be investigated by the sponsor. Any corrective action required will be undertaken by the CI and REC informed. If necessary a protocol amendment will be submitted for review.

12. STATISTICS AND ANALYSIS

12.1 Description of Statistical methods

All paired proportions between sampling techniques will be analysed using the two-sided McNemar's test. Binary logistic regression (BLR) will be used to assess the effect of potential confounders, including age, the presence of respiratory symptoms, and the ability to expectorate spontaneously before the procedure, on sampling success rates. Generalised estimating equations (GEE) will be used to account for correlation between any repeated measurements in the same individual.

Test-specific detection rates will be used when comparing different approaches to sampling, to interrogate the relative pathogen yield and help understand the relative sampling ability of each approach. We will generate a sensitivity analysis for *early morning saliva* and *home sputum-induction* sampling against a standard consisting of all pathogens isolated from all matched samples taken in clinic, to help understand how it might surrogate for health-care based interventions currently performed in the clinic.

This research team have used similar statistics for the CF-SpIT trial which was successfully published in The Lancet Respiratory Medicine 2018

* Ronchetti K, Tame J, Paisey C, Thia LP, Doull I, Howe R, Mahenthiralingam E, Forton JT (2018). The CF-*Sputum-induction* Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. Lancet Respir Med. 2018 Jun;6(6):461-471

12.2 Sample size calculations

Primary Outcome:

- 1) To compare microbiological yield from matched *sputum-induction* performed at home by parents, with *Gold-standard clinic cough swab* performed by health-care professionals on the same day, in children with cystic fibrosis.

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Results from the CF-SpIT study showed *sputum-induction* in clinic to be far superior to *cough swab* in clinic, in all age groups. In children aged 6-18 years, there was a 35% discordance in pathogen positivity results between cough swab and *sputum-induction* with an Odds ratio (OR) of 10.3 $p < 0.00001$ in favour of *sputum-induction*.

No data exists to evaluate the potential success of the home *Sputum-induction* procedure when compared to clinic oropharyngeal sampling.

We assume home *sputum-induction* would be less successful than clinic *sputum-induction*, but estimate that in comparison to oropharyngeal samples, an OR 5.0 with discordance in pathogen positivity of 25% would identify home *sputum-induction* as a clinically important procedure. In a 2-sided McNemar Test sample size calculation using discordant proportions, 69 *sample pairs* would be required to demonstrate this magnitude of effect with a power of 80% at a significance level of $p < 0.05$.

No data exist comparing *home-sputum-induction* sampling or *early-morning-saliva* sampling with *clinic-sputum-induction* sampling. We aim to collect 80-100 matched sample sets to analyse the relative merits of these approaches to sampling.

13. DATA MANAGEMENT

13.1. Access to Data

Direct access will be granted to authorised representatives from the sponsor, host institution and Regulatory Authorities for monitoring and/or audit of the study to ensure compliance with the relevant data protection legislation.

13.2. Data Recording and Record Keeping

- Paperwork from data collection in the clinic will be stored in the site file, in a secure environment in the CYARU. This paperwork will include patient name, date of birth, hospital number, trial patient number, samples taken, the researcher timetable checklist from study visit and the patient/parent questionnaire.
- Access to the data will be limited to research and administrative staff in the CYARU on the delegation log.

13.3. Participant Confidentiality and Data Protection

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.



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- Recruitment dates, trial patient number and a record of which samples were collected will be recorded on an Excel spreadsheet. This will be depersonalised, with trial patient number as the only patient identifier.
- Clinical Microbiology results and clinical data will be recorded on the same spreadsheet.
- Depersonalised Data on the Excel spreadsheet will be password protected and stored on the C&V hospital server in a restricted access folder
- The chief investigator and other members of the *clinical* research team will have access to the linking code which will be kept distinct from the trial data in a password protected XL spreadsheet stored in a separate location to the data.
- Depersonalised Data on the Excel spreadsheet will automatically be backed up on NHS C&V server back-ups, but also stored in duplicate and updated monthly on Cardiff University One Drive.
- Data will not be transferred outside of the EAA
- The research team are responsible for data entry and quality as per the delegation log
- The CI will be responsible for data analysis
- The CI is the data custodian

13.4 Record Storage and Retention

The TMF and ISF containing essential documents will be kept for a minimum of 5 years after completion of study. Documents (paper and electronic) will be retained in a secure location during and after the study has finished. A label stating the required retention time should be placed on the inside front cover of the medical records for study participants.

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

14. QUALITY ASSURANCE PROCEDURES

The study may be subject to inspection and audit by Cardiff and Vale UHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

15. ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of GCP and in accordance with all applicable



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regulatory guidance, including but not limited to the UK Policy Framework for Health and Social Care 2017.

This protocol and related documents (and any subsequent amendments) will be submitted for review to the relevant parties (HCRW and REC).

Annual progress reports and a final report at the conclusion of the study will be submitted to the REC within the timelines defined.

15.1. Review and Approvals

15.1.1. Ethical Approval and HRA/HCRW approval

- Before the start of the study, approval will be sought from HCRW and REC for the protocol, informed consent forms and other relevant documents e.g. information letters
- Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to their National Coordinating Unit, HCRW). The HCRW Permissions Service will assess and approve the amendment.
- The chief investigator (or delegate) also needs to notify the R&D offices and local research teams the amendment(s). The R&D Office(s) will have 35 days from receipt of the amendment to confirm capacity and capability.
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

15.1.2. Peer Review

The study has reviewed competitive funding from The American Cystic Fibrosis Foundation in collaboration with Prof Mahenthiralingam in the department of Biosciences, Cardiff University, to look at approaches to sampling and approaches to sample processing.[Grant: MAHENT20GO]

15.1.3. Governance Review



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The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence until confirmation of capacity and capability is also received via email by the CI.

15.2. Reporting

The CI shall submit once a year throughout the study or on request, a progress report to the REC and sponsor. In addition, an end of study notification and final report will be submitted to the same parties.

15.3. Expenses and Benefits

There are no plans to pay participants any money or provide any other benefits (Declaration of Helsinki requirement).

16. INDEMNITY AND FINANCE

16.1. Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

16.2. Financial and other competing interests

The Research Group have no financial or competing interests

17. PUBLICATION AND REGISTRATION POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analyzed and tabulated, and a clinical study report will be prepared. Authors will acknowledge the study funders and other contributors will be acknowledged.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

The study will be registered with the UK Clinical Research Network (UKCRN) and with the International Standard Randomised Controlled Trial Network Registry (ISRCTNR)



18. REFERENCES

1. **Forton JT**. Invited Editorial. Pathogen detection. The Bread and Butter (2022). *J Cyst Fibros*. 2022, 21(1), pp. 13–14
2. Weiser R, Oakley J, Ronchetti K, Tame J, Mahenthalingam E, **Forton JT** (2022). The lower airway microbiota in children with cystic fibrosis captured by induced sputum sampling. *J Cyst Fibros*. 2022 Jan 22:S1569-1993
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4. Ronchetti K, Tame J, Paisey C, Thia LP, Doull I, Howe R, Mahenthalingam E, **Forton JT** (2018). The CF-*Sputum-induction* Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. *Lancet Respir Med*. 2018 Jun;6(6):461-471
5. **Forton JT** (2015). Induced sputum in young healthy children with Cystic Fibrosis (2015). *Paediatr Respir Rev*. 2015 Oct; 16 Suppl 1:6-8

APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made