TITLE	Exploring the effect of Azithromycin on oesophageal motility and respiratory symptoms in patients with chronic respiratory disease: a prospective observational study
PROTOCOL NUMBER	Version 4
TRIALINTERVENTION	N/A
LEAD TRIALINVESTIGATOR	Dr Dominic Sykes Academic Clinical Fellow in Respiratory Medicine Correspondence Address: Academic Respiratory Medicine Castle Hill Hospital Cottingham HU16 5JQ Mobile. 077694342595 Email. Dominic.sykes2@nhs.net
DATE OF PROTOCOL	18/01/2023
TRIAL SPONSOR	Hull University Teaching Hospitals NHS Trust R&D Department, 2nd Floor Daisy Building, Castle Hill Hospital, Cottingham, HU16 5JQ Tel. 01482 461903: Fax: 01482 461886
RESEARCH REFERENCE	IRAS Project ID: 1006318 Sponsor No: R2807 ISRCTN no:
Confidentiality Statement	Information in this protocol should not be disclosed, other than to those involved in the execution or ethical review of the study, without written authorisation from the Sponsor.
Regulatory Statement Protocol Preparation	All trial procedures will be conducted within ICH GCP guidelines and all other regulatory requirements. This protocol has been prepared in accordance with CONSORT guidelines and has regard for the HRA guidance. It complies with Guidelines for Good Clinical Practice in clinical research.

PROTOCOL SIGNATURE PAGE

Protocol No v4 – 08.03.2023

The undersigned confirm that the following clinical trial protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved clinical trial protocol and will adhere to the Clinical Trials Regulations and subsequent amendments, ICH GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Funder and Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies regarding the trial are explained.

Trial Sponsor:

Signature: DocuSigned by: James Illingworth 3DDA0F96873F430... Date: 9/6/2023

Name (please print): James Illingworth

Position RDI Manager

Principal Investigator:

Signature: DocuSigned by: Dr Dominic Sykes 4BB530B1F0B04F4... Date: 6/6/2023

Name (please print): Dr Dominic Sykes

Position Academic Clinical Fellow in Respiratory Medicine

Statistician:

Signature: DocuSigned by: Michael Crooks D93709D10BFC494... Date: 9/6/2023

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Funder			
Trial Sites	Castle Hill Hospital Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Cottingham, HU16 5JQ		

PLAIN ENGLISH SUMMARY

Symptoms such as cough, wheeze, and breathlessness are among the most common reasons for patients to visit their general practitioner or emergency department in the United Kingdom, accounting for up to 20% of healthcare visits. Such symptoms are known to have a profound impact on the ability of such patients to live a fulfilled life, as they can often render people unable to work and socialise. Patients are often left with lasting symptoms despite being treated with all currently recommended therapies, suggesting that there is ample reason to keep searching for new treatments for patients with chronic lung disease.

Azithromycin is a type of antibiotic which has been found to improve symptoms and reduce flare-ups of common diseases such as asthma and chronic obstructive pulmonary disease (COPD). The reason why it works is still unclear. Many people believe in one of two theories, either that it decreases the

number of bacteria in the lungs or that it reduces inflammation in the lungs and the upper airways. Neither of these theories are proven and there has been a different mechanism suggested, although it has been much less studied. Azithromycin is thought to encourage the body to move food and fluid through the gut more quickly, and this may help to prevent small food particles and stomach to reflux into the airways. It has been shown that lung damage can occur when gut contents enter the airways, which may contribute to the symptoms of patients with chronic lung disease.

In this trial we will be testing the effect of azithromycin on the gut in patients with chronic lung diseases. We will measure the strength of a patients swallow by measuring the pressures in their gullet, using high-resolution oesophageal manometry (HROM), before and after treatment with azithromycin. We will also measure the effect that azithromycin has on their symptoms and observe whether there is a relationship between the strength of their swallow and their symptoms.

At the end of this study, we will hope to better understand the way in which azithromycin helps to improve the symptoms of patients with chronic lung diseases. We also hope to open the door to investigate the effect of other drugs that improve gut function in patients with chronic lung diseases.

PROTOCOL SYNOPSIS

Sponsor	Hull University Teaching Hospitals NHS Trust
Intervention	Pilot study
Trial Number	IRAS ID: 1006318
Title of Study	Exploring the effect of Azithromycin on oesophageal motility and respiratory symptoms in patients with chronic respiratory disease: a prospective observational study
Trial Centres	- Castle Hill Hospital, Cottingham, HU16 5JQ
Phase of Development	Pilot
Objectives	**Aim**: To investigate the feasibility and acceptability of High-resolution oesophageal manometry (HROM) in the diagnosis and treatment strategies of chronic respiratory diseases. Exploratory analysis will be performed on the effect of azithromycin on oesophageal motility and how it relates to symptomatic improvement in patients with chronic respiratory disease who are being commenced on azithromycin as part of routine clinical care. **Objectives:** Specific trial objectives will address both the feasibility and acceptability outcomes as well as exploratory outcomes **Feasibility outcomes** 1. Recruitment: eligibility to consent ratio, recruitment rate, and participant retention to follow-up. 2. Data quality: Completion of clinical outcomes at follow-up and patterns of missing data for the trial measures. Completion of participant symptom questionnaires throughout the study. Completion of trial processes, principally HROM. 3. Acceptability of assessment: Quantify the proportion of participants who judge the trial investigations, principally HROM, to be acceptable. **Exploratory clinical outcomes** 1. Oesophageal functioning: To evaluate the effect of azithromycin on the contraction vigour and swallow coordination. This will be evaluated by investigating patients with HROM before and 1 month after initiation of azithromycin as part of routine clinical care. 2. Symptom burden: Symptoms will be assessed before and 1 month after initiation of azithromycin as part of routine clinical care. Symptoms will be measured using validated symptom questionnaires, visual analogue scale for cough, and numeric rating scales for breathlessness

	3. Relationship between oesophageal motility and symptoms: The change in oesophageal functioning and presence of respiratory symptoms will be examined in each participant. The relationship between these two parameters will then be examined using statistical analysis. 4. Effect of azithromycin therapy on continuous objective cough frequency as measured by the Hyfe Cough Tracker©. 5. Relationship between continuous objective cough frequency data and subjective repetitive cough evaluation as measured by cough VAS.
Trial Design	A prospective pilot trial of a single group of patients with chronic respiratory disease being investigated with HROM and treated with azithromycin as part of routine clinical care.
Number/Type of Participants	Thirty individuals with chronic respiratory disease who are being commenced on azithromycin as part of routine clinical care.
Inclusion Criteria	- Males and females aged ≥18 years. Have a diagnosis of chronic respiratory disease (COPD, asthma, interstitial lung disease, chronic cough, cystic fibrosis, and/or bronchiectasis) confirmed by a consultant respiratory physician. - Exhibit symptoms consistent with airway reflux, demonstrated by a score ≥14 on the Hull Airways Reflux Questionnaire - Are being initiated on azithromycin treatment as part of routine clinical care by their usual clinician. This will include all common treatment regimes, 250mg once daily, 250mg three times per week, and 500mg three time per week. - Are willing and able to consent to all trial procedures.
Exclusion Criteria	- Previous treatment with long-term macrolides in the past 3 months. - Unable to be investigated with HROM due to contraindications such as anatomical abnormalities or diseases of the oesophagus or unwilling/ unable to be investigated with HROM based on the clinical judgement of the investigators due to severity of lung disease. - Have another cardiorespiratory cause for their symptoms (such as heart failure or lung cancer). - Are unable or unwilling to consent to or complete the trial procedures. - Women of child bearing potential not using effective means of contraception. Effective methods of contraception include any oral contraceptive pill, any intrauterine device, any long term contraceptive implant, and any long-acting contraceptive injection - Have been involved in another medicinal trial (CTIMP) within past four weeks.

Trial Treatment(s)	Trial Participants will be commenced on azithromycin therapy as part of usual clinical care.
Trial Endpoints and Statistical Methods	For trial endpoints, appropriate statistical analysis will be performed to compare HROM metrics and symptom questionnaire data at baseline and at follow-up. A table showing baseline demographic and clinical characteristics for each group will be presented. Participant characteristics will be summarised using appropriate statistics. Medians (interquartile range) will be reported for ordinal data, mean (standard deviation) for continuous data and raw count (number, %) will be reported for nominal data. For participant outcome data, descriptive statistics, mean (standard deviation) for continuous outcomes and raw count (%) for categorical outcomes, will be reported for each group at baseline and at 1-month follow-up, and for continuous objective and subjective cough data where applicable.
Safety Analyses	AEs/SAEs will be listed and summarized using descriptive statistics.
Sample Size Rationale	As this is a pilot study, a formal sample size calculation has not been performed. We will recruit 30 participants over 12 months based on National Institute for Health Research recommendations for pilot/feasibility studies.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Visit	Screening Visit	Baseline visit	Minimum 1 month on azithromycin therapy	Follow up visit
Day	**-28 to -7**	**0**		**28 to 42**
Procedure/Assessment				
Written Informed Consent	X			
Inclusion/ Exclusion Criteria	X	X		
Invitation Experience survey	X			
Setup of the Hyfe Cough Tracker©	X			
Monitoring of cough frequency using the Hyfe Cough Tracker©	X**	X		X
Vital signs		X		X
Weight and Height		X		X
Physical Examination		X		X
Electrocardiogram		X		X
Past Medical History		X		
Review of previous laboratory results		X		
AE Monitoring		X		X
MRC Dyspnoea grade		X		X
Hull Airway Reflux Questionnaire	X	X		X
Breathlessness, Cough, and Sputum Scale		X		X
St George's Respiratory Questionnaire		X		X
Leicester Cough Questionnaire		X*		X*
King's Brief Interstitial Lung Disease Questionnaire		X*		X*
COPD Assessment Test		X*		X*
Asthma Control Questionnaire		X*		X*
Visual Analogue Scales (Cough)		X		X
Numeric Rating Scale (Breathlessness)		X		X
Spirometry		X		X
High-Resolution Oesophageal Manometry†		X		X
Health Care Utilisation				X
Evaluation of usual care received				X
Trial Experience Survey				X

*Questionnaires will be administered dependent on patients' main respiratory diagnosis.

**If willing, patients would have the possibility to begin objective unobtrusive continuous cough monitoring after the screening visit.

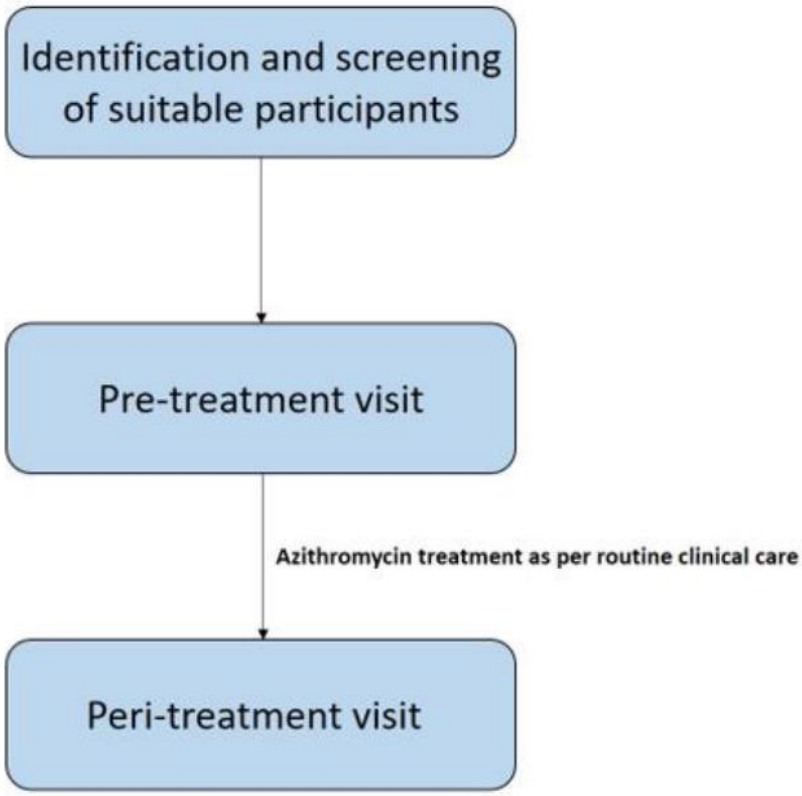
†Patients will be eligible if they have had HROM performed up to 3 months prior to screening, however they must not have been treated with macrolide antibiotics during this time.

TRIAL FLOW CHART

Day -28 to -7
Consent
Inclusion/Exclusion Criteria
Invitation Experience Survey
Hull Airway Reflux Questionnaire
Setup of Hyfe Cough Tracker© equipment and download of Hyfe Research© smartphone app

Day 0
Inclusion/Exclusion Criteria
Hull Airway Reflux Questionnaire
Physical Examination
Vital Signs
Spirometry
ECG
HROM
Past Medical History
Questionnaires as per schedule and based on patients primary diagnosis
Review of Hyfe Research© app data

Day 28-42
Inclusion/Exclusion Criteria
Hull Airway Reflux Questionnaire
Physical Examination
Vital Signs
Spirometry
HROM
ECG
Past Medical History
AE Monitoring
Questionnaires as per schedule and based on patients primary diagnosis
Review of Hyfe Research© app data



LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
AR	Adverse Reaction
CA	Competent Authority
CC	Chronic Cough
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GORD	Gastro-oesophageal Reflux Disease
HROM	High-Resolution Oesophageal Manometry
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IPF	Idiopathic Pulmonary Fibrosis
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

CONTENTS

1. BACKGROUND AND RATIONALE

Respiratory symptoms such as cough, wheeze, and breathlessness are amongst the commonest reasons for presentation to healthcare in the United Kingdom, accounting for up to 22% of total patient contacts.(1) Chronic respiratory diseases also account for more than 10% of productive life lost secondary to medical issues, and are known to cause great detriment to the physical, psychological, and socioeconomic wellbeing of patients.(2-4) In recent years, the utility of macrolide antibiotics has been examined in a multitude of respiratory diseases. They are now recommended as add-on therapies in patients who continue to require regular treatment or hospitalisation for exacerbations of their chronic condition.(5)

The efficacy of macrolide antibiotics such as azithromycin in patients with asthma has been shown in large scale clinical trials. The AMAZES trial demonstrated a significant reduction in exacerbation frequency in those with persistent asthma, and both the AMAZES and AZISAST trials demonstrated an improvement in the quality of life in such patients.(6, 7) The reduction in exacerbation rates offered by azithromycin treatment is echoed in trials examining patients with COPD.(8, 9) Significant quality of life benefits, as measured by the SGRQ, were also observed in a pooled analysis of the trials examining COPD patients, but this did not reach the minimum clinically important difference of 4.(10) There is also high quality RCT evidence to support the use of long-term macrolides in patients with bronchiectasis, in the form of the EMBRACE, BAT, and BLESS trials.(11-13) Evidence for the use of long-term macrolides in other chronic respiratory diseases such as Interstitial Lung Diseases (ILD) and Chronic Cough (CC) is less clear, however this is largely due to the relative paucity of high-quality RCTs performed. There has been promising retrospective analysis performed on patients with Idiopathic Pulmonary Fibrosis (IPF). One trial demonstrated a reduction in hospital admissions and antibiotic courses prescribed for exacerbations of IPF, when comparing patients' records a year before treatment with the subsequent year where they were treated with azithromycin.(14) Two very small studies have examined the effect of long-term macrolides on CC, with only one trial measuring 24 hour cough counts in their analysis.(15, 16) However, other studies have shown benefit in cough-specific health status in other respiratory diseases.(17, 18) This suggests that the effect of long-term macrolides on patients with CC warrants further investigation with large-scale RCT, measuring their effect on both cough-specific QoL and 24-hour cough counts.

Despite the litany of evidence to support the use of long-term macrolide antibiotics in the management of respiratory disease, the mechanism of how they confer such a benefit to patients

remains obscure. One of the most popular proposed theories is that concerning the immunomodulatory effects of macrolides in the airways.(19, 20) Reduction of immune cell infiltration and neutrophil chemotaxis in the airways has been shown *in vitro* with erythromycin(21) and *in vivo* via the measurement of sputum interleukin-8 levels of asthmatic patients after treatment with clarithromycin.(22) Effects of macrolides on the function of innate immune cells have also been described, such as increasing the phagocytic capacity of macrophages(23) and promoting neutrophil apoptosis and therefore reducing airway inflammation.(24) Despite extensive study, there is still reasonable doubt that immunomodulatory properties are the sole mechanism for the beneficial effects of long-term macrolides. An alternative, more traditional, proposed mechanism is that of the antimicrobial effects of long-term macrolides on the airway. It is thought that macrolides may inhibit bacterial protein synthesis, toxin production, and biofilm function in respiratory disease where colonisation of common pathogenic bacteria is common.(25) Furthermore, long-term treatment with macrolides has been shown to alter the airway microbiota of patients with bronchiectasis, conveying their antibacterial effects.(26) Despite much research around these two processes, the pro-kinetic effects of long-term macrolides on the gastrointestinal system in relation to patients with chronic respiratory disease has been scarcely studied.

Macrolide antibiotics, such as azithromycin, have been shown to promote gastrointestinal motility and reduce the rates of gastro-oesophageal reflux events in patients with gastro-oesophageal reflux disease (GORD).(27, 28) Indeed, erythromycin has been used to promote gastric motility for patients in the intensive care unit for many years.(29, 30) This effect is engendered by agonism of the motilin receptor that macrolides such as erythromycin exhibit.(31) The link between gastrointestinal dysmotility and respiratory disease is well established, with both acidic GORD and non-acid gaseous airway reflux mechanisms implicated in the natural history of many chronic respiratory diseases.(32-36) Indeed, in our retrospective analysis of 441 patients with chronic respiratory disease and symptoms suggestive of airway reflux it was revealed that 66% of patients had evidence of oesophageal dysmotility, proven on High-Resolution Oesophageal Manometry (HROM).

Despite the evidence that gastrointestinal dysmotility is implicated in the natural history of respiratory disease and the fact that macrolides improve motility, there have been no studies investigating the effect of macrolides on oesophageal motility in this cohort of patients. We believe it important to perform a trial examining the effect of azithromycin, the most frequently used long-term macrolide, on oesophageal motility in patients with chronic respiratory disease. We will also investigate the relationship between the effect of oesophageal function and on symptom burden in this group of patients.

2. TRIAL AIMS AND OBJECTIVES

Aim: To investigate the feasibility and acceptability of HROM in the diagnosis and treatment strategies of chronic respiratory diseases. Exploratory analysis will be performed on the effect of azithromycin on oesophageal motility and how it relates to symptomatic improvement in patients with chronic respiratory disease who are being commenced on azithromycin as part of routine clinical care.

Objectives: Specific trial objectives will address both the feasibility and acceptability outcomes as well as exploratory outcomes.

Feasibility outcomes

1. Recruitment: eligibility to consent ratio, recruitment rate, and participant retention to follow-up.

2. Data quality: Completion of clinical outcomes at follow-up and patterns of missing data for the trial measures. Completion of participant symptom questionnaires throughout the study. Completion of trial processes, principally HROM.

3. Acceptability of assessment: Quantify the proportion of participants who judge the trial investigations, principally HROM, to be acceptable.

Exploratory clinical outcomes

1. Oesophageal function: To evaluate the effect of azithromycin on oesophageal contraction vigour and swallow coordination. This will be evaluated by investigating participants with HROM before and 1 month after initiation of azithromycin as part of routine clinical care.

2. Symptom burden: Symptoms will be assessed before and 1 month after initiation of azithromycin as part of routine clinical care. Symptoms will be measured using validated symptom questionnaires, visual analogue scale for cough, and numeric rating scales for breathlessness

3. Relationship between oesophageal motility and symptoms: The change in oesophageal functioning and presence of respiratory symptoms will be examined in each participant. The relationship between these two parameters will then be examined using statistical analysis.

4. Effect of azithromycin therapy on continuous objective cough frequency as measured by the Hyfe Cough Tracker©.

3. TRIAL DESIGN

A prospective observational trial evaluating the effect of 1 month (up to 6 weeks) of azithromycin treatment on oesophageal motility and symptom burden in patients with chronic respiratory disease who are being commenced on azithromycin as part of routine clinical care. Participants will be investigated using HROM before and during treatment with azithromycin to evaluate the change in oesophageal function.

The trial team will not be prescribing the azithromycin treatment for the participants, as this will be the decision and the responsibility of their usual treating clinician. However, it is anticipated that all participants will be treated with azithromycin 250 milligrams once daily or three times per week throughout the duration of the study. The acceptability of HROM as a diagnostic tool will be assessed through participant experience surveys. We will also analyse other feasibility outcomes such as eligibility to recruitment ratio and participant retention rate to ascertain how willing participants will be to engage in all trial procedures to inform larger clinical trials/ mechanistic studies.

Participants will be investigated with validated questionnaires to ascertain their symptom burden before and during treatment with azithromycin. With this information we will correlate changes in oesophageal function and symptom burden in this group of patients. Participants will also be asked to use the Hyfe Cough Tracker© equipment (to be further determined - if a dedicated smartphone running the application or a wearable smartwatch running the application) for at least one week prior to their initiation of azithromycin and for the duration of their azithromycin treatment whilst in the trial. We will then observe the difference between daily cough counts before and after azithromycin treatment and be able to ascertain how this correlates with oesophageal function. Additionally, we will look into the relationship of objective cough frequency data and repetitive subjective cough evaluation using cough VAS.

4. TRIAL POPULATION

Participants will be identified by their usual clinical team treating their chronic respiratory disease in secondary care outpatient services. Potential participants who are being considered for treatment with long-term azithromycin (defined as >6 months daily or three times weekly

treatment) will be alerted to the trial team and will be approached for potential participants in the study. All staff working within the study, including clinicians and specialist nurses, will undergo training in the trial protocol, including the inclusion and exclusion criteria.

For this study, all patients with a chronic respiratory disease, as diagnosed by a consultant respiratory medicine physician, who are being considered for long-term azithromycin therapy will be eligible for participation in the study.

Participants that do not meet all the inclusion criteria or who meet any of the exclusion criteria will be ineligible to participate in this study.

4.1 Inclusion Criteria

- Males and females aged ⩾18 years.
- Have a diagnosis of chronic respiratory disease (COPD, asthma, interstitial lung disease, chronic cough, cystic fibrosis, and/or bronchiectasis) confirmed by a consultant respiratory physician.
- Exhibit symptoms consistent with airway reflux, demonstrated by a score ⩾14 on the Hull Airways Reflux Questionnaire.
- Are being initiated on azithromycin treatment as part of routine clinical care by their usual clinician. This will include all common treatment regimes, 250mg once daily, 250mg three times per week, and 500mg three time per week.
- Are willing and able to consent to all trial procedures.

4.2 Exclusion Criteria

- Previous treatment with long-term macrolides in the past 3 months.
- Unable to be investigated with HROM due to contraindications such as anatomical abnormalities or diseases of the oesophagus or unwilling/ unable to be investigated with HROM based on the clinical judgement of the investigators due to severity of lung disease.
- Have another cardiorespiratory cause for their symptoms (such as heart failure or lung cancer).
- Are unable or unwilling to consent to or complete the trial procedures .
- Women of child bearing potential not using effective means of contraception. Effective methods of contraception include any oral contraceptive pill, any intrauterine device, any long term contraceptive implant, and any long-acting contraceptive injection
- Have been involved in another medicinal trial (CTIMP) within past four weeks.

4.3 Participant Identification and Screening

All patients attending the Hull University Teaching Hospitals NHS Trust (HUTH) respiratory medicine outpatient department for management of their chronic respiratory disease and are being considered for long-term treatment with azithromycin will be considered suitable for participation. Respiratory medicine clinicians and specialist nurses working within the trust will be trained and instructed in the recruitment procedure and any patients who may meet the eligibility criteria will be referred to the trial team and contacted, with the patients' consent and after given time to consider participation and ask questions, for screening to assess eligibility to participate in the study.

Participants expressing an interest in the trial will be provided with a participant information sheet and informed consent will be obtained. All eligible patients who are approached for the trial will be invited to complete a short anonymous questionnaire (Appendix: Trial Invitation Experience Survey) assessing their experience of recruitment and why they consented to participate or declined.

Participants that fail screening can be re-screened (to a maximum of 3 times) if the reason for screen failure is resolved prior to completion of trial recruitment. Participants entering the trial following re-screening after an earlier failed screening will be allocated a new trial ID and have their earlier trial ID and the reason for initial screen failure recorded in their CRF and the Participant Master Index.

4.4 Participant Withdrawal

Each participant must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating clinician. The investigator(s) or sponsor may withdraw participants from the trial only if indicated by safety/clinical issue or trial protocol. Participants that discontinue azithromycin will not repeat the HROM trial but will be asked to complete all other trial processes such as questionnaires and spirometry if they are willing and have consented to do so. Participants who decline a second HROM trial after their initial trial will be asked to complete all other trial processes if they are willing and have consented to do so.

Participants should remain in the trial for follow-up unless they request to fully withdraw. All data up to the point of withdrawal should be stored. Participants who choose to withdraw or who complete will be invited to complete a short anonymous survey (Appendix B: Trial Experience Survey) to determine their experience of trial participation and any reasons for withdrawal.

In the event of participant withdrawal, the investigator(s) will promptly explain to the participant that their involvement in the trial will discontinue and explain why. The patients' treating clinician will provide medical treatment and/or other necessary measures deemed appropriate by the usual clinician or the participant. This information will be recorded in the CRF. If a participant loses capacity to consent to trial procedures during the trial period, they will be withdrawn from the study. Any data already collected from their participation may be used in the final analysis.

Participants who discontinue early from the trial treatment and/or follow-up will do so for one of the following primary reasons: AE(s), participant deterioration of disease, participant death, lost to follow-up, participant withdrew consent, significant protocol violation. Trial discontinuation information will be documented on the participants CRF.

5. TRIAL ASSESSMENTS

5.1 Summary

Participants who fulfil all eligibility criteria and present no contraindications will be observed for 28 days (up to 42 days) on their azithromycin treatment as part of usual care as decided by their treating clinician. Participants will be advised to continue to take all other usual treatments as instructed by their treating clinician.

Participants will be encouraged to comply with other usual treatments of their respiratory disease, including inhaled and oral medications, throughout the duration of the study.

5.2 Assessment Fidelity

Any deviation from the protocol regarding azithromycin treatment, either curtailment or inconsistent administration of treatment, will result in exclusion from analysis.

5.3 High-resolution oesophageal manometry protocol

All participants will be investigated using a standardised HROM technique. Participants will be advised to fast 4 hours prior to investigation and will be investigated with a 36-channel combined

manometric and impedance monitoring catheter. This catheter will be inserted trans-nasally to a length of 60cm from the nostril. Participants will then be asked to lay supine for 5 minutes prior to measurement.

A standardised protocol of oesophageal function tests will be followed, with further tests utilised if felt appropriate by the clinical scientist performing the test. The mandatory tests include:

- 10 separate swallows of 5mls of water with an interval of 15 seconds between each swallow.
- The participant will then be asked to complete 5 rapid swallows, ingesting 2mls of water at each swallow.
- The final test will consist of the participant swallowing 5 small pieces of white bread in 5 separate swallows.

Each trial will be analysed manually by an expert gastrointestinal physiologist and a full analysis report will be produced each individual trial in each participant.

6. OUTCOMES AND MEASURES

6.1 Feasibility outcomes

This study's primary outcomes will be the feasibility and acceptability outcomes, these include:

- Recruitment: eligibility to consent ratio, recruitment rate, and participant retention to follow-up.

- Data quality: Completion of clinical outcomes at follow-up and patterns of missing data for the trial measures. Completion of participant symptom questionnaires throughout the study. Completion of trial processes, principally HROM.

- Acceptability of assessment: Quantify the proportion of participants who judge the trial investigations, principally HROM, to be acceptable.

6.2 HROM Testing Measures

The following HROM test variables will be assessed:

- Distal Contractile Integral: The average DCI from the 10 liquid swallows will be collected and will be used to quantify the vigour of oesophageal contraction.
- Integrated Relaxation Pressure: The average IRP4sec is defined as the average minimum oesophagogastric junction pressure for 4 seconds of relaxation and will be ascertained by the collecting the average measurement over the 10 liquid swallows. This will give a quantification of the adequacy of relaxation at the oesophagogastric junction.
- Lower Oesophageal Sphincter Resting Pressure: Basal and relaxation LOS pressure measurements will be taken, and the LOS Resting Pressure will be measured for all participants.
- Chicago Classification: Using Version 4.0 of the Chicago Classification we will provide each participant with a manometric diagnosis. These diagnoses include: Normal Motility, Ineffective Oesophageal Motility, Absent Contractility, Achalasia, EGJ Outflow Obstruction, Hypercontractile Oesophagus, and Distal Oesophageal Spasm. Participants will receive a classification at baseline and at follow-up.
- Presence of a Hiatus Hernia: All HROM examinations will be analysed for likelihood of the presence of a hiatus hernia.

6.3 Symptom Burden Measures

In this study, we will measure symptom burden broadly with general symptom scores on cough, sputum production, breathlessness, and symptoms associated with airway reflux. We will also assess disease-specific symptom burden for the participants' diagnoses.

6.3.1 Hull Airway Reflux Questionnaire

- All participants included in the trial will be assessed with the HARQ, a validated tool for assessing symptoms of reflux, at screening, baseline (pre-treatment), and follow-up (post-treatment). Participants successfully enrolled on the trial will have an abnormal HARQ score of ≥14. We will compare the differences between participants at baseline and follow-up and correlate this to their HROM findings.

6.3.2 Breathlessness, Cough, and Sputum Scale (BCSS)

- All participants will be assessed using the validated Breathlessness, Cough, and Sputum Scale at baseline and follow-up as a generic measure of their symptom burden. We will compare the differences between participants at baseline and follow-up and correlate this to their HROM findings.

6.3.3 Medical Research Council (MRC) Dyspnoea Scale

- All participants included in this trial will have a baseline and follow-up MRC dyspnoea scale recorded.

6.3.4 Visual Analogue Scales (VAS) – Cough severity

- All participants will be asked to complete a VAS assessment at baseline and follow-up, and repetitive VAS measures through the use of a physical 'cough diary' while being monitored with the Hyfe Cough Tracker. This records the participants' assessment of cough severity on a 100mm linear scale ranging from 'no cough' (0mm) to 'worst cough imaginable' (100mm). We will ask participants to complete a cough severity VAS tool daily for the duration of the study.

6.3.5 COPD Assessment Test (CAT)

- All participants whose primary respiratory diagnosis is COPD will be assessed using the CAT at baseline and at follow-up. This is an 8-item questionnaire which aims to quantify the symptom burden of patients with COPD and how this impacts their life.

6.3.6 Asthma Control Questionnaire (ACQ)

- All participants whose primary respiratory diagnosis is asthma will be assessed using the ACQ at baseline and at follow-up. This is a 7-item questionnaire that aims to assess the symptomatic control of patients with asthma.

6.3.7 Numerical Rating Scale – Breathlessness Severity

- All participants will be asked to complete a numerical rating scale of their breathlessness at baseline. This will be a horizontally arranged scale numbered 0-10, with 0 representing no breathlessness and 10 representing the worst breathlessness imaginable.

6.4 Disease Specific Health Status and Quality of Life

6.4.1 Leicester Cough Questionnaire (LCQ)

- All participants with a primary respiratory diagnosis of chronic cough will be assessed using the LCQ at baseline and at follow-up. This 19-item questionnaire uses a 7 point Likert scale to assess the impact of cough on the physical, social, and psychological welfare of the patient.

6.4.2 St. George's Respiratory Questionnaire

All participants will be assessed using the short-form SGRQ at baseline and at follow-up. This 40-item questionnaire is aimed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.

6.4.3 King's Brief Interstitial Lung Disease Questionnaire

- All participants with a primary respiratory diagnosis of interstitial lung disease will be assessed using the KBILDQ. This is a 15 item 7-point Likert scale questionnaire aimed to measure the impact of ILD on quality of life and health status. Measurements will be taken at baseline and follow-up.

6.4.4 Cystic Fibrosis Questionnaire

All participants with a primary respiratory diagnosis of cystic fibrosis will be asked to complete a CFQ at baseline and at follow-up. This is a 50-item questionnaire aimed to assess the overall health, daily functioning, and wellbeing of patients with cystic fibrosis.

6.5 Continuous cough monitoring using the Hyfe Cough Tracker

The Hyfe Cough Tracker is a wellness information tool (artificial intelligence-based software for smartphones or wearable devices, such as smartwatches) to objectively, continuously and passively monitor cough. The app captures, records and processes only 0.5s sound snippets after some explosive sound is detected that is greater than a set threshold above background noise signal. This period of time is enough for the artificial intelligence cough classifier to determine if the sound was a cough or not, and not enough to discover some personal data out of this 0.5s sound snippet, therefore allowing for continuous cough monitoring and preserving privacy. Such sound snippets, classified as "cough", are stored in a secure server and made available for the investigator playback. Each sound recording includes a time stamp and, if users enable location sharing, a GPS coordinate. Daily cough counts, their dynamics (diurnal variation, mean counts, among other) and sound playbacks are available for the investigator on a web-based dashboard. The dashboard only displays anonymised data as every participant receives a

dedicated Hyfe ID, which is only known to the investigator, and not for the staff at Hyfe.
We will assist in setting up the Hyfe Cough Tracker equipment and hand out dedicated devices with the application (to be determined - either a dedicated smartphone, or a smartwatch) to the study participants who provide separate consent to record cough sounds over at least a 7-day period prior to azithromycin initiation. Participants will then be asked to "wear" the cough recording device in between the two study visits.
The captured data from the Hyfe Cough Tracker will be accessible by the investigator at any time through the web-based, secure dashboard and will be used to share objective cough dynamics with the participants on their visits.
Basic, non-identifiable demographic information will be shared with Hyfe (with participant consent), including sex, year of birth, respiratory diagnosis, and date of testing.

7.1 Participant Recruitment and Consent

Potential participants will be identified from the Hull University Teaching Hospitals NHS Trust respiratory medicine outpatient department. Participants will be eligible for screening if their usual treating clinician feels it appropriate to initiate long-term azithromycin treatment as part of their usual NHS care. Patients can be included in the trial if they have already undergone HROM investigation in the past 3 months prior to identification and are being initiated on long-term azithromycin treatment, however patients cannot have been taking azithromycin at the time of their previous HROM investigations.

All participants will be given adequate time to consider the trial and formulate questions. Any questions will be addressed and answered fully by the PI or delegated trial doctor. An actual period is not specified. All potential participants will be given a Participant Feedback Questionnaire to complete and return.
The PI retains overall responsibility for obtaining informed consent of participants at site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, the UK clinical trial regulations, GCP and the Declaration of Helsinki.

Only delegated trial doctors will be allowed to take consent in this study. All consent forms will be completed and stored in accordance with local ethics and general data protection regulation requirements.

7.2 Screening for Eligibility

A Participant Screening Log will be kept of all potentially eligible participants including the reasons for non-entry and/or non-approach, if applicable by all the study team.

An initial screening assessment will be undertaken prior to signing the informed consent form to ascertain that the participant may be potentially suitable for the trial and can be approached. Only eligible, consenting participants will proceed to undertake trial measures as outlined in Section 7.3.

The plan of management will be checked with the potential participant's usual treating physician to identify any planned or expected change to management during the trial period that may impact trial participation.

Participants identified as being potentially suitable for entry into the trial and who are approached about the trial and have given consent will undergo a review of eligibility criteria and complete eligibility screening.

Information about eligibility will be obtained from discussion with the potential participant and review of the participant's medical record.

7.3 Screening Visit (Day -28 to -7)

Suitable participants who have been identified on specialist assessment by the HUTH respiratory medicine department or the trial team will be screened for eligibility and will obtain informed consent if eligible. If the participant agrees to take part in the study, they will undertake screening. The following procedures will be performed during this visit:

Eligibility Assessment:

- Review of inclusion and exclusion criteria
- Consent if eligible
- Participant invitation experience questionnaire*
- Hull Airway Reflux Questionnaire
- Set up of the Hyfe Cough Tracker© device
- Cough VAS

7.4 Baseline Assessment Visit (Day 0)

Participants will be invited to attend the Respiratory Medicine Clinical Trials Unit at Castle Hill Hospital for baseline assessment visit within 1 month of screening. Participants who have not had an HROM performed within 3 months prior to screening will also undertake their initial HROM investigation during this visit.

Baseline Assessments:

- Medical history
- Review of previous laboratory results (provided they have been performed as part of routine clinical care in the 3 months prior to recruitment):
    - Blood Haemoglobin level
    - Total blood white cell count
    - Total blood eosinophil count
    - Blood alanine transaminase
    - Blood alkaline phosphatase
    - Blood bilirubin level
    - Blood albumin level
    - Sputum microscopy, culture, and sensitivity results.
- Physical examination
- Monitoring of vital signs
- Weight and height
- Electrocardiogram
- Spirometry
- BSCC
- HARQ
- MRC Dyspnoea Scale
- St George's Respiratory Questionnaire
- Disease-specific symptom questionnaires
- Disease-specific quality of life questionnaires
- Cough Visual Analogue Scale
- Monitoring of cough frequency using the Hyfe Cough Tracker
- Initial HROM investigation as per the HROM protocol in section 6, performed by a clinical scientist specialising in GI physiology.

All individuals undergoing screening will be asked to complete an anonymous survey ('Invitation Experience Survey'*:) whether they consent to take part in the trial or not. If participants agree to complete the questionnaire this will be taken as implied consent for the information they provide in the survey to be used for the purposes of this study. This survey will be completed with the help of a member of the trial team and stored in the site file.

7.5 Follow-up Visit (Day 28 to 42)

Participants will be asked to attend for follow-up assessments at 28-42 days after initiation of azithromycin therapy. The participants will undertake a full follow-up assessment and will also have a full review of their condition, including healthcare utilisation, side effects from azithromycin treatment, and experience of HROM investigation.

Follow-up assessment:

- physical examination
- Vital signs
- Electrocardiogram
- Spirometry
- BSCC
- HARQ
- MRC Dyspnoea Scale
- St George's Respiratory Questionnaire
- Cough Visual Analogue Scale
- Disease-specific symptom questionnaires
- Disease-specific quality of life questionnaires
- Monitoring of cough frequency using the Hyfe Cough Tracker©
- Follow-up HROM investigation as per the HROM protocol in section 6, performed by a clinical scientist specialising in GI physiology.
- SAE/ AE reporting
- Health care utilisation recording
- Evaluation of usual care received
- Trial experience survey

7.6 Allowable Therapies

Usual care will be provided throughout the trial to all participants. Details of usual care received will be recorded in the CRF during trial visits. Usual care includes any intervention that would ordinarily be offered out-with the trial setting.

Usual care includes, but is not limited to, oral corticosteroids, inhaled or nebulised bronchodilators, mucolytic therapy, and pulmonary rehabilitation.

8 Trial Investigation of Medicinal Product (IMP)

8.1 IMP supply, storage and Dispensing

Azithromycin will be supplied from pharmacy stock and stored in ambient temperature conditions within the drug cupboard. Azithromycin will be standard treatment for the participants as prescribed by the treating clinician.

8.2 Dosing of IMP

The dosage for Azithromycin will be as per common treatment regimens and be administered orally.

9. PHARMACOVIGILANCE

9.1 Definitions for safety reporting

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ▪ results in death ▪ is life-threatening ▪ requires inpatient hospitalisation or prolongation of existing hospitalisation ▪ results in persistent or significant disability/incapacity ▪ consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: ▪ in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product ▪ in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.1.1 Reporting Adverse Events

All adverse events will be reported in accordance with HUTH R&D department's Safety Reporting standard operating procedure (R&D GCP SOP 07) to ensure compliance with UK Clinical Trial Regulations. All SUSARs relating to Azithromycin will be reported to the competent authority/authorities using the SUSAR reporting routes.

9.1.2 Adverse Event reporting period

The AE reporting period for this trial begins when the participant has consented to the trial and ends at the participant's final trial visit. Each trial participant will be questioned about adverse events at each visit and the trial team will examine medical records at each visit to identify any AEs that may have occurred. The investigator will record all directly observed AEs and all AEs spontaneously reported by the trial participant. A pre-existing condition (i.e. a disorder present before the AE reporting period started and noted on the pre-trial medical notes), is not to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-

reporting period. All adverse events (serious and non-serious) will be recorded in participants data collection forms (CRFs) using the adverse event report form. All adverse events will be recorded in participants' medical records. All AEs will be followed-up until the event has resolved or a decision has been taken for no further follow-up.

However, if a patient provides informed consent but is subsequently found to be ineligible, then the reporting period will end at the point that the decision was made that the patient was ineligible.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes.

9.2 Assessment of SAE's

Severity Assessed by the Co-I and PI or just PI	The assessment of severity of an SAE will be based on the investigator's clinical judgement using the following definitions: **Mild:** An event that is easily tolerated by the trial subject, causing minimal discomfort, and not interfering with everyday activities. **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities. **Severe:** An event that prevents normal everyday activities.
Seriousness Assessed by the Co-I and PI or just PI	An event is considered serious if it meets one or more of the following criteria: (a) results in death (b)life-threatening (c) requires hospitalisation or prolongation of existing hospitalisation (d) results in persistent or significant disability or incapacity (e) consists of a congenital anomaly or birth defect. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above should also be considered serious.

	Additionally, the investigator must assess whether the AE is unexpected (ie. not listed in the trial protocol as an expected occurrence).
Causality Assessed by the Co-I and PI or just PI	The investigator will assess whether the SAE is likely to be related to the IMP according to the following definitions: • **Unrelated**: Where an event is not considered to be related to the IMP. • **Possibly related**: The nature of the event, the underlying medical condition, concomitant medication, or temporal relationship make it possible that the SAE has a causal relationship to the study drug.
Expectedness Assessed by the R&D Director (on behalf of the Sponsor) for single-site trials	To assess expectedness, the R&D Director will need to check if the SAR is listed in the Reference Safety Information (RSI). The RSI for IMPs with a marketing authorization (MA) is section 4.8 (Undesirable Effects) of the MHRA approved Summary of Product Characteristics (SmPC) or for IMPs without an MA, the RSI is the relevant section in the Investigator Brochure (IB). If the SAR is listed in the RSI then it is expected. If the event is not listed in the RSI then it is unexpected and is a SUSAR and subject to expedited reporting to the MHRA and REC.

9.2.1 Reporting Serious Adverse Events

All SAEs (except those defined as not requiring expedited reporting – see section 8.2.2) will be reported to the Sponsor using the study specific SAE report form, within 24 hours of the research staff becoming aware of the event. For SAE's, the following information will be collected:

- Full details in medical terms and case description

- Event duration (start and end dates, if applicable, and if admitted, admission and discharge dates, with specialty noted)
- Action taken
- Outcome
- Seriousness criteria
- Causality (ie. related or unrelated to the intervention)
- Whether the event would be considered expected or unexpected (this assessment is made by the Sponsor).

Assessment of severity, seriousness and causality will be made by the PI or another authorised study doctor. The PI or authorised study doctor will need to decide whether the serious event is an SAE or SAR by assessing whether the event is either unrelated or possibly related to the IMP (causality). If the event is possibly related then it is a SAR, and an assessment needs to be made by the Sponsor as to whether the event is expected or not for the IMP. If the SAR is listed in Section 4.8 of the MHRA approved Summary of Product Characteristics then it is expected.

In addition to the PI, the Sponsor will also be required to assess causality and document their assessment on the SAE form. The Sponsor must assess causality after the PI and must confirm that they have not influenced the PI. The PI's assessment of causality must not be downgraded by the Sponsor.

If an authorised study doctor from the reporting site is unavailable, initial reports without the causality assessment will be submitted to the Sponsor by a healthcare professional within 24hours of becoming aware of the SAE but will be followed-up by medical assessment as soon as possible thereafter. The PI must always review the SAE form and sign to confirm the contents of the report are accurate and complete and that he/she has also assessed the severity, seriousness, and causality of the SAE.

Any change of condition or other follow-up information should be reported to the Sponsor using the study specific SAE follow-up form as soon as it becomes available. Events will be followed up until the event has resolved or a final outcome has been reached. The PI is required to assess causality again on the follow-up form. If the PI has a change of opinion on causality after considering the additional follow-up information, the Sponsor will be required to reassess causality and if a SAR, then to assess expectedness.

All SAEs assigned by the PI or authorised study doctor as possibly related to IMP-treatment and those the Sponsor has assessed as unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA.

Responsibilities

The responsibilities regarding AE and AR reporting as follows:

Principal Investigator (PI):

1. Checking for AEs and ARs when participants attend for treatment / follow-up.

2. Using medical judgement in assigning severity, seriousness, and causality.

3. Ensuring that all SAEs and SARs are recorded and reported in line with the requirements of the protocol and SUSARs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

4. Ensuring that AEs and ARs are recorded and reported in line with the requirements of the protocol.

5. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

A medical R&D Director will assess causality and expectedness of behalf of the Sponsor:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.

2. Using medical judgement in assessing, causality of SAEs.

3. In order to assess expectedness, the R&D Director will need to check if the SAR is listed in the Reference Safety Information (RSI). If the SAR is listed in the RSI then it is expected. If the event is not listed in the RSI then it is unexpected and is a SUSAR and subject to expedited reporting to the MHRA and REC.

4. Immediate (within 24 hours) review of all SUSARs.

5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

6. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.

7. Reporting safety information to the Sponsor Oversight Group for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

8. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.

9. Notifying Investigators of SUSARs that occur within the trial.

10. The unblinding of a participant for the purpose of expedited SUSAR reporting.

11. Checking for (annually) and notifying the PI of updates to the Reference Safety Information for the trial.

12. Preparing standard tables and other relevant information for the DSUR in collaboration with the PI and ensuring timely submission to the MHRA and REC.

Unexpected SAE's related to the intervention will be reported to the MHRA, Research Ethics Committee that gave a favourable opinion of the trial and the sponsor (Hull University Teaching Hospitals NHS Trust R&D department) **within 7 days** of the principal investigator becoming aware of the event using the electronic SUSAR (eSUSAR) reporting form available from: https://esusar.mhra.gov.uk/ Any additional relevant information must be sent within 8 days of the initial report.

A SUSAR which is not fatal or life-threatening must be reported to the MHRA and REC as soon as possible and no later than **15 days** after learning of the event.

9.2.2 Reporting SUSARs

The Sponsor (HUTH R&D dept.) will report fatal or life-threatening SUSARs to the MHRA within 7 days and follow-up information within a further 8 days. The sponsor will send all other SUSAR reports to the MHRA within a maximum of 15 days. The Sponsor will report fatal or life-threatening SUSARs to the Research Ethics Committee (REC) within 7 days and follow-up information within a further 8 days by following the request on the Serious Event Initial and Follow-up report forms. The Sponsor will send all other SUSAR reports to the REC within a maximum of 15 days.

9.2.3 Expected Serious Adverse Events

Due to the seriousness of the disease in this study, the following expected SAEs will not require reporting within 24hrs on the initial and follow-up SAE forms, but will still need to be reported on the trial AE report form.

Expected serious adverse events in this trial include:

Expected Serious Adverse Events
Hospital admission due to respiratory condition
Admission to hospital or prolongation of existing hospitalisation for a pre-existing condition such as heart failure
Death due to exacerbation of respiratory disease or known pre-existing condition
Elective surgery

Hospital admissions and deaths are common in certain patient groups in the study, such as COPD and ILD, due to their underlying disease. Thus, admissions related to such participants' underlying condition or co-morbidities will be classified as an expected SAE in which case the report will not have to be submitted within the timeframe of 24 hours but should be recorded in the participant's CRF.

9.3 Pregnancy Reporting

If a trial participant becomes pregnant whilst participating in the trial, the patient will be withdrawn from trial treatment but will continue to be followed-up for trial outcomes. The pregnancy will not be considered an AE. The patient will be followed up by one to two monthly visits/telephone contacts during pregnancy, and at birth and at 3 months after the birth of the baby. Should there be a congenital anomaly or birth defect, then this will be reported as an SAE/SAR/SUSAR.

9.4 Reporting urgent safety measures

If any urgent safety measures are taken the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.These urgent safety measures may be taken without prior authorization from the MHRA, EC or Trust (HUTH R&D). The investigator must alert HUTH R&D (Sponsor) as soon as possible of the urgent measures taken by contacting the R&D Office telephone number 461883 or 461903 (Mon – Fri 8am – 5pm) or the Trust Switchboard 875875 (out-of-office hours) and asking for either the R&D Manager (James Illingworth) or R&D Director (Professor Sathyapalan). The CI/PI or HUTH R&D should phone the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor as soon as possible. Contact the MHRA CTU via the clinical trials for medicines helpline 020 3080 6456 (Monday - Friday 08.30am to 4.30pm).HUTH R&D should notify pharmacy clinical trials staff as soon as possible. The CI/PI must notify the MHRA, REC and Trust (HUTH R&D) in writing **within 3 days** after the urgent measures have been taken, by emailing the clinical trial helpline at clintrialhelpline@mhra.gov.uk and by submitting a substantial amendment notification form. Note that if the decision is made with HUTH R&D to halt the study due to the urgent safety measures then this can be added to the substantial amendment form and would save submitting another substantial amendment for the temporary halt.

The substantial amendment form and any supporting documents should be sent with a covering letter detailing;

- the urgent measures taken
- the reasons for them
- the medical assessor contacted

9.5 Development safety update reports

The PI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee and Sponsor. The MHRA approved SmPCs will need to be reviewed for up-dates annually at the time the DSUR is completed. If the SmPC(s) has been updated, the PI and Sponsor will risk assess the changes and decide if they have an impact on patient safety. If the decision is that the updated SmPC(s) need to be used as the new Reference Safety Information (RSI) then this must be submitted to the MHRA as a substantial amendment. The updated SmPC(s) can be used once approved by the MHRA. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) or the MHRA clinical trial authorisation of the trial each year until the trial is declared ended.

9**.6 Concerns with the Investigational Medicinal Product**

The investigator team must alert the Sponsor straight away of any concerns regarding the IMP, this may be to do with the expiry of the IMP or the reaction of patients to the IMP or other concerns. The Sponsor will inform pharmacy and with pharmacy and the PI will decide whether it is appropriate to trigger the IMP recall SOP.

9.7 Notification of serious breaches to GCP and/or the Clinical Trial Protocol

A serious breach is defined as likely to effect to a significant degree:

(a) the safety, physical or mental integrity of the patients

(b) the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The Sponsor will notify the competent authority in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with this trial

(b) the Clinical Trial Protocol and its amendments (if applicable) relating to this trial within 7 days of becoming aware of that breach.

Safety Assessments:

The collection and reporting of data on adverse events and serious adverse events will be in accordance with ICH GCP and The UK framework for health and social care research.

10. DATA HANDLING AND QUALITY ASSURANCE

10.1 Data Collection

Investigators will enter the information required by the protocol onto the CRFs in accordance with the CRF Completion Instructions that are provided with the CRFs. Source Data Verification will be performed by the HUTH R&D Clinical Trials Monitor at regular intervals during the study according to the Monitoring Plan. Data discrepancies will be flagged to the investigator and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

10.2 Database, Data Handling, and Quality Assurance

All data management (use, control, storage) will be according to the requirements of the General Data Protection Regulation 2018. The database will be password protected and stored on a shared drive belonging to the Hull University Teaching Hospitals NHS Trust. Access will only be granted to staff associated with the trial that already agree and abide to the HUTH CP134 – Confidentiality and Information Security Policy. These staff will have individual log in and password details. Entry of data to database will be via transfer of information from paper copy (Case Report Form) with all information necessary as delineated by protocol

Participants will be informed that their personal data will be pseudo-anonymised and related forms and questionnaires will be identified using a participant trial number only. All hard copy data will be stored in a locked filing cabinet in accordance with data protection requirements for the retention of research data and local site data management policies.

The main trial database will be developed by the Respiratory Clinical Trials Unit at Castle Hill Hospital. Access to the database is controlled by encrypted password on secure NHS computers

at the Respiratory Clinical Trials Unit. The Sponsor will review the database prior to data entry and ensure there is an audit trail *in-situ*.

HUTH IT Services Department has a backup procedure approved by auditors for disaster recovery of files held on the Y: drive servers. The servers are backed up to disk media each night. The disks run on a 4 week cycle. Files stay on the server unless deleted by accident or deliberately. Anything deleted more than 4 weeks previously is therefore lost. Additional 'archive' backups are taken for archived data, so data should not be lost from this type of system. Disks are stored in a fireproof safe.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

10.3 Hyfe Cough Tracker© Cough Data Storage

All participants are provided a unique study ID and will also be provided with a unique Hyfe Cough Tracker app user identifier if they provide consent to participate in this activity. Only local investigators will have access to the key allowing for linkage of cough data and recordings with patient identification and any other metadata collected as part of the study.

Putative cough sounds (i.e., "explosive" sounds) recorded using the Hyfe Research app will be <0.5 seconds in duration and uploaded to a secure server. Non-explosive sounds are immediately discarded upon processing. The short length of the recordings means they cannot be used to identify the patient (unlike prolonged sound recordings, like Amazon's Alexa device). Standard data encryption and safety tools will be employed.

At all points, participants can opt out of the study and monitors/phone apps will be removed. Our consent process will explicitly describe exactly what is and is not recorded. We will employ standard data encryption and safety tools at rest and in transit. Specifically, this project will use the Hyfe Cough Tracker app, which uses the Google Cloud platform for data management and storage. Firebase uses industry-standard encryption and security protocols.

Fire store, the Google Cloud storage architecture (where audio files and associated meta-data are stored) is HIPAA-compliant. Both audio files and associated meta-data are encrypted in transit using HTTPS. When the server receives a file, it is processed through the Hyfe algorithms, and sounds likely to be cough are stored in <=0.5 second files on encrypted disks.

Data will be transferred from Hyfe to the research team via a data dump occurring at regular intervals (usually one week). Each research participant/site will be associated with a "Hyfe ID" number; all audio files and meta-data transferred from Hyfe to the research team will be linkable to the study participant/site via this "Hyfe ID" number. Hyfe will not have access to the study participants' identity. Basic non-identifiable demographic information such as year of birth, sex, and diagnosis will be shared with Hyfe. Data will be transferred in encrypted form over a secure line (HTTPS); only the PI or authorized delegate on the research team will have the decryption key. The software used for handling transfers will be a custom-made web application, hosted on the Google Cloud platform on servers physically located in the United States.

11. STATISTICAL METHODS

The primary feasibility outcomes will consist of recruitment rate, retention rate, adverse events, compliance, and acceptability of the HROM assessment. The recruitment rate, consisting of the eligibility and consent rate will be calculated with 95 % confidence intervals (CI). A table showing baseline demographic and clinical characteristics for each group will be presented to indicate any differences between groups. Participant characteristics will be summarised using appropriate statistics. Medians (IQR) will be reported for ordinal data, mean (standard deviation) for continuous data and raw count (number (%) will be reported for nominal data.

For the clinical outcomes, all HROM data will be recorded, and median metrics will be recorded for the overall participant cohort and will be broken down into smaller categories based on primary respiratory diagnoses. Questionnaire data will be reported for all participants and mean scores will be reported. A table showing baseline demographic and clinical characters will be presented. Participant characteristics will be summarised using appropriate statistics. Medians (IQR) will be reported for ordinal data, mean (standard deviation) for continuous data and raw count (number [%]) will be reported for nominal data.

Comparison of baseline and follow-up HROM and questionnaire data will be made using paired t-tests for normally distributed data and Mann-Whitney U testing for skewed data. Averages of all

HROM metrics and questionnaire data will be presented in tables and p-values of the statistical tests will be displayed alongside this data.

Safety data will be summarised using descriptive statistics.

12. TRIAL MANAGEMENT

12.1 Trial Oversight

Hull University Teaching Hospitals NHS Trust will act as sponsor for the study. There will be a trial management group (TMG) set up to oversee the operation of the study.

Membership details of these committee:

The TMG consists of the Principal Investigator (Dr Dominic Sykes) and other trial investigators Dr Michael Crooks, Dr Simon Hart, and Prof Alyn Morice. The TMG will meet before recruitment begins, and every 3 months. Additional meetings will be arranged if required. The TMG will oversee progress and achievement of milestones. Minutes of the meetings will be stored in the Investigator Site File.

These committees will function in accordance within standard operating procedures/NIHR terms of reference.

132. PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

13.1 Ethics

The protocol, participant information leaflet (PIL), informed consent form (ICF) and appropriate related documents must be reviewed and approved by a REC. Any protocol amendment and/or revision to the PIL or ICF will be resubmitted to the REC for review and approval (except for changes involving only logistical or administrative aspects of the study).

A signed letter of trial approval from the REC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to trial start. If the REC decides to suspend or terminate the study, the Investigator will immediately send the notice of trial suspension or termination by the REC to the Sponsor.

Trial progress is to be reported to RECs as required by the Investigator(s) or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the REC, they will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the REC of any reportable AEs as per ICH guidelines and local REC standards of practice. Upon completion of the study, the Investigator will provide the REC with a brief report of the outcome of the study, if required.

13.2 Participant Information and Informed Consent

As part of the informed consent process, the Investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each participant must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating clinician.

This informed consent should be confirmed by the signing of the REC approved consent form by the participant. The participant should understand the information in the participant information leaflet and the statements on the consent form before signing and dating it. The participant will be given a copy of the signed form. The participant will be asked to sign the consent form prior to any study-specific procedures being performed.

The form must be signed and dated by an appropriately trained member of the research team directly after the participant has signed. A copy of the signed ICF will be given to the participant and a copy will be filed in the participant's medical records. The original signed ICF for each participant will be kept in the Investigator Site File.

The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information should be documented.

13.3 Discontinuation/Withdrawal of Participants from Study

Each participant has 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 including:

- Pregnancy

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event, which requires discontinuation of the study medication or results in an inability to continue to comply with study procedures
- Consent is withdrawn
- Lost to follow up
- Loss of participant mental capacity to follow the trial protocol

If the participant withdraws consent, no further trial activity will occur, and any samples will be destroyed and the reason for withdrawal will be recorded in the CRF.

As part of the consent process the participant will be asked if all data collected up until the time of withdrawal can be used as part of the study results. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. Their data may still be used for analysis.

13.4 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any substantial change to the protocol requires a written protocol amendment that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of participants, or the scientific quality of the trial require additional approval by the REC and HRA. These requirements should in no way prevent any immediate action from being taken by the Investigator(s), or by the Sponsor, in the interest of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt by the Investigator(s) to be necessary for safety reasons, the Sponsor must be notified promptly and the REC must be informed as soon as possible.

Changes affecting only administrative aspects of the trial are known as non-substantial amendments and only require notifying to the HRA.

The Investigators will conduct the trial in strict accordance with the protocol.

13.5 Monitoring Procedures

The Sponsor representatives (HUTH R&D QA staff) will maintain contact with the Investigator(s) and designated staff by email or telephone between trial visits. Monitoring visits to the investigational sites will be conducted by the HUTH R&D monitor. The Investigators will allow the monitor to view the clinical facilities to assure compliance with the regulations and GCP. The CRFs and participant's corresponding original medical records (source documents) are to be fully available for review by the R&D monitor at regular intervals. These reviews are to verify adherence to the protocol and data accuracy in accordance with the regulations and GCP.

The trial will be monitored in accordance with HUTH R&D department's standard operating procedures to ensure compliance with UK Clinical Trial Regulations and ICH GCP. All trial related documents will be made available upon request for monitoring by R&D monitors and for inspection by the MHRA.

Protocol non-compliance are departures from the approved protocol.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations for Clinical Trials and therefore will not be permitted for this trial.

Accidental protocol deviations can happen at any time. If they occur they must be documented on the Protocol Deviation Log and reported to the Sponsor

13.6 Recording of Data

In order that data are accurate, complete, and legible, the following criteria are to be maintained:

- The Investigator(s) will enter the information required by the protocol onto the CRFs.
- Paper records will be kept by the Investigators in a secure location at the investigational site during the conduct of the study.
- When data are corrected, the previous data is still visible and the reason is written next to the correction.
- The Principal Investigator signs off the CRFs after checked and confirmed as fully completed by Investigators.
- Data reported on the CRF that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- The Investigators uses participant's initials and trial number to identify participants.

13.7 Source Documents

Participant's hospital records

A trial participant may see a variety of clinicians, GPs and other health care professionals over the course of the trial. It is important that the data from a participant's trial visit is written clearly into their medical records so that other clinicians and health care professionals are informed of any relevant results or information that may affect the patient's ongoing medical care.

As a minimum, the following information will be recorded in patient's medical records from trial visits or telephone contacts:

- Clearly written date of visit or contact, trial acronym and visit number.
- Date participant given participant information sheet
- Date consent form signed
- Date of screening
- Medical history, concomitant diseases and medication including trial medication, and any changes in concomitant diseases and medication at subsequent visits.
- Anything which is relevant to the ongoing care of the subject;
- Relevant results and trial medic's assessment of these results.
- Brief description of any AEs with start & stop times/dates and any significant test results or a medical summary of events if more appropriate.
- Any other relevant information.

13.8 Archiving

At completion or termination of the study, the Sponsor and Principal Investigator have the responsibility to retain all trial documents, including but not limited to the protocol, copies of CRFs, regulatory agency documents, ICFs, and REC correspondence. The trial documents should be retained for 5 years following trial completion/termination. If relevant, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of paper medical records of trial participants.

For study purposes all blood samples will be for standard of care and therefore there will be no requirement for storage or archiving.

Data will be stored in the Castle Hill Hospital Clinical Trials Unit archive or moved to a commercial archive with overall responsibility being retained by the Sponsor, after the trial team have stopped requiring regular access. Access to data, including the Trial Master File, will be restricted to the

sponsor. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive.

13.9 Publication of Results

A publication policy will be developed and a core publication group will be appointed. The publication policy will contain guidelines on how to approach authorship and a regularly updated publication plan. Results of this pilot trial will be submitted for presentation in the form of an abstract at regional, national and international conferences. Scientific manuscripts will be prepared and submitted for publication in appropriate peer-reviewed journals. The Sponsor will review all papers before they are submitted for publication.

14 Protocol Deviations

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials and will not be used. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Principle Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach

15. Indemnity

This is an NHS-sponsored research trial. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the Trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

16. End of trial

The end of the trial is defined as the date the last patient has completed their last trial visit.

An end of trial declaration form will be submitted to the MHRA, REC and HUTH R&D within 90 days from completion of the trial and within 15 days if the trial is discontinued prematurely. A

summary of the trial final report/publication will be submitted to the MHRA, REC and HUTH R&D within 1 year of the end of trial. HUTH R&D will be notified immediately of any reason to halt the trial. The Principal investigator and HUTH R&D as sponsor will decide if the trial should be halted temporarily. The MHRA, REC and HUTH R&D will be notified within 15 days of a decision to temporarily halt the trial by submitting a substantial amendment notification.

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