Academic and Clinical Central Office for Research and Development

Study Protocol

Seven versus Fourteen Days Antibiotics for Patients with Bronchiectasis Requiring Intravenous Antibiotics

(SBIVA Study)

Co-Sponsors	The University of Edinburgh & Lothian Health Board ACCORD Usher Building, The University of Edinburgh, 5□7 Little France Road, Edinburgh BioQuarter □ Gate 3, Edinburgh, EH16 4UX
Funder	National Institute for Health Research Health Technology Assessment Programme (NIHR HTA)
Funding Reference Number	NIHR 133876
Chief Investigator	Professor Adam Hill
Sponsor Reference	AC23072
Registration Number	ISRCTN14057228
REC Number	23/SS/0101
Version Number and Date	Version 4.0 17 Sep 2025

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Summary of Protocol Changes

Version Number	Date	Changes
1.0	23 Aug 2023	New document
2.0	23 Nov 2023	• Addition of document history table. • Addition of collaborators to key trial contacts page. • Spirometry for BSI calculation for randomisation – changed from within last year to permit use of latest available spirometry results. • Clarification of verification of first exacerbation in sections 2.2.1 and 7.2.5 (7 points instead of 6 as points 6 + 7 were merged). Removal of 'clinician determines' from point 7 (no longer in keeping with current practice). • Investigator choice of IMP wording clarified to at the discretion of the PI or suitably delegated investigator consistently throughout the protocol. • Adherence changed to fourth sevenths or more days of treatment to be adherent to take in to account potential differing daily treatment regimes. • Section 5.2.3 - Recovered capacity consent to continue. If consent is not obtained after 3 attempts, patient is withdrawn from the study. • Section 8 - clarification around questionnaires not returned. • Other minor administrative changes.
3.0		• Addition of five protocol permitted alternative IMPs • Clarification around use of a second antibiotic treatment for study entry exacerbation • Clarification around use of continued antibiotic treatment beyond treatment allocation • Increase in number of sites • Clarification around baseline sputum microbiology results • Addition of the definition of women of childbearing potential (WOCBP) • Monthly follow up calls – permitted to be carried out in person • Change of the Trial Statistician • Extension of recruitment window from 72 to 96 hours • Other minor administrative changes
4.0		• Correction of typographical error in Protocol v 3.0 Summary of Protocol Changes Table from 'Change of the Unblinded Trial Statistician' to 'Change of the Trial Statistician'. • Removal of the option to complete monthly questionnaires electronically.

PROTOCOL APPROVAL SIGNATURE PAGE

Seven versus Fourteen Days Antibiotics for Patients with Bronchiectasis Requiring Intravenous Antibiotics

(SBIVA Study)

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Prof Adam Hill			
Chief Investigator	**Signature**		**Date**
Mr Richard Parker			
Trial Statistician	**Signature**		**Date**
Dr Fiach O'Mahony			
Lead Co-Sponsor Representative	**Signature**		**Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name				
Principal Investigator	**Signature**		**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

ACBT	Active Cycle of Breathing Technique
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
BHQ	Bronchiectasis Health Questionnaire
BLF	British Lung Foundation
BSI	Bronchiectasis Severity Index
CAT	COPD Assessment Test
CI	Chief Investigator
CHI	Community Health Index
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
ECTU	Edinburgh Clinical Trials Unit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HCRU	Health Care Resource Use
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous

ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Patient Information Sheet
PLR	Personal Legal Representative
PPI	Patient and Public Involvement
PSS	Personal Social Services
QA	Quality Assurance
QALY	Cost per Quality Adjusted Life Year
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBIVA	Seven versus Fourteen Days Antibiotics for Patients with Bronchiectasis Requiring Intravenous Antibiotics
SDV	Source Data Verification
SGRQ	St Georges Respiratory Questionnaire
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	Seven versus Fourteen Days Antibiotics for Patients with Bronchiectasis Requiring Intravenous Antibiotics- SBIVA Study
Study Acronym	SBIVA Study
Clinical Phase	Phase 4
Trial Design	Open pragmatic United Kingdom (UK) multi-centre parallel randomised controlled trial
Trial Participants	Patients with bronchiectasis throughout the UK who are needing to start intravenous antibiotics for exacerbations of bronchiectasis
Planned Number of Participants	400
Planned Number of Sites	Approximately 30
Countries Anticipated to be Involved in Trial	UK
Treatment Duration	7 or 14 days
Follow up Duration	1 year
Total Planned Trial Duration	48 months
Primary Objective	To compare which duration of intravenous antibiotic treatment is superior for a bronchiectasis exacerbation, 7 days or 14 days. Superior is defined by a longer time elapsed until the next verified bronchiectasis exacerbation requiring antibiotic treatment (up to one year).
Secondary Objectives	To determine whether 7 days of intravenous antibiotic treatment is superior to 14 days of treatment in terms of: 1. Heath related quality of life at day 14; 2. Clinical response at day 14, defined as a 4 or more-unit improvement in either the St. George's Respiratory Questionnaire[13] or the CAT questionnaire.[14]; and/or by change in sputum colour from baseline; a. purulent to muco-purulent, mucoid, or no sputum, or b. muco-purulent to mucoid or no sputum. 3. Adverse events up to day 60; 4. Drug resistant pathogens at day 14 and at time of next exacerbation needing antibiotic therapy; 5. Health economic benefits; 6. Adherence with allocated intravenous antibiotic intervention.
Primary Endpoint	The duration of time elapsed between starting intravenous antibiotics until needing another course of antibiotics for a protocol defined exacerbation of bronchiectasis (up to 1 year post randomisation).

Secondary Endpoints	Secondary Outcomes comparing 7 versus 14 days intravenous antibiotics: A] St. George's Respiratory Questionnaire score at day 14; B] Bronchiectasis Health Questionnaire[15] at day 14; C] CAT Questionnaire at day 14; D] Sputum colour at day 14 and at next exacerbation; E] Adverse events recorded up to day 60; F] Sputum pathogen and drug resistance patterns following treatment (samples collected at baseline, day 14 and at the time of next exacerbation needing another antibiotic course (up to 1 year post randomisation); G] Cost per Quality Adjusted Life Year (QALY) from a UK National Health Service (NHS and Personal Social Services (PSS) perspective, as simulated via decision analytic modelling over 1, 3, and 5-year time horizons. H] Adherence with allocated intravenous antibiotic intervention assessed by diary card, at day 14 visit and routine prescribing data, having greater than or equal to four sevenths of treatment days to be adherent.
IMP(s)	Meropenem (preferred choice) Piperacillin-Tazobactam Ceftazidime Ciprofloxacin Aztreonam Gentamicin Colistimethate Sodium Ceftolozone/tazobactan Levofloxacin Ertapenem Tobramycin Fosfomycin
IMP Route of Administration	Intravenous
NIMP(s)	N\A

Lay Summary of Trial	Bronchiectasis affects around 300,000 people in the UK, according to British Lung Foundation research.[1] Hospital admissions due to bronchiectasis cost the NHS around £40 M per year. International guidelines recommend that patients receive intravenous antibiotics for 14 days if they are particularly unwell, have an infection with resistant organisms, or if oral antibiotics are ineffective.[2] The duration is based on expert advice[2,3] but there have not been any randomised placebo controlled trials telling us what length of course is best. The dilemma being that treating for too long may keep people in hospital too long or increase their risk of antibiotic side effects, whereas treating for too short a period may increase the risk of an infection soon after completion of antibiotic therapy. We have shown both patients and clinicians would enter a trial of shorter courses of intravenous antibiotic treatment in a study in Edinburgh of 90 patients.[4] We found patients receiving 7 days of intravenous antibiotics took longer to next flare up compared to those getting current recommendations of 14 days. This challenges the current thinking that “more is better”. A multi-centre trial is now needed to confirm this and change the national and international guidelines 14-day treatment recommendation. This study could add to the goal of reducing inappropriate antibiotic use and reduce the chance of developing antibiotic resistance. We will select 400 patients with bronchiectasis throughout the UK who need intravenous antibiotics. Half, at random, will receive 7 days of intravenous antibiotics and the other half will receive 14 days of intravenous antibiotics. Both groups will get standard care in addition.[2] The primary outcome is the duration of time elapsed between starting intravenous antibiotics until needing another course of antibiotics for a protocol defined exacerbation of bronchiectasis (up to 1 year post randomisation). We are using the internationally agreed definition of a bronchiectasis exacerbation.[5] Our grant proposal has been reviewed by an expert patient panel who agreed this is an important study and that any treatment prolonging the time to next needing an antibiotic is welcome. They agreed the need for a multi-centre study, advised against bringing participants into hospital for the next flare-up after the intravenous antibiotic course, and agreed that an unblinded study was better value for money in view of the costs required to blind the study. The expert patient panel helped write the lay summary. The Asthma UK-British Lung Foundation alliance will provide strategic oversight of PPI work. We’ll present our findings at local, national, and international meetings. This study will help the NHS provide optimal care, and the findings will be of interest internationally and so we will publish the results in a high impact factor peer reviewed journal. The Asthma UK- British Lung Foundation alliance have also agreed to help disseminate the results to the public.

1. INTRODUCTION

1.1 BACKGROUND

Bronchiectasis is a chronic lung condition characterised by persistent cough, daily sputum production, shortness of breath and recurrent chest infections.[2] According to British Lung Foundation research, it affects around 300,000 people in the UK.[1] The British Thoracic Society have produced a set of national guidelines for when patients should be prescribed intravenous antibiotics for pulmonary exacerbations (worsening of bronchiectasis or 'flare ups'). These guidelines recommend intravenous antibiotics in patients who are particularly unwell, have an infection with resistant organisms or when oral antibiotics are ineffective.[2] National audit data over a 2 month period suggests that 16-18% of patients attending hospital outpatient bronchiectasis clinics require this treatment.[6,7]

There are no randomised placebo-controlled trials on duration of intravenous antibiotics (PubMed search 9.03.2023).

1.2 RATIONALE FOR STUDY

Both the British Thoracic Society and European Respiratory Society Bronchiectasis Guidelines recommend that 14 days of antibiotics is used to treat pulmonary exacerbations needing intravenous antibiotic therapy, which is based on expert opinion only.[2,3]

There are no randomised placebo-controlled studies evaluating the efficacy of intravenous antibiotics in exacerbations in adults, and current practice relies upon cohort studies that show that participants treated with intravenous antibiotic therapy as an inpatient or at home therapy had a good clinical response.[8-11] However, these studies lacked a control group that did not receive antibiotics.

A multicentre study is needed to inform evidence-based practice that can be incorporated into national and international guidelines.

A feasibility study has been completed in which 90 patients were randomised to receive 14 days of intravenous antibiotics (n=47) or a shortened treatment arm (n=43) if bacterial load was low after 7 days of intravenous antibiotic therapy. The concept being that when bacterial load was low, it may be safe to stop antibiotics early.[4] 114 patients were screened and 90 participants were randomised, confirming a high rate of eligible patients. Eighty-eight percent of participants in the shortened arm were able to stop antibiotics by day 8, showing that the bacterial load is reduced in most patients after 7 days of antibiotic therapy. This was an intention to treat analysis and overall group data showed the median (interquartile range) time to next exacerbation was 27.5 (12.5-60) days in the group receiving antibiotics for 14 days and 60 (18-110) days in the in shortened treatment arm; p=0.003. In the Cox proportional hazard model, participants who had 14 days of intravenous antibiotics were more likely to experience exacerbations (Hazard Ratio (95% CI) 1.80 (1.16-2.80), p=0.009 compared with the shortened arm. *Stenotrophomonas maltophilia* at days 14 and 21 was identified in the pilot study as being more common with 14 days antibiotic treatment and the emergence of this could drive the difference in outcomes. As expected, those with mild bronchiectasis, defined by the Bronchiectasis Severity Index,[12] were less likely to experience exacerbations than patients with more severe bronchiectasis (HR 0.36 (0.13-0.99), p=0.048). [4] On this basis, the SBIVA study will use Bronchiectasis Severity Index as a stratification variable.

The Research question being addressed by this study is: for bronchiectasis-related pulmonary exacerbations, is 7 days or 14 days duration of intravenous antibiotic treatment better for delaying the next exacerbation?

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective of the study is to compare which duration of intravenous antibiotic treatment is superior for a bronchiectasis exacerbation, 7 days or 14 days. Superior is defined by a longer time elapsed until the next verified bronchiectasis exacerbation requiring antibiotic treatment (up to one year).

2.1.2 Secondary Objectives

To determine whether treatment with 7 days of intravenous antibiotics is superior to treatment with 14 days of intravenous antibiotics in terms of:

1. Heath related quality of life at day 14;
2. Clinical response at day 14, defined as a 4 or more-unit improvement in either the St. George's Respiratory Questionnaire[13] or the CAT questionnaire[14]; and/or by change in sputum colour from baseline;
    a. purulent to muco-purulent, mucoid, or no sputum, or
    b. muco-purulent to mucoid or no sputum.
3. Adverse events up to day 60;
4. Drug resistant pathogens at day 14 and at time of next exacerbation needing antibiotic therapy;
5. Health economic benefits;
6. Adherence with allocated intravenous antibiotic intervention.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary endpoint is the duration of time elapsed between starting intravenous antibiotic therapy, until needing another antibiotic course for a protocol defined exacerbation of bronchiectasis (up to 1 year post randomisation).

The following internationally agreed consensus definition of a bronchiectasis exacerbation for clinical trials will be used[5]:

Deterioration in three or more of the following key symptoms for at least 48 hours:

1. Cough;
2. Sputum volume and/or consistency;
3. Sputum purulence;
4. Breathlessness and/or exercise tolerance;
5. Fatigue and/or malaise;
6. Haemoptysis;

AND antibiotic treatment is required (either oral or intravenous or inhaled).[5]

Exacerbations will be confirmed within 7 days by a clinical member of the research team contacting the participant and reviewing their symptoms (described in protocol section 7.2.5). The team member verifying the exacerbation may be an appropriately qualified doctor, nurse or allied health care professional who has been delegated this task by the PI on the site delegation log. Participants will be asked to contact their local research team as soon as possible at the onset of an exacerbation, or on a

Monday if an exacerbation starts on a weekend. Participants will be given a study card to remind them of this along with contact details for their local research team. They will also be reminded at each monthly follow up call. If the verifying person deems the exacerbation does not meet the agreed criteria, the participant will continue in the study until they feel they have another exacerbation. At this point they will then be checked again as described above. This will continue until the participant meets the primary outcome measure (up to one year). All further exacerbations within one year after study entry will be recorded but not verified. These conversations will be documented in the patient medical records and exacerbation data entered in to the eCRF.

2.2.2 Secondary Endpoints

The following secondary outcomes will be assessed comparing 7 versus 14 days intravenous antibiotics:

A] St. George's Respiratory Questionnaire score at day 14[13];

B] Bronchiectasis Health Questionnaire at day 14[15];

C] CAT Questionnaire at day 14[14];

D] Sputum colour at day 14 and at next exacerbation[16];

E] Adverse events recorded up to day 60;

F] Sputum pathogen and drug resistance patterns following treatment (samples collected at baseline, day 14 and at the time of next exacerbation needing another antibiotic course (up to 1 year post randomisation).

G] Cost per Quality Adjusted Life Year (QALY) from a UK National Health Service (NHS and Personal Social Services (PSS) perspective, as simulated via decision analytic modelling over 1, 3, and 5-year time horizons.

H] Adherence with allocated intravenous antibiotic intervention assessed by diary card, at day 14 visit and routine prescribing data, having greater than or equal to four sevenths of treatment days to be adherent.

The study primary and secondary objectives and endpoints are summarised in table 1.

Table 1 Summary of Study Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare which duration of intravenous antibiotic treatment is superior for a bronchiectasis exacerbation, 7 days or 14 days. Superior is defined by a longer time elapsed until the next verified bronchiectasis exacerbation requiring antibiotic treatment (up to one year).	• The duration of time elapsed between starting intravenous antibiotic therapy, until needing another antibiotic course for a protocol defined exacerbation of bronchiectasis (up to 1 year post randomisation).
Secondary	
To determine whether 7 days of intravenous antibiotic treatment is superior to 14 days of treatment in terms of:	
1. Heath related quality of life at day 14.	A] St. George's Respiratory Questionnaire score at day 14[13]; B] Bronchiectasis Health Questionnaire at day 14[15]; C] CAT Questionnaire at day 14[14].

2. Clinical response at day 14, defined as a 4 or more-unit improvement in either the St. George's Respiratory Questionnaire[13] or the CAT questionnaire[14]; and/or by change in sputum colour from baseline; a. purulent to muco-purulent, mucoid, or no sputum, or b. muco-purulent to mucoid or no sputum.	A] St. George's Respiratory Questionnaire score at day 14[13]; C] CAT Questionnaire at day 14[14]; D] Sputum colour at day 14.
3. Adverse events up to day 60.	E] Adverse events recorded up to day 60.
4. Drug resistant pathogens at day 14 and at time of next exacerbation needing antibiotic therapy.	F] Sputum pathogen and drug resistance patterns following treatment (samples collected at baseline, day 14 and at the time of next exacerbation needing another antibiotic course (up to 1 year post randomisation).
5. Health economic benefits.	G] Cost per Quality Adjusted Life Year (QALY) from a UK National Health Service (NHS and Personal Social Services (PSS) perspective, as simulated via decision analytic modelling over 1, 3, and 5-year time horizons, primarily utilising: • Rates of exacerbation • Adverse event rates • EQ-5D-5L data • Health Care Resource Use data
6. Adherence with allocated intravenous antibiotic intervention.	H] Adherence with allocated intravenous antibiotic intervention, having greater than or equal to four sevenths of treatment days to be adherent, assessed: • by diary card, • at day 14 visit • routine prescribing data.

3. STUDY DESIGN

This is a multi-centre pragmatic 1:1 randomised parallel group trial in patients with bronchiectasis needing intravenous antibiotic therapy to treat a protocol defined exacerbation, comparing 7 days of intravenous antibiotics and standard care with 14 days of intravenous antibiotics and standard care.[2]

The intravenous antibiotics will be delivered as per local standard of care and will be determined by the clinical care team (either out-patient, home or as an in-patient).[2] Patients who have never self-administered intravenous therapy at home will be trained by a clinical nurse specialist or other suitably trained health care professional at, or prior to commencing a course of intravenous antibiotics as per usual local standard of care. They can only do this independently once they demonstrate their ability to self-administer intravenous therapy safely and confidently. Intravenous access is usually via a peripherally placed central catheter e.g., midline, subcutaneously tunnelled central catheter or peripheral venous cannula. The decision for out-patient, at home or in-patient intravenous therapy is part of standard care management embedded into all bronchiectasis services and will be documented in medical records.

For both arms of the study, participants will have a baseline appointment and be randomised to receive Meropenem (or an alternative protocol permitted intravenous antibiotic if Meropenem is unavailable/unsuitable) for either 14 days or 7 days, with preference for three times daily treatment. We

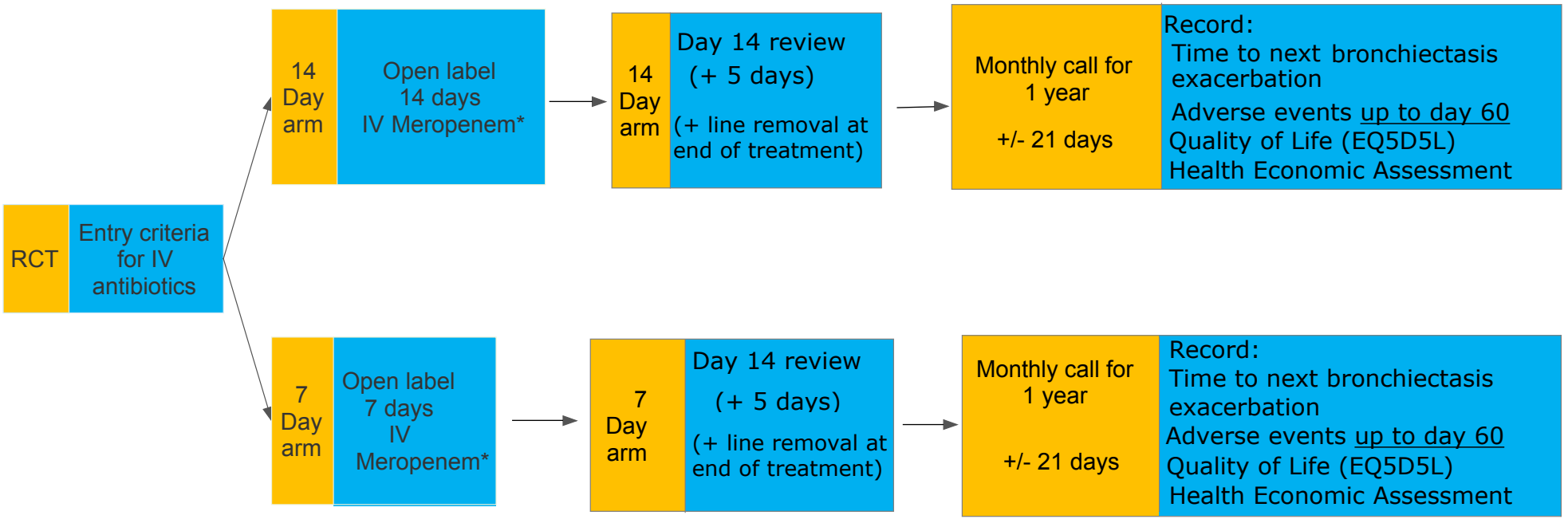
will align to local practice for alternative doses and regimens (e.g., twice daily, elastomeric devices, or for renal impairment). Participants will be asked to complete a diary to document adherence to their allocated treatment and record if they have undertaken any chest clearance exercises (e.g. airway clearance breathing techniques; ACBT). Participants will have their access line removed at the end of IV treatment, as per usual local practice. Participants on both arms will be reviewed 14 days after starting their IV treatment, which may be carried out remotely.

Participants will receive monthly follow up telephone calls for 1 year after starting trial treatment to collect exacerbation information, adverse events (up to day 60), and quality of life and health economic assessment. Monthly follow ups may also take place in person where this is preferred by the participant. The study design is summarised in figure 1.

All future exacerbations following trial treatment will be treated and managed as per their local standard of care for the participants.

Figure 1 –Study Design Summary

RCT = Randomised Controlled Trial; IV= intravenous



*Or protocol permitted alternative anti-pseudomonal antibiotic

4. STUDY POPULATION

Adults with a clinical diagnosis of bronchiectasis who require intravenous antibiotic treatment for a protocol defined exacerbation of bronchiectasis will be invited to participate in the study.

Setting: Hospital inpatients and secondary care outpatient clinics from all four nations of the U.K. targeting clinics with large cohorts. We will use our existing network (www.bronch.ac.uk) that has recruited over 1500 patients into a cohort study. We will leverage previous experience in the NIHR CRN to ensure we have strong representation of sites with high prevalence / rates of admissions (e.g. emergency hospital admissions, higher rates of emergency admission).[1]

4.1 NUMBER OF PARTICIPANTS

Recruitment and stratification: We plan to recruit 400 participants from hospital in-patient wards and out-patient settings throughout the U.K. - estimated around 30 centres (for a recruitment rate of approximately 0.5 per site per month).

4.2 INCLUSION CRITERIA

- Adults (age 16 or over)
- Provision of informed consent (from participant or when lacking capacity due to bronchiectasis severity, by their legal representative)
- A clinical diagnosis of bronchiectasis made by a respiratory specialist supported by CT scan or equivalent clinical confirmation of bronchiectasis
- Exacerbation* where intravenous antibiotics are deemed clinically appropriate**
- Ability to adhere to the study assessments/protocol in the opinion of the Investigator

*The internationally accepted definition for bronchiectasis exacerbations within clinical trials[5] will be used, which is as follows: a deterioration in three or more of the following key symptoms for at least 48 hours including cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis.

**Participants may be recruited from attendances seeking urgent care (such as inpatients, emergency outpatient clinics, ambulatory clinics etc.), and in this instance patients that have received an intravenous antibiotic for up to 96 hours (i.e. 4 full days' worth of treatment) before consent may be considered for the study. They will then receive Meropenem or one of the protocol permitted alternatives for the duration of study treatment (see Protocol section 5.1.2 for full details). Ideally participants should be randomised prior to receiving treatment or as early as possible after beginning IV antibiotic treatment.

Eligibility does not rest on having a Meropenem sensitive organism from current or previous sputum microbiology results, as in practice patients can improve despite in vitro sensitivity resistance patterns.

4.3 EXCLUSION CRITERIA

- Patients who are asymptomatic at start of intravenous antibiotics
- Known homozygous cystic fibrosis
- Known active tuberculosis
- Breast feeding, pregnancy, or plan to become pregnant within study
- End of life care with anticipated life span less than 6 months
- Current enrolment in a CTIMP where co-enrolment has not been approved
- Previous recruitment to the SBIVA trial
- Allergy to Meropenem and protocol permitted alternatives^
- Where trial enrolment is not in the best interest of the patient in the opinion of the Investigator

^ While the aim is to use Meropenem for both arms of the study, we will accept the use of a protocol approved alternative anti-pseudomonal antibiotic (at the discretion of PI or suitably delegated investigator), for example due to local antibiotic use policy, patient allergy or if there are supply issues, etc. Patients will only be excluded on the grounds of allergy if found to be allergic to Meropenem and as well as all the protocol approved alternatives. See section 6 for details of protocol permitted alternative antibiotics.

4.4 CO-ENROLMENT

This will be in accordance with the ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy).

If we co-enrol with other CTIMPs, the co-enrolment checklist (POL008-F01) will be completed by the Co-Sponsor Representative in conjunction with the CI prior to the co-enrolment proceeding.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential participants may be identified ahead of experiencing an exacerbation of their bronchiectasis via secondary care outpatient clinics or services, or whilst experiencing a bronchiectasis exacerbation in hospital, or in secondary care settings such as outpatient clinics or virtual wards (also known as Hospital at Home) outpatient services. In all cases, a member of the direct care team (which may include embedded research nurses) will make the first approach/contact.

5.1.1 Participant recruitment via outpatient settings

This study aims to recruit patients who will require IV antibiotics for an exacerbation of bronchiectasis. This can be done prospectively through targeted approaches (e.g., via database searches or screening clinic lists) to patients that the local site anticipate may need IV antibiotics for a future exacerbation. For example, by focusing on those with a past history of needing IV antibiotics. At participating secondary care sites, potentially suitable participants may be informed about the study during routine clinical visits or by letter or telephone, and offered the opportunity to discuss the study with a member of the research team.

Potential participants identified prospectively this way will be provided with a patient information sheet (PIS) and a Consent to Contact form sent in the post or via email in accordance with local policy. If the Consent to Contact form is returned, a member of the research team will contact the potential participant to discuss the study. The potential participant will be given as long as needed to decide whether to take part in the study prior to experiencing an exacerbation of their bronchiectasis.

At the onset of an exacerbation where IV antibiotics are deemed clinically appropriate, the potential participant will be asked to contact the research team. They will be provided with a PIS, and if happy to do so, sign consent to participate in the study. Ideally patients will consent to participate in the study before commencing IV antibiotic treatment. To allow for prompt initial treatment patients can consent to participate up to 96 hours after receiving their first dose of IV antibiotic treatment.

5.1.2 Participant recruitment whilst experiencing an exacerbation

Participants will also be recruited from attendances seeking urgent care/treatment for their bronchiectasis, such as hospital inpatients, emergency or routine outpatient clinics, ambulatory clinics and from virtual wards (also known as Hospital at Home) etc. Potential participants will be provided with a PIS and where appropriate also given the information verbally. They will be given the opportunity to discuss the study with the research team and have any questions answered. Potential participants will

be given as long as practicable to decide whether to take part in the study, in the context of their urgent care requirements. This may mean patients are consented within 24 hours of receiving the PIS.

Where a patient has not yet started any IV antibiotic treatment and has been provided with the PIS, they may sign consent when happy to do so prior to commencing study IV antibiotic treatment.

Where a patient has begun treatment with one of the protocol permitted alternative IV antibiotics, they may consent to participate in the study up to 96 hours after their first dose of IV antibiotics. They will then receive the remainder of the allocated duration of study treatment, i.e., the doses of IV antibiotics taken prior to entering the study will count towards their 7- or 14-day allocation.

Patients that have started an IV antibiotic treatment that is **not** a protocol-permitted alternative antibiotic may be consented and enrolled into the study within 96 hours of receiving their first dose of (non-protocol permitted) IV antibiotic. In these cases, patients will be changed onto a protocol permitted IV antibiotic and will receive 7 or 14 days of IV study treatment. The doses of non-protocol permitted IV antibiotics taken prior to entering the study will not count towards their 7- or 14-day allocation.

In all cases, participants should sign consent no longer than 96 hours after receiving their first dose of IV antibiotics for their current bronchiectasis exacerbation.

The process for identifying potential participants for the study is summarised in figure 2.

Approved study posters may be displayed at participating sites to both staff and patients with information about the study and how to get in contact with the local site research team.

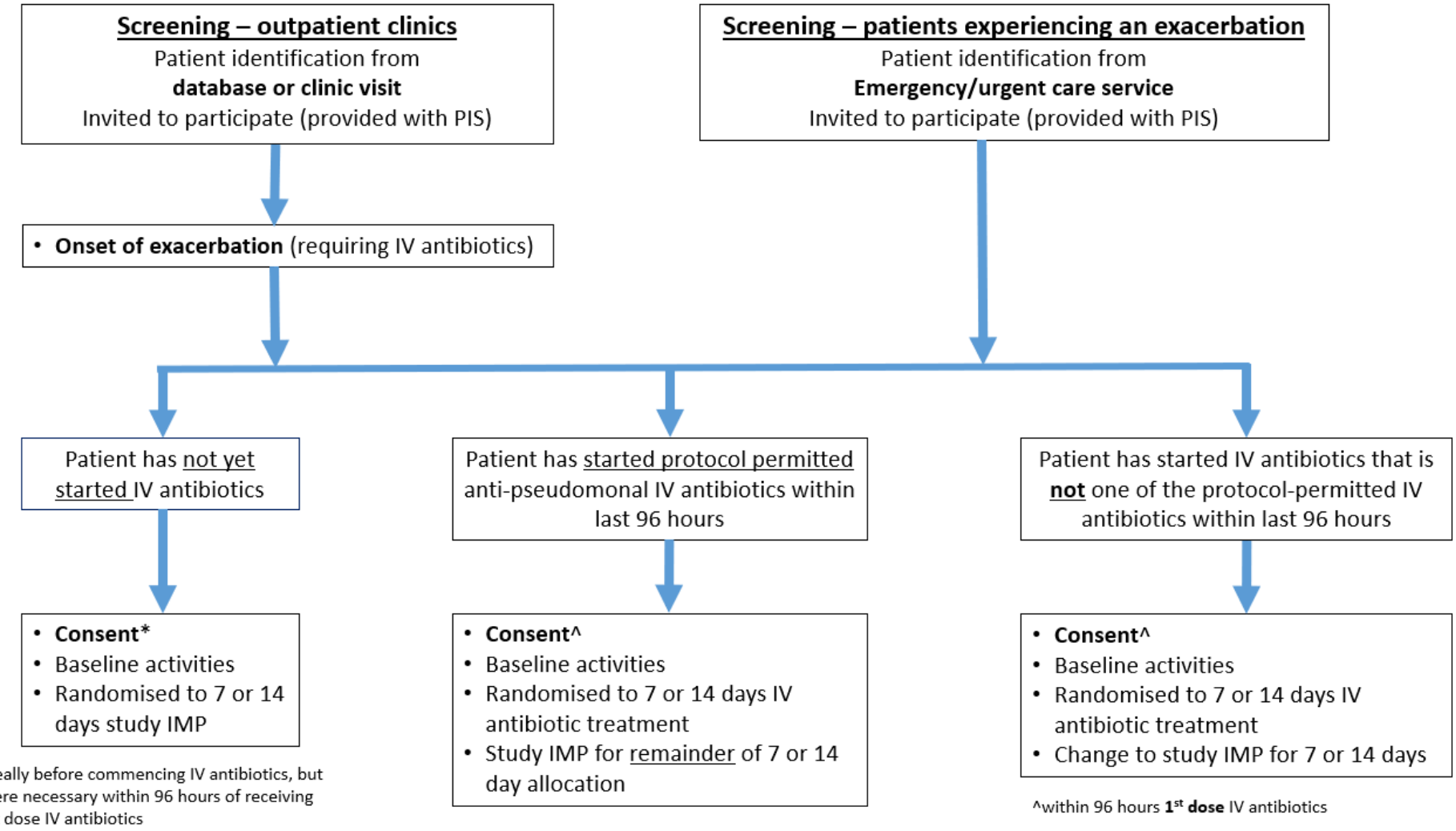


Figure 2 – Participant identification pathway

5.2 CONSENTING PARTICIPANTS

The Principal Investigator (PI) (or member of the research team delegated by the PI on the delegation log) will ensure that informed consent is obtained from each participant, or their legal representative, prior to entry into the study and completing any study specific procedures. The PI (or delegate) taking informed consent will be Good Clinical Practice (GCP) trained, suitably qualified and experienced.

5.2.1 Face-to-face Consent:

When the potential participant attends the clinic/hospital appointment (which may take place in the department where they have already started IV antibiotic treatment), they will be given the opportunity to ask the research team any questions they have. When the participant confirms they are happy to participate, written informed consent will be obtained. Where appropriate, witnessed verbal consent may be obtained. Consent will be documented in the participant's medical records.

A copy of the signed informed consent form will be given to the participant, a copy will also be filed in the participants medical notes and the original will be kept by the PI in the Investigator Site File at each research site. The participant's general practitioner (GP) will be informed by letter of their participation in the study.

5.2.2 Participants Lacking Capacity:

To ensure inclusivity across the population, we will actively facilitate inclusion of participants who temporarily lack capacity to consent for themselves due to being acutely unwell with bronchiectasis. In these circumstances a personal legal representative (PLR) can be asked to give consent on their behalf. Consent procedures will adhere to the legal frameworks that govern the inclusion of adults not able to consent for themselves in research which are: Adults with Incapacity (Scotland) Act 2000, the 2005 Mental Capacity Act (2005), Mental Capacity Act (Northern Ireland) 2016 and the Medicines for Human Use (Clinical Trials) Regulations (2004). Capacity will be assessed prior to consent by the PI / research nurse or a clinician responsible for the treatment of the participant and documented in the participant's medical records.

The research team will establish if a PLR is available, i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult and is willing to do so. Up to three attempts may be made to contact an individual identified as a potentially suitable PLR, which will be documented in the patient medical records. If no PLR can be identified or contacted, this will be documented in the patient medical notes and under these circumstances' patients lacking capacity will be excluded from the trial.

The PLR will be:

- Informed that they are being asked to give consent on behalf of the incapacitated adult.
- Informed that they are free to decide whether they wish to make this decision or not.
- Informed that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision.
- Given sufficient information, in an understandable form, about the trial to ensure that they can make an informed decision. They will be provided with the participant information sheet (PIS-PLR) either in person, by post or by email, and given the opportunity to discuss the study with the research team, either in person or by telephone or video call, and have any questions they may have answered.

Written consent from PLRs will be taken by trained members of the research team delegated this task on the site delegation log.

Alternatively, if the PLR is unable to meet with a member of the research team in person, consent may be taken over the telephone using the telephone version of the PIS-PLR consent form. This must be done by a trained member of the research team delegated this task on the site delegation log in the presence of an independent witness who will sign and date the consent form. If consent is taken from the PLR in this way, the research team should endeavour to have them sign the consent form at the earliest opportunity.

The consent process will be documented in the patient's medical record.

5.2.3 **Recovered Capacity – Consent to Continue**

Participants entered into the trial by a PLR will have their capacity monitored by their clinical care team. If / when they are assessed as having recovered capacity, they will be made aware of their trial enrolment and approached by a delegated member of the research team. They will be provided with a recovered capacity PIS (PIS-RC), given the opportunity to discuss the study with a member of the research team and have their questions answered. They will then be asked to provide informed consent to continue in the trial by completing a Recovered Capacity consent form, if they so wish. This can be carried out in person or over the telephone where appropriate, using the relevant version of the regained capacity PIS. This should be done as soon as possible, and when considered clinically appropriate after the participant has regained capacity. Consent must be taken by a trained member of the research team delegated this task on the site delegation log, and, where consent is taken over the telephone, in the presence of an independent witness who will sign and date the consent form. The consent process will be documented in the patient's medical record.

Where a participant regains capacity in the opinion of the clinical team, up to three attempts should be made over the course of a month to establish whether they are happy to continue in the trial and to obtain consent (either verbally over the telephone, or written). If willingness to continue is not established and consent is not provided within the three contact attempts the participant will be considered lost to follow up and withdrawn from the study.

Where a participant does not recover capacity, they will remain in the trial and continue in follow up until the end of the study unless consent is withdrawn by their legal representative, in which case they will be withdrawn from the study.

Where consent is refused following regained capacity, the participant will be withdrawn from the study from that time.

Information about the SBIVA trial may be displayed on posters in waiting areas. This will raise awareness of the study, promote understanding of the research in anticipation of the participants regaining capacity and provide information for Personal Legal Representatives that may aid their discussions with the participant when they have regained capacity and are considering providing informed ongoing consent.

5.3 **SCREENING FOR ELIGIBILITY**

Patients identified by a member of the study team as potentially suitable for the study and provided with a PIS will be recorded on the study screening log. Participant eligibility will be confirmed by an appropriately trained and delegated clinical trial physician after informed consent has been obtained. This will be based on routinely collected clinical data and review of clinical records. Confirmation of eligibility will be recorded within the participants' medical records and in the Case Report Form (CRF).

The following assessment may need to be undertaken in order to confirm eligibility after consent has been taken and before a participant can be randomised:

- A pregnancy test for women of child bearing potential will be performed and the results recorded in the CRF. Childbearing potential is defined: as i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses without an alternative medical cause for 12 months for women over 50 years old, and for 24 months for women under 50 years old. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. This is a study specific assessment.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

All ineligible and non-recruited participants who are considered for entry into the study (defined as given written information about the study) will be recorded on the screening log with the reason given for being ineligible and/or not recruited e.g., patient decision, clinician decision, inclusion and/or exclusion criteria prohibited entry.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After written informed consent has been obtained and eligibility confirmed, a member of the research team will perform the randomisation using a web-based randomisation service managed by the Edinburgh Clinical Trials Unit (ECTU). Participants will be randomised on a 1:1 basis to receive intravenous antibiotics for either 7 days or 14 days.

The randomisation system will stratify for bronchiectasis severity (score of nine or more versus less than 9 on the Bronchiectasis Severity Index (BSI)), and on receiving antibiotics as an inpatient vs. ambulatory or home intravenous antibiotics. BSI will be calculated using the patient's latest spirometry reading. Where a participant has not undergone lung function testing using spirometry, spirometry testing will be carried out prior to randomisation for the purpose of stratification. This will be a study specific test.

5.5.2 Treatment Allocation

Following randomisation, both the participant and the Investigator will be notified of the assigned treatment allocation. Treatment will be prescribed and medication dispensed at the local trial site as per usual local practice. For participants who have already received up to 96 hours of Meropenem (or permitted equivalent), their prescription may be changed, where necessary, for the remainder of their allocated 7 or 14 days.

Participants who receive their allocated treatment in hospital or at home will receive intravenous antibiotics as per local standard of care.

For participants who are able to self-administer their intravenous antibiotic treatment at home, the clinical team will provide dosing instructions once the participant is fully trained and deemed capable of doing so as per their site usual practice. Medication will be collected as per local practice.

5.5.3 Emergency Unblinding Procedures

The study is not blinded so there is no procedure in place.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants (or their Legal Representative) are free to withdraw (the participant) from the study at any point without providing a reason. Anonymised data prior to the point of complete withdrawal will be included for analysis. A participant may also be withdrawn by the Investigator, if they feel this is in their

best interest. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's medical records, if provided, and in the eCRF.

The participant (or their Legal Representative) will have the option of:

(i) withdrawal from the study medication only, with continued participation in study procedures, questionnaires and collection of clinical and safety data;

(ii) withdrawal from study medication, study procedures and questionnaires, with permission to collect information from ongoing routine health records;

(iii) withdrawal from all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be collected.

This will be explained within the participant information sheet. All available data will be included in an intention-to-treat analysis regardless of time-point of withdrawal from intervention.

There will be no stopping criteria for participants in the study, since all treatments are used in routine clinical practice.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 STUDY DRUG

6.1.1 Study Drug Identification

We have chosen to use a broad-spectrum antibiotic, Meropenem IV Powder for solution for injection or infusion, as it covers both gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa* (the most frequent pathogen identified in those that need IV antibiotics), as well as anaerobes. In addition, it is the antibiotic of choice for patients with penicillin allergy.
While the aim is to use Meropenem for both arms of the study, the use of a protocol approved alternative anti-pseudomonal antibiotic (at the discretion of the PI or suitably delegated investigator) is permitted. For example, due to local antibiotic use policy, if there are supply issues or patient allergies etc. The decision will be documented in the patient medical records. Permitted protocol approved alternatives to Meropenem are as follows:

- Piperacillin-Tazobactam
- Ceftazidime
- Ciprofloxacin
- Aztreonam
- Gentamicin
- Colistimethate Sodium
- Ceftolozane/tazobactam
- Ertapenem
- Levofloxacin
- Tobramycin
- Fosfomycin

Each site hospital pharmacy should plan to supply stock IMP as per the brand(s) available according to their local practice. Site pharmacists should maintain communication with site investigators regarding available stock to ensure that participants are only enrolled when sufficient stock is available. As IMP will be taken from local clinical stock, accountability will be risk adapted. There is no requirement for trial specific accountability. Sites may document accountability in accordance with local policy / practice but this will not be monitored by the Sponsor.

6.1.2 Study Drug Manufacturer

Any preparation of Meropenem or the following alternative anti-pseudomonal antibiotics that have marketing authorisation in the UK and are stocked by local hospital pharmacies at participating sites may be dispensed for use in this study:

A representative manufacturer of Meropenem is Pfizer Ltd.
A representative manufacturer of Piperacillin-Tazobactam is Pfizer Ltd.
A representative manufacturer of Ceftazidime is Wockhardt UK Ltd.
A representative manufacturer of Ciprofloxacin is Fresenius Kabi Ltd.
A representative manufacturer of Aztreonam is Bristol Myers Squibb Pharmaceuticals Ltd.
A representative manufacturer of Gentamicin is Wockhardt UK Ltd.
A representative manufacturer of Colistimethate Sodium is Teva UK Ltd.
A representative manufacturer of Ceftolozane/tazobactum is Merck Sharp & Dohme (UK) Ltd.
A representative manufacturer of Ertapenem is Bowmed Ibisqus Ltd.
A representative manufacturer of Levofloxacin is Bowmed Ibisqus Ltd.
A representative manufacturer of Tobramycin is Hospira UK Ltd
A representative manufacturer of Fosfomycin is InfectoPharm Ltd

6.1.3 **Marketing Authorisation Holder**

The study drugs have marketing authorisation for the study condition (bronchiectasis). As several brands of Meropenem as well as the permitted alternatives listed above are marketed in the UK, the IMP is defined by the active substance only. All authorised brands may be used and hospitals and pharmacies may provide the brand of drug which is available to them.

The following are examples of Marketing Authorisation Holders for the protocol permitted study drugs:

- Pfizer Meronem 1 g PL 00057/1536 – Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.
- Pfizer Tazocin 4 g / 0.5 g PL 00057/1294 - Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.
- Wockhardt 2 g PL 29831/0032 – Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, United Kingdom.
- Fresenius Kabi Ciprofloxacin 200mg/100ml - Fresenius Kabi Limited, Cestrian Court, Eastgate Way Manor Park, Runcorn Cheshire, WA7 1NT UK.
- Bristol Myers Squibb Pharmaceuticals Azactam 1 g PL 12038/0002 - Bristol-Myers Squibb Pharmaceuticals Unlimited Company, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, Dublin, D15 T867.
- Wockhardt Gentamicin 40 mg/ml PL 29831/0660 – Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF.
- Teva Colomycin 1 million IU PL 00289/2255 – Teva UK Ltd, Ridings Point, Whistler Drive, Castleford, WF10 HX.
- Merck Sharp & Dohme Zerbaxa 1g/0.5g PLGB 53095/0083 - Merck Sharp & Dohme (UK) Limited 120 Moorgate, London, EC2M 6UR, United Kingdom.
- Bowmed Ibisqus Ertapenem 1g PL 05539/0006 - Bowmed Ibisqus Limited, The Old Dairy, Brynkinalt Business Centre, Brynkinalt, Chirk, Wrexham, LL14 5NS, United Kingdom.
- Bowmed Ibisqus Levofloxacin 5 mg/ml PL05448/0003 - Bowmed Ibisqus Limited, The Old Dairy, Brynkinalt Business Centre, Brynkinalt, Chirk, Wrexham, LL14 5NS, United Kingdom.
- Hospira Tobramycin 40 mg/m PL 04515/0066 – Hospira UK Ltd, Walton Oaks, Walton-On-The-Hill, Dorking Road, Tadworth, Surrey, KT20 7NS, United Kingdom.
- InfectoPharm Fomicyt 40 mg/ml PL 15011/0017 – InfectoPharm Ltd, 34-44 Spittal Street, Marlow, Buckinghamshire, SL7 1DB, United Kingdom

6.1.4 **Labelling and Packaging**

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK and will be used according to their marketing authorisation. The IMPs will not require a study specific label as they will be labelled as standard.

Participants self-administering their treatment at home will be provided with instructions from the local clinical care team, as per their usual local practice.

6.1.5 Storage

Storage and dispensing of the IMP will be undertaken by the local hospital pharmacy department at each participating site. The IMP will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures. Meropenem and Ciprofloxacin should not be stored above 30°C, while Piperacillin-Tazobactam, Ceftazidime, Aztrenam, Gentamicin and Colistimethate Sodium should not be stored above 25°C. The reconstituted solutions should not be frozen. Participants self-administering their treatment at home will be provided with instructions from the local clinical care team, as per their usual local practice.

6.1.6 Regulatory Release to Site

Not applicable.

6.1.7 Destruction of Trial Drug

Any unused medication should be discarded in accordance with local policy/practice. If the participant has self-administered treatment at home, any unused medication can be brought with them when they attend clinic to have their line removed and discarded by the clinical care team in accordance with local policy/practice. Used medication should be discarded as per local guidelines. Information regarding the destruction of used and unused medication will also be provided to patients self-administering treatment at home, e.g., in sharps bins provided as part of the treatment package.

6.1.8 Summary of Product Characteristics (SPC) Booklet

The NHS does not have a preferred brand or a generic Meropenem, or for any of the permitted alternative anti-pseudomonal antibiotics. Each hospital pharmacy may stock different brands and these may change over the course of the study. The pharmacy can dispense any brand of Meropenem or brand of the permitted alternatives currently in stock. A representative Summary of Product Characteristics (SPC) for Meropenem 1 g powder for injection of infusion and each of the permitted alternatives listed in section 6.1.3 are provided in separate documents with a cover sheet and signature page (signed and verified by the CI and Co-Sponsors) and are filed in the TMF. These are also available online.

6.2 PLACEBO

There is no placebo in this study.

6.3 DOSING REGIME

Participants will be randomised to receive Meropenem (or protocol approved alternative) for either 14 or 7 days with preference for three times daily antibiotic treatment. Antibiotic choice, dose and frequency will be determined by the clinical team as per their local practice (e.g. twice daily, continuous infusion or elastomeric devices). Dosing information will be recorded in the participant's medical records and entered in to the eCRF.

Patients can be enrolled in the study up to 96 hours after starting Meropenem or a protocol permitted equivalent (to Meropenem) intravenous antibiotic. Participants not already receiving Meropenem, but receiving one of the permitted alternatives described above in section 6.1 may have their antibiotic changed to Meropenem, or remain on the permitted alternative at the PI or Investigator's discretion where appropriate. These participants will have the number of days of antibiotics already received

included in their overall 7- or 14- day allocation. For example: a participant in the 7- day allocation group who received 2 days of intravenous antibiotics prior to randomisation, would receive a further 5 days of intravenous antibiotics, thus receiving 7 days in total.

Participants already receiving antibiotics not included on the permitted list above, should be switched to Meropenem or one of the protocol approved alternatives listed above and will not have their earlier doses of IV antibiotics counted towards their total allocated duration – i.e. they will receive 7 or 14 days of a protocol approved study drug.

Representative preparations of the preferred IMP, Meropenem, are described below (NB clinical study teams are permitted to prescribe and administer IMP according to their local guidelines and practice):

Intravenous bolus injection administration:

A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used as soon as possible after the solution has been prepared for infusion.

Intravenous infusion administration:

A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used as soon as possible. Reconstituted solution of the product in 5% dextrose solution should be used immediately. The constituted solutions should not be frozen.

6.4 DOSE CHANGES

Meropenem doses recommended for use in patients with renal impairment are as follows (however study teams are permitted to prescribe IMP according to their local guidelines and practice):

- use normal dose every 12 hours if creatinine clearance 26-50 ml/min;
- use half normal dose every 12 hours if creatinine clearance 10-25 ml/min;
- use half normal dose every 24 hours if creatinine clearance <10 ml/min.

Dose changes recommended for other permitted antibiotics for use in the study are specified in the relevant SPCs however as before, study teams are permitted to prescribe IMP according to their local guidelines and practice.

6.5 PARTICIPANT COMPLIANCE

The following will be completed to assess adherence and fidelity with the randomised duration of antibiotic therapy: review of participant diaries, patient review at the day 14 study visit and routinely collected prescribing/drug administration data (in medical records) where possible for the purposes of the study outcomes. Compliance will be tabled, reported to and monitored by the TSC and DMC. Review of compliance will be added to meeting agendas to ensure action is taken when appropriate. Dosing will be recorded in the eCRF.

6.6 OVERDOSE

Relative antibiotic overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 6.4. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile and are generally mild in severity and resolve on withdrawal or dose reduction. In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove Meropenem and its metabolite if clinically needed. To minimise the risk of overdose, participants will either receive treatment as an inpatient, or will be trained and assessed as competent prior to being able to self-administer treatment. Renal function monitoring while on treatment is not recommended and is not standard NHS practice. In practice renal function tends to improve on treatment, not worsen.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

None.

6.7.2 Permitted Medications

For those that have met the inclusion and exclusion criteria, the participants are permitted to take all their prescribed medications. Participants are allowed oral corticosteroids as part of the exacerbation- the dose and duration will be recorded in the CRF. Secondary antibiotics are permitted to be administered concurrently with the IMP and there is no protocol restriction to the type of antibiotic used. It is important however to shorten the duration of the secondary antibiotic in line with the randomisation outcome, i.e., if participant is randomised to receive 7-day treatment, the secondary antibiotic should also be prescribed for 7 days. This should be annotated in the patient medical records.

6.7.3 Prohibited Medications

There are no prohibited medications, as per standard NHS practice. The patient cohort entering the study are not at high risk of complications (e.g., immunocompromised). Local investigators are permitted to use discretion around any potential contraindicated concomitant medicine.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

There are no specific safety assessments required for the study. Pregnancy testing will be carried out as part of eligibility assessment as pregnant women should be excluded from the trial.

7.2 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures are summarised in table 2.

7.2.1 Screening

After obtaining written informed consent, eligibility will be confirmed as per the study inclusion and exclusion criteria. Pregnancy test will be performed if applicable. Prior to randomisation, Bronchiectasis Severity Index (BSI)[12] will be calculated for stratification purposes, using the calculator embedded in the database. Results from the participant's latest available spirometry reading may be used to calculate the BSI. If the participant has not undergone spirometry, lung function assessment should be undertaken using spirometry after consent and prior to randomisation for the purpose of calculating BSI.

7.2.2 Baseline

Following confirmation of eligibility, randomisation will take place as described in protocol section 5.5. Smoking status, medical history and concomitant medications will be collected.

Participants will be asked to complete the following questionnaires electronically by sending a link to the questionnaires held in REDCap to their email address;

- St. George's Questionnaire;
- Bronchiectasis Health Questionnaire;
- CAT Questionnaire,
- Euroqol 5 Dimension Health Related Quality of Life Survey (5 level version, EQ-5D-5L);
- Health Care Resource Use (HCRU).

If the participant is unable or unwilling to complete the questionnaires electronically, paper copies will be provided in person at the baseline appointment and collected by the study team for review after completion. A member of the local study team will complete the Charlson Comorbidity Index and Rockwood Frailty Index.

If the participant is able to spontaneously expectorate, a sample will be collected, sputum colour will be recorded using a sputum colour chart[16] and the sample will be sent to local NHS microbiology laboratory for routine analysis. If a participant provides a sputum sample during an exacerbation but before providing consent, the information, including the results from this sample, may be used to complete baseline data.

To measure compliance with the antibiotic regime, participants will be given a weekly diary card to complete. The diary card will also record if the participant has undertaken any chest clearance exercises (active cycle of breathing techniques, ACBT, etc.). The diary cards will either be posted back to the research team or handed over in person.

Participants will be provided with a study card containing contact details for their local research team and a reminder to contact the team to have their first subsequent exacerbation verified.

The study drug will be prescribed and dispensed as per usual local standard practice.

7.2.3 **Day 14 (- 2 / + 5 days since start of IV antibiotic treatment)**

The day 14 visit should take place 14 days after starting protocol permitted antibiotic and may take place in person at hospital or clinic or remotely if preferred.

After completion of antibiotic treatment, participants who have self-administered and completed their course of treatment at home will return to clinic to have line removal as per local practice. This will not be recorded as a deviation if not removed at the specified time point. Participants who received their treatment as an inpatient will have their lines removed prior to hospital discharge.

If participants require further antibiotic treatment immediately after completion of their randomised allocation that is permitted. Details of the treatment must be recorded in REDCap, and the concomitant medications log should be updated accordingly. However, if there is any gap between the completion of the randomized allocation and the need for further antibiotics, the criteria for exacerbation should be assessed before initiating the new treatment.

All participants will be asked to complete the following questionnaires electronically as before;

- St. George's Questionnaire;
- Bronchiectasis Health Questionnaire;
- CAT Questionnaire,
- Euroqol 5 Dimension Health Related Quality of Life Survey (5 level version, EQ-5D-5L);
- Health Care Resource Use (HCRU).

If unable or unwilling to complete the questionnaires electronically, paper copies will be provided and collected by the study team for review after completion. If the day 14 visit is taking place remotely, paper copies can be provided at any prior visits or posted out to the participant along with return stamped addressed envelopes.

Participant diaries will be returned and reviewed by the study team for completeness. Participants will be asked if they have been carrying out daily ACBT and this will be recorded in the participant diary and eCRF. Adverse events and concomitant medications will be collected.

Where questionnaires and/or diaries are not returned, the study team will make up to three attempts to contact the participant (or their legal representative where appropriate) requesting return of the questionnaire after which, if unsuccessful, the data will marked unavailable.

If the participant is able to spontaneously expectorate, a sample will be collected, sputum colour will be recorded using a sputum colour chart[16] and the sample will be sent to local NHS microbiology laboratory for routine analysis Where the day 14 visit is taking place remotely, participants will be provided with a sputum colour chart* and a sputum collection pack by the research team before leaving hospital/clinic, which will contain specimen pots, postage boxes and instructions for collection and postage.

7.2.4 **Monthly call up until 1 year since start of IV antibiotic treatment (+/- 21 days):**

Participants will receive a monthly call from the local research team to record subsequent exacerbations, collect adverse events (up to day 60, including SAEs) and concomitant medication, and health economic evaluation. Participants will also be asked if they have carried out any breathing exercises (e.g. ACBT) and this will be recorded until the first verified exacerbation (see section 7.2.5 below). Reminders to contact the research team to verify their first subsequent exacerbation will be given at the monthly calls. The monthly follow ups may take place in person where preferred by the participant.

Euroqol 5 Dimension Health Related Quality of Life Survey (5 level version, EQ-5D-5L) and Health Care Resource Use (HCRU) questionnaires will be carried out over the telephone during monthly calls. Data from the questionnaires will be entered directly into the REDCap eCRF by appropriately delegated members of the local research team. If unable or unwilling to complete the questionnaires over the telephone, participants may complete the questionnaires on paper and return to the local research team for entry in to the database. HCRU information may be collected from routine medical records, where consent is provided to do so.

All follow up visits are calculated from the date protocol permitted treatment has started and not from randomisation date.

A final sputum sample will be handed in or posted to the hospital at the time of verified first subsequent protocol defined exacerbation (up to 1-year post randomisation), if the participant is able to spontaneously expectorate. Participants will be provided with a sputum collection pack by the research team before leaving the hospital or clinic, which will contain specimen pots, postage boxes and instructions for collection and postage.

Protocol deviations will not be recorded where sputum samples cannot be collected at any of the time points described above.

Up to three attempts will be made to contact the participant (or their personal legal representative) at each follow up time point. If the participant is not contactable after three attempts at three consecutive monthly follow ups the participant will not be contacted again by the trial team and visits will be marked ‘not done’ in the database. If the participant does not contact the study team before the end of the 12 month follow up period, they will be considered lost to follow up and withdrawn from the study. If the participant contacts the study team within the 12 month follow up period, visits may re-commence.

7.2.5 **Verification of first subsequent exacerbation**

Participants will be asked to call their local study team if they feel unwell with an exacerbation of bronchiectasis and have started taking antibiotics, or feel they may need antibiotics. Participants’ first

*Sputum colour chart reproduced with permission of the © ERS 2023: European Respiratory Journal Aug 2009, 34 (2) 361-364; **DOI:** 10.1183/09031936.00163208

exacerbation may be an appropriately qualified doctor, nurse or allied health care professional who has been delegated this task by the PI on the site delegation log.

The definition of exacerbation being used is: a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 hours[5]:

1) Cough;
2) Sputum volume and/or consistency;
3) Sputum purulence;
4) Breathlessness and/or exercise tolerance;
5) Fatigue and/or malaise;
6) Haemoptysis

AND antibiotic treatment is required (oral, intravenous or inhaled).

To mitigate against the risk of subjectivity, questions will be standardised and detailed in the eCRF.

If the clinical member of the research team deems this is not an exacerbation by the agreed criteria, the participant will continue until they feel they have the next exacerbation, which will then be checked again by a clinical member of the research team. This will continue until the participant meets the primary outcome measure. All further exacerbations will be recorded but not verified by the research team, until the last monthly call.

Due to the nature of teams at site being too small, it is not possible to have someone blinded to treatment allocation to verify the first exacerbation.

Participants should return to their usual care team for treatment and management of all future exacerbations of their bronchiectasis.

Table 2: Schedule of study assessments and procedures:

	Screening Pre-randomisation	**Baseline**	**Day 14 - 2 /+ 5 days (Both arms)**	**Month 1 +/- 14 days**	**Month 2 (Day 60) +/- 7 days**	**Monthly Call** +/- 21 days**	**At time of 1st subsequent exacerbation$**
Eligibility	X						
Informed Consent	X						
Pregnancy test (for participants of childbearing potential)	X						
Lung function assessment- spirometry*	X*						
BSI calculation	X						
Randomisation		X					
Smoking history		X					
Medical history		X					
Concomitant medication		X	X	X	X	X	X
Sputum colour		X	X				
St. George's Questionnaire		X	X				
Bronchiectasis Health Questionnaire		X	X				
CAT Questionnaire		X	X				
EQ-5D-5L		X	X	X	X	X	
HCRU		X	X	X	X	X	
Charlson Comorbidity Index		X					
Rockwood Frailty Index		X					
IMP Prescription		X					
Diary card		X	X				
Study card		X					
Record prescribing data		X	X				
Line removal			X^				
Frequency of chest clearance exercise#			X	X#	X#	X#	X
Record of Exacerbations$			X	X	X	X	X
Adverse Events			X	X	X		

Sputum Sample to NHS microbiology laboratory (where provided) + to Cambridge laboratory for sub-study[+]		X[$$]	X^^				X***

*Where spirometry has not taken place or results are not available.

**Monthly call from day 1 of IV antibiotics for 1 year +/- 21 days.

***Sputum sample will be handed or posted to the hospital at the time of needing another antibiotic course (up to 1 year post randomisation).

^ +/- 7 days.

^^ When possible, sputum to be collected at day 14

[$] Telephone call to research team to verify first exacerbation as soon as possible and ideally within 7 days of onset.

[#] Until time of first subsequent exacerbation.

[+] If participant has consented to sub-study. See appendix 3

[$$] Results from a routine sputum sample provided prior to commencing intravenous antibiotics and before consent may be used

7.3 COMPLIANCE ASSESSMENTS

Compliance will be reviewed through the completion of patient treatment diary, at study visits/calls and from routine prescribing, dosing and administration information in patient medical records. IMP compliance will be recorded as outlined in section 6.5.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

Participation in the study is for 1 year with the final appointment being completed remotely (either by telephone or video call, if per local practice) 52 weeks +/- 21 days after study treatment completion.

7.5 STORAGE AND ANALYSIS OF SAMPLES

A sputum sample will be collected in a sputum pot at baseline, day 14 and at the time of first exacerbation, where the participant can spontaneously produce one. It will not be recorded as a deviation if a sample cannot be collected. These samples will undergo routine microbial testing for pathogenic organisms and the results recorded in the CRF. If a participant has already provided a clinical sputum sample prior to starting antibiotics for their study entry exacerbation and before providing consent to the study, the results from this sample can be used and there is no need to provide another sputum sample at baseline.

All sputum samples for the main SBIVA study will be collected and stored as per site usual practice and analysed in NHS microbiology labs of the respective trial site in accordance with standard of care. Once routine testing is complete any remaining sample will be disposed of as per local practice. Where sample collection takes place remotely participants will receive instructions for collection and postage and asked to post samples on the same day, or store in the fridge overnight until posting the next day.

8. DATA COLLECTION

Trial data will be collected by appropriately trained members of the local research team delegated to do so by the PI, except for where it is self-reported by the participant. Baseline appointments will take place in person face to face. Day 14 visits may take place either in person or remotely via telephone or video call where local practice permits. Monthly follow ups will be conducted remotely in all cases. Information which will fulfil the requirements of the study primary and secondary endpoints will be collected. Data is primarily collected from source and entered in to the CRF (REDCap database) once available.

The study team will collect medical history, lung function assessment data, smoking status and pregnancy status (where applicable) data at baseline from medical records and from participants. Data required for stratification during randomisation will be collected prior to randomisation, including BSI calculation and whether participants will receive treatment as an inpatient or are suitable for self-administration of antibiotics at home.

Data will be collected for health outcomes, quality of life and health care resource use (HCRU) at baseline and at day 14 via a web based portal. If participants are unable or unwilling to receive emails and complete the questionnaires (detailed in section 7) online, paper copies will be provided by the site team, returned and reviewed for completeness. The local research team as delegated will be responsible for data entry, including Charlson Comorbidity Index and Rockwood Frailty Index at baseline.

Quality of life and HCRU (detailed in section 4) data will be collected over the telephone during monthly calls or in person, and entered directly in to the study database, REDCap. Alternatively, where preferred, participants may complete the questionnaires on paper and return to the local research team for entry in to the database. Up to three attempts will be made to contact the participant at each follow up time point. If the participant is not contactable after three attempts at three consecutive monthly follow ups the participant will not be contacted again by the trial team and visits will be marked ‘not done’. If the participant does not contact the study team before the end of the 12 month follow up period, they will be considered lost to follow up and withdrawn from the study. If the participant contacts the study team within the 12 month follow up period, visits may re-commence.

Antibiotic prescribing and dosage data will be collected from patient medical records and entered in REDCap by appropriately delegated local research team members. Antibiotic treatment adherence data will be collected using a

weekly patient treatment diary card, which will be provided to trial participants in paper format, and/or routine prescribing and administration data. Participants will be asked to complete and return diaries to the research team by post, or in person at a later visit. The local research team as delegated will be responsible for data entry of treatment adherence in to the eCRF.

Where questionnaires and/or diaries are not returned, the study team will make up to three attempts to contact the participant requesting return of the questionnaire after which if no success the visit will marked not done and the reason recorded in the database. If the questionnaires and/or diaries are returned at a later date within the 12 month follow up period, the data may be entered in to the database. Missing questionnaire or diary data will be reported as non-compliance with the protocol (deviations).

Chest clearance exercise (ACBT) data will be collected from patient diaries and/or at day 14 visit, and during monthly telephone calls until the participant's first subsequent exacerbation.

Adverse event data (including SAEs) will be collected at day 14 and at monthly telephone calls until day 60, as per section 7.2 of the protocol.

Concomitant medication data will be collected at baseline, day 14 and at monthly telephone calls, until month 12.

Exacerbation record data will be collected at monthly telephone calls. Only the first exacerbation will be verified by a member of the study team.

Data will be collected from sputum samples (where applicable) at baseline, day 14 and at the time of first subsequent exacerbation. Sputum colour (using a sputum colour chart[16]) data will be recorded at baseline and at day 14. Where participants carry out day 14 visit remotely (via telephone or video call), they will be provided with a sputum colour chart and report their sputum colour to the study team during the call. Microbiology results and resistance patterns will be collected at baseline, day 14 and at the time of first subsequent exacerbation from local NHS laboratory analyses. Microbiology results collected will include the identification of; *streptococcus pneumonia, haemophilus influenza, staphylococcus aureus, Moraxella catarrhalis, Escherichia coli, pseudomonas aeruginosa, acinetobacter baumanii* and any other bacteria identified during routine analysis. Data will be entered in to the eCRF by the local research team.

Where a participant has withdrawn from study medication, study procedures and questionnaires with permission to collect information from ongoing routine health records, data may be collected from the participants medical records and entered in to the database.

8.1 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time. The source data will be the patient's medical records, electronic records, data collection sheets, diaries and questionnaires completed on paper or entered directly in to the eCRF. Source data locations will be documented in the source data plan.

8.2 CASE REPORT FORMS

Data will be directly entered into the eCRF but where this is not possible, will be collected via source data collection sheets and transcribed in a timely manner. All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation) and all electronic case report forms are subject to Sponsor approval.

8.3 TRIAL DATABASE - REDCap

The study database will be created and maintained by ECTU. Trained and delegated members of the study team will be given password protected logins to the database to complete data entry. The data will be stored in a secure server in the University of Edinburgh for the minimum retention period for the study data.

9. DATA MANAGEMENT

9.1 Data Management Plan

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving will be detailed in a separate Data Management Plan (DMP) compiled by the Data Management Team at the Edinburgh Clinical Trials Unit.

9.2 Personal data

The following personal data will be collected about participants as part of the study;

- Name
- Initials
- Address
- Telephone number
- Email address (where possible participants will be asked to share their own personal email address, not a shared account)
- Date of Birth
- National Health Service (NHS) Number or Community Health Index (CHI) number
- Demographics
- Medical History

Where consent is provided, NHS number or CHI and the participant's email address will be entered in to the eCRF. Some indirectly identifiable personal data (age, ethnicity, gender, sex at birth) will also be entered onto the eCRF, which is stored on University of Edinburgh servers.

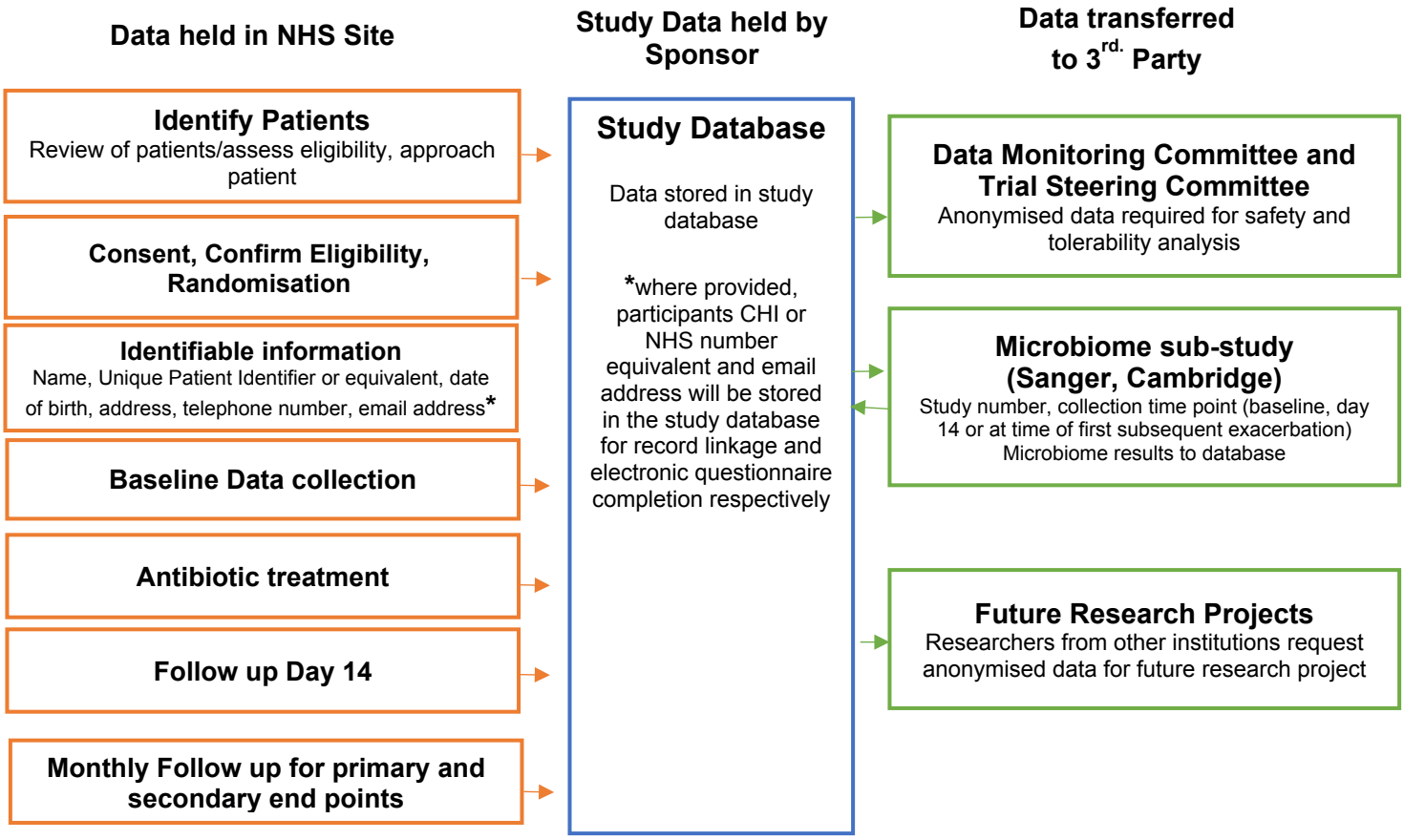
Name, address, telephone number and email address will be collected from personal legal representatives for the purpose of study follow up and stored on secure local NHS servers.

The availability of personal data, including NHS number (e.g. CHI number), will allow us to perform record linkage with other national health registries to ascertain how the intervention affects the participants' future health status. We will seek consent from participants to retain their data for future research and this will be optional on the consent form. Any future research would be approved by a research ethics committee first.

9.3 Data Information Flow

The flow of data comprises:

- Patient data will be collected by the local research teams at sites.
- Data will be recorded on the patient's medical records and/or source data worksheets, which may serve as source documents.
- Indirectly identifiable data will be entered into the eCRF.
- An anonymised data set will be provided to the DMC for analysis of safety and tolerability and to make a recommendation on the duration of treatment received by participants.
- At the end of the study, the pseudo-anonymised data will be analysed by ECTU. A project report will be provided to the stakeholders and will be published in peer review journals.
- Following publication of the primary SBIVA Trial results, a de-identified individual participant data set may be made available to other researchers upon receipt of a reasonable data sharing request.



9.4 Data Storage

Personal data will be physically stored by the research teams on NHS sites in locked offices. Paper files containing personal data will be held in storage cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only. Consent forms will be held at site, as part of the Investigator Site File (ISF).

Personal data will be digitally stored by the research teams on NHS sites using password-protected NHS computers in locked offices. Some indirectly identifiable personal data (initials, age, ethnicity, gender, sex at birth), and where consent is provided, personal data in the form of NHS or CHI number and email address will also be entered onto the eCRF, which is stored on University of Edinburgh servers.

Personal data will be stored for a maximum of 5 years to conduct future ethically approved non-commercial studies. The availability of personal data will allow us to perform record linkage with other national health registries to ascertain how the intervention affects the participants' future health status.

Edinburgh Clinical Trials Unit (ECTU) will provide and maintain a secure web-based database compliant with the relevant regulations and Sponsor SOPs. Data will be entered by those staff delegated to do so on the delegation log held at site.

9.5 Data Retention

Paper records will be archived for a minimum of 5 years from the protocol defined study end date.

The electronic data set will be anonymised and held securely on a University of Edinburgh server indefinitely. De-identified individual participant data set may be made available to other researchers upon receipt of a reasonable data sharing request. Date of presentation will be removed as this is potentially identifiable. This will be managed by Edinburgh Clinical Trials Unit.

Personal data will only be as held as long as it is necessary and then the data will be destroyed.

9.6 Disposal of Data

The electronic data set will be anonymised and held securely on a University of Edinburgh server indefinitely. Paper records will be destroyed, with Sponsor permission, after the 5-year retention period has elapsed.

9.7 External Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s). There are specific circumstances of note:

- Data to be transferrable to the Data Monitoring Committee for review.
- Data request from external parties (e.g., clinical researchers).

In these cases, data will not contain personal data; they will be anonymised and subject to review by University of Edinburgh and NHS Lothian sponsors before permission is obtained.

9.8 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g., the site).

9.9 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

In our pilot single centred study, the Hazard Ratio for exacerbation (95% CI) for the 14-day arm was 1.80 (1.16-2.80), p=0.009 but this was a small study, and a more conservative estimate of a Hazard Ratio of 1.5 has been used. Any therapy that can prolong time to next exacerbation is welcome as exacerbations cause significant morbidity and mortality. With a two-sided 5% level of significance, 90% power, total number of events required are 256. 181 per group are needed assuming the proportions who are exacerbation-free at 90 days in the two randomised groups is 0.2 and 0.342. To allow 10% dropouts, we have increased the sample size to 400.

10.2 PROPOSED ANALYSES

Analyses will be based on an intention-to-treat population and will be adjusted for the variables used to stratify the randomisation. A full Statistical Analysis Plan will be completed before database lock. Statistical analyses will follow the Standard Operating Procedures of the Edinburgh Clinical Trials Unit. The primary analysis of the primary outcome will be a Cox proportional hazards regression, and results will be presented as Hazard Ratios with 95% confidence intervals. Other outcomes will be analysed using appropriate methods that report point estimates and confidence intervals. Statistical analyses of continuous measures and ordinal scales will utilise methods that use the full scores, to maximise power; and will adjust for baseline scores where these are measured. They will also be reported using binary cut-offs to aid clinical interpretation: St. George's Respiratory Questionnaire score[13]-improvement of 4 or more units; CAT Questionnaire score- improvement of 4 or more units.[14]

11. HEALTH ECONOMIC EVALUATION

Full details of these analyses will be specified in a comprehensive Health Economic Analysis Plan (HEAP), authored by the study health economist(s), and signed off by the PI prior to analysis, however the following section offers an overview for ease of reference:

For Health Economic analysis: To maximise UK policy relevance, health economic analysis will follow National Institute for Health and Care Excellence (NICE) reference case recommendations[17] including: adoption of an NHS and Personal Social Services (PSS) costing perspective for primary analyses; cost-utility approach (results presented in terms of incremental cost per QALY derived from EQ-5D-5L); discount rate of 3.5% for both costs and QALYs; and the use of probabilistic sensitivity analysis, to generate cost effectiveness acceptability curves.[17]

An economic model will be developed utilising survival curves from primary analysis and any appropriate pilot study data to extrapolate rates of exacerbation, and associated health impacts, healthcare resource utilisation, and cost over 1, 3, and 5-year time horizons.[18] We anticipate utilising Markov modelling though other options will be explored. Rates and costs of community HCRU (GP/Practice & District nurse consultations, prescribing, physiotherapy, other outpatient visits, and NHS Direct/NHS24 calls), and EQ-5D-5L will be recorded in monthly contacts alongside other measures separately for those associated with normal life and during exacerbation. Modelling will additionally draw upon targeted literature searches to top up parameters as needed, as well as data from our ongoing MucAct Trial [HTA 128443], which includes daily recording of EQ-5D-5L and HCRU over 14 days within/following an exacerbation. HCRU will be combined with standard UK price weights[19,20] to generate costs.

12. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) booklet.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent **until Day 60** (including SAEs) must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

12.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

12.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit/call during the study until Day 60. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence.

Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g., laboratories.

12.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g., hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

AE/SAE are to be recorded until Day 60.

12.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e., existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

12.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs, including worsening of asthma, COPD or bronchiectasis.

12.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double-blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

12.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 12.1.

12.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- 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 AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

12.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC booklet (section 4.8).

The event may be classed as either:

- **Expected**: the AR is consistent with the toxicity of the IMP listed in the SPC booklet (section 4.8).
- **Unexpected**: the AR is not consistent with the toxicity in the SPC booklet (section 4.8).

Fatal and life-threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

12.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

12.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log.

12.6 REPORTING OF SAEs/SARs/SUSARs

*Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 12.4.2, Assessment of Causality and 12.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

12.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the Co-Sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported

during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

12.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

12.9 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy or any pregnancy of a female partner of a male participant, who became pregnant while taking the allocated study medication. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

There will be no stopping criteria for participants in the study, since all treatments are used in routine clinical practice.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the Co-Sponsors, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the Co-Sponsors direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the Co-Sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Co-Sponsors.

The Investigator or delegated member of the trial team and the participant (or their Personal Legal Representative) will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

14.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

14.3.6 Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance Data Protection training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies.

14.3.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

14.3.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Co-Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Co-Sponsors for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

15.2 PROTOCOL NON-COMPLIANCE

15.2.1 Definitions

- **Deviation** - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.
- **Violation** - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Co-Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Co-Sponsors every 3 months. Each protocol violation will be reported to the Co-Sponsors within 3 days of becoming aware of the violation.Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Co-Sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Co-Sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Co-Sponsors.

15.6 END OF STUDY

The end of study is defined as the last participant's last visit or call.

The Investigators and/or the trial steering committee and/or the Co-Sponsors have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, MHRA, R&D Office(s) and Co-Sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Co-Sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Co-Sponsors (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload the clinical trial results on to the ISRCTN database on behalf of the Sponsor.

15.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Not applicable- this is standard treatment already in clinical practice.

15.8 INSURANCE AND INDEMNITY

The Co-Sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Co-Sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Co-Sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analyzed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

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

16.3 DATA SHARING

All requests for study data will be made in writing via email to ECTUdatashare@ed.ac.uk in the first instance and will be reviewed in accordance with ECTU_SOP_OP_15 Data Access Request and Application Management

16.4 PEER REVIEW

The trial underwent peer review during the funding application to the NIHR HTA.

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APPENDIX 1 SBIVA Sputum Microbiome Sub-Study

The SBIVA study has a built-in optional microbiome sub-study. Participants in the main study will also be invited to participate in this sub-study by providing an extra sputum sample, if they are able, at baseline, day 14 and at their first verified exacerbation. Participation in the sub-study is optional and separate consent will be sought for this, as described in the PIS.

Where a participant consents to be part of the sub-study, samples will be either stored locally for future transportation to the University of Edinburgh or sent straight to the University of Edinburgh. Samples will then be sent in batches on to the Wellcome Sanger Institute. Where the visits take place remotely, participants will be provided with a sputum collection pack by the research team before leaving hospital/clinic, which will contain specimen pots, postage boxes and instructions for collection and postage.

The aim of the sub-study is to understand the microbial basis of exacerbations in bronchiectasis and how the microbiome is associated with treatment and clinical outcome. The aims of the sub-study are tertiary to those in the main trial. Sputum samples collected during the trial will be subjected to deep metagenomic sequencing. The data will be used to measure both community and strain level microbial diversity, which will be compared both within and between individuals. Statistical tests will be used to determine associations between the lung microbiome and clinical outcome.

All sample processing will occur at the Wellcome Sanger Institute, including sputum processing and DNA extraction. Next generation sequencing will be carried out and the data will be processed using in-house pipelines. Anonymised sequence data will be deposited in an open access public nucleotide sequence database collaboration repository (the European Nucleotide archive (ENA)) for microbial sequencing data. A pseudonymised (linked anonymised) dataset will be prepared by the research team at the University of Edinburgh and sent to the Wellcome Sanger Institute which will include: unique pseudonymised (linked anonymised) patient ID, hospital name, the date and time point of sample collection and clinical response at day 14 and first verified exacerbation.

In addition, an aliquot of the sputum may be sent to an external commercial service for metabolomics in order to identify host and bacterial metabolites. This will be used to identify chemical biomarkers relating to the onset of an exacerbation and treatment outcome. No data will be shared with the external service.

A data use and materials transfer agreement or research collaboration agreement will be in place before any samples or data are transferred to the Wellcome Sanger Institute.

Deviations will not be recorded where the participant has consented to the sub-study but is unable to produce a sample at the requested time point.