FULL/LONG TITLE OF THE TRIAL

Exacerbation and Symptom Control After Pseudomonas Eradication Treatment in Adult Bronchiectasis: a multicentre randomized controlled trial (ESCAPE)

SHORT TRIAL TITLE / ACRONYM

ESCAPE: Investigating whether prolonged antibiotics can prevent permanent *Pseudomonas* infection in bronchiectasis

PROTOCOL VERSION NUMBER AND DATE

ESCAPE Protocol V2 20-12-25

RESEARCH REFERENCE NUMBERS

IRAS Number: 1011311

ISRCTN Number:

SPONSORS Number: 1-060-25

FUNDERS Number: NIHR164131

This protocol has regard for the HRA guidance and order of content V1.2 March 2016

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures, and other regulatory requirements as amended.

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

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Patricia Burns

Date: 22.12.2025

Name: Patricia Burns
Position: Senior Research Governance Manager

Chief Investigator:

Signature:

Date: 20/12/2025

Name: Prof. James Chalmers

Statistician:

Signature: J. Stobo

Date: 22/DEC/2025

Name: Jamie Stobo

KEY TRIAL CONTACTS

Chief Investigator	Prof. James Chalmers. Division of Molecular and Clinical Medicine, Level 5, Mailbox 12, Ninewells Hospital, Dundee, DD1 9SY, 01382 383642 j.chalmers@dundee.ac.uk
Collaborators	Professor Michael Loebinger, Professor of Respiratory Medicine, Royal Brompton Hospital, London, UK Dr Charles Haworth, Consultant Respiratory Physician, Respiratory Medicine, Royal Papworth Hospital , UK Professor Kathleen Boyd, Professor of Health Economics, University of Glasgow. Professor Anthony De Soyza, Professor of Respiratory Medicine, University of Newcastle, UK Professor Nick Francis, Head of School, Primary Care, Population Sciences and Medical Education, University of Medicine Margaret Band, Senior Clinical Trial Manager, University of Dundee Dr Jamie Stobo, Statistician, University of Dundee Dr Arietta Spinou, Lecturer in Cardiorespiratory Physiotherapy Practice and Research, Kings College London Jeanette Boyd, Co-Ordinator, The European Lung Foundation Bronchiectasis patient advisory group.
Trial Coordinator	Margaret Band, Senior Trial Manager, Tayside Clinical Trials Unit (TCTU), Tayside Medical Science Centre (TASC), Residency Block, Level 3, Ninewells Hospital, Dundee, DD1 9SY 01382383097 m.band@dundee.ac.uk
Co-Sponsor	University of Dundee & NHS Tayside Patricia Burns, Senior Research Governance Manager, Research & Development Office, TASC, Residency Block Level 3, George Pirie Way, Ninewells Hospital, Dundee DD1 9SY, 01382 383297, TASCgovernance@dundee.ac.uk
Funder(s)	NIHR Health Technology Assessment Programme
Clinical Trials Unit	Tayside Clinical Trials Unit, TASC, Residency Block, Level 3, Ninewells Hospital, Dundee, DD1 9SY 01382 383581, TCTU@dundee.ac.uk

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Database Manager	Emma Falconer, Database Manager, TCTU, TASC, Residency Block, Level 3, Ninewells Hospital, Dundee, DD1 9SY e.falconer@dundee.ac.uk

LIST of CONTENTS

I. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BEST	Bronchiectasis Exacerbation and Symptom Tool
CAAT	Chronic Airways Assessment Test
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMBARC	European Bronchiectasis Registry
ePRO	Electronic Patient Reported Outcomes
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IF	Incidental Finding
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LPLV	Last Participant Last Visit
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health and Care Research

PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
TRuST	Tayside Randomisation System
TSC	Trial Steering Committee
UoD	University of Dundee

II. TRIAL SUMMARY

Trial Title	Exacerbation and Symptom Control After Pseudomonas Eradication Treatment in Adult Bronchiectasis: a multicentre randomized controlled trial (ESCAPE)	
Short Title	ESCAPE	
Clinical Phase	III	
Trial Design	Open label, controlled randomised, multi-centre trial	
Trial Participants	Adults with bronchiectasis and *Pseudomonas aeruginosa infection*	
Planned Sample Size	326	
Treatment duration	12 – 14 weeks	
Follow up duration	2 years (104 weeks)	
Planned Trial Period	4½ years	
	Objectives	Outcome Measures
Primary	To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on rate of exacerbations	Frequency of pulmonary exacerbations (EMBARC definition)
Intervention	*P. aeruginosa* eradication treatment consisting of systemic antibiotics (either oral or intravenous as clinically indicated) alongside or followed by inhaled anti-pseudomonal antibiotics for 3 months, in addition to background therapy.	
Formulation, Dose, Route of Administration	As per British Thoracic Society Guidelines	
Comparator	Background therapy only.	

III. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
NIHR Health Technology Assessment Programme	Trial funding

IV. ROLE OF TRIAL SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

V. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders, including the CI, collaborators, statistician, research assistant, trial manager and research nurse where appropriate. TMG membership details will be held in the Trial Master File (TMF). The TMG will meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. Minutes of the TMG meetings will be maintained in the TMF.

The trial will have an independent Trial Steering Committee (TSC). The role of the TSC will be detailed in a TSC charter and will include oversight of the conduct of the trial. TSC terms of reference are detailed in the TSC Charter and held in the TMF. Minutes of the TSC will be maintained in the TMF.

A Data Monitoring Committee (DMC) will be established to oversee the safety of trial participants and will be independent of the Sponsor. The DMC will be unblinded to allocation. The DMC will meet prior to participant recruitment to decide on the frequency of DMC meetings, timings will be documented in the DMC charter. DMC terms of reference are detailed in the DMC Charter and held in the TMF. Minutes of the DMC will be maintained in the TMF.

The Chief Investigator (CI) will be responsible for the conduct of the trial. Site delegate(s) will oversee the trial and will be accountable to the CI. A trial-specific Delegation Log will be prepared for each trial site, detailing the duties of each member of staff working on the trial.

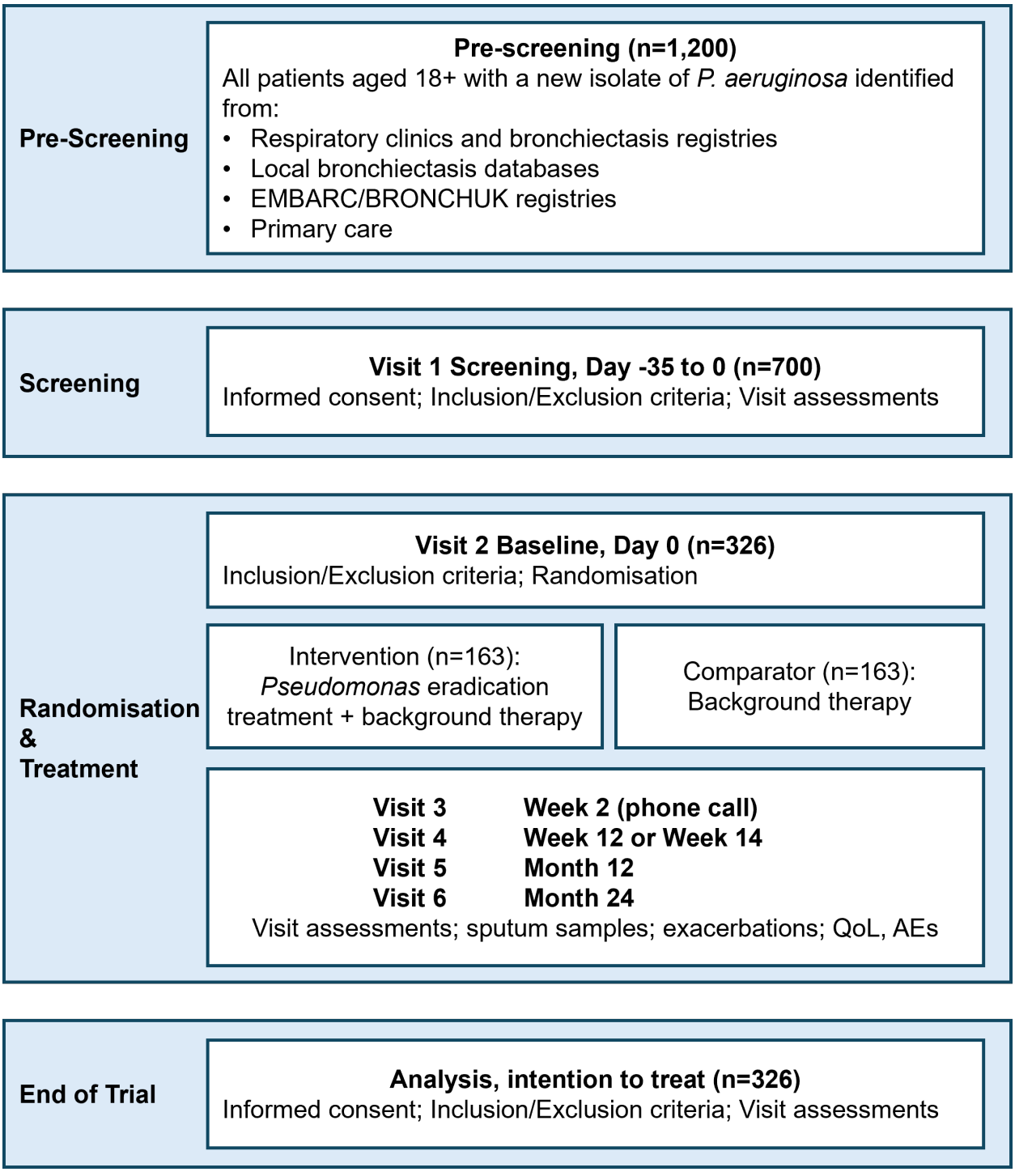
VI. PROTOCOL CONTRIBUTORS

CI: Prof James Chalmers, review and final approval
TCTU Senior Trial Manager: Margaret Band, initial draft, review
Senior Research Statistician: Jamie Stobo, review
Lead Scientist: Dr Rebecca Hull, review
TCTU Database Manager: Emma Falconer, review

VII. KEY WORDS:

Bronchiectasis, *Pseudomonas aeruginosa,* eradication, exacerbation

VIII. TRIAL FLOW CHART



1. BACKGROUND

Bronchiectasis is a common chronic lung disease which affects more than 200,000 people in the UK (1). The disease is defined by abnormal permanent dilation of the airways leading to symptoms of cough, sputum production and recurrent chest infections. Patients may develop bronchiectasis due to a number of underlying health conditions but no cause is found in up to 60% of cases (2,3). Patients with bronchiectasis develop chronic lung infections, most commonly with *Pseudomonas aeruginosa*, a multidrug resistant Gram negative bacteria (4,5). Patients infected with *P. aeruginosa* are at increased risk of exacerbations and mortality (4). Once established *P. aeruginosa* infections are almost impossible to clear because of the formation of dense biofilms and adaptations in the lung that favour immune evasion (6). In the early stages of infection patients may feel well but it is believed that there is a "window of opportunity" following initial acquisition of infection to eradicate the infection with antibiotics (7).

Consequently guidelines from the British Thoracic Society and European Respiratory Society make a conditional recommendation in favour of performing "eradication treatment" against *P. aeruginosa* by providing a combination of systemic (oral or intravenous) and inhaled antibiotics for 3 months (8,9). There are no large randomized controlled trials to prove that this approach is effective (9). Eradication treatment is therefore variably applied across the NHS. It is essential to establish the efficacy, safety and cost effectiveness of *P. aeruginosa* eradication treatment in bronchiectasis.

This randomized controlled trial will be performed in which patients with new *P. aeruginosa* infection will be randomized to eradication treatment (systemic + inhaled antibiotics) in addition to background therapy, compared to patients receiving only background therapy to answer the questions: Does *P. aeruginosa* eradication treatment result in reduced frequency of exacerbations over 24 months? Is *P. aeruginosa* eradication cost-effective when compared with standard care?

2. RATIONALE

This trial will determine future guideline recommendations for patients with bronchiectasis. *P. aeruginosa* is difficult to treat and patients are at high risk of hospitalization, lung function decline and death (4,5) Preventing long term *P. aeruginosa* infection is therefore highly desirable. The NHS spends more than £30m annually on managing bronchiectasis (8). A US study comparing healthcare costs before and after acquisition of *P. aeruginosa* reported an 87% increase from $36,213 to $67,764 annually per patient (10,11). Determining the efficacy of *P. aeruginosa* eradication treatment was the top research priority identified in a prioritisation exercise involving a survey of European bronchiectasis experts and 711 patients with bronchiectasis, published in 2017 (12).

A systematic review and meta-analysis (CRD42021287027) of studies of *P. aeruginosa* eradication therapy in bronchiectasis was carried out. Eligible publications were identified by searching MEDLINE and EMBASE. Studies in cystic fibrosis were excluded. Study endpoints were *P. aeruginosa* eradication from sputum at 12 months and frequency of exacerbations. Random-effects meta-analysis was used to pool individual studies. 212 studies were identified. No randomized controlled trials were identified. After applying the inclusion and exclusion

criteria, six single-centre observational studies were selected for the meta-analysis(13–18) corresponding to a total of 287 patients. The meta-analysis found a 12-month *P. aeruginosa* eradication rate of 42% 95%CI 36-47%; p<0.00001 with no significant heterogeneity. Five studies provided data allowing a subgroup analysis to test whether the specific antibiotic regimen ("combined systemic and inhaled antibiotics" or "systemic antibiotics") modifies the effect. The eradication rate for combined therapy was 48% (95%CI 41-55%) while systemic antibiotics alone provided an efficacy of 27% (13-45%). The test of subgroup interaction was statistically significant (p=0.01). In two studies(14,16), there was a significant reduction in exacerbation rate post-eradication but the limited data precluded firm conclusions regarding exacerbation benefit. It was concluded that there is insufficient data to establish the efficacy of eradication treatment. There are no randomized trials in bronchiectasis and existing observational studies are small and at high risk of bias. The existing evidence supports the ERS guideline recommendations to include inhaled antibiotics as part of the regimen, since systemic antibiotics alone are associated with low eradication rates (9) This has informed the study design to compare systemic plus inhaled antibiotics with background therapy.

2.1. Assessment and Management of Risk

This trial is categorised as:

- Type A = No higher than the risk of standard medical care.

Treatment will be as per British Thoracic Society Guidelines

See Appendix 1

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1. Research Questions

1) Is there a difference in the rate of exacerbations over 24 months in patients given *P. aeruginosa* eradication treatment compared to patients receiving background therapy only?
2) What are the costs and consequences of *P. aeruginosa* eradication treatment and is it cost-effective when compared to patients receiving background therapy only?

3.2. Aims

1) To estimate the effects of 3 months eradication treatment vs background therapy alone in bronchiectasis patients with new *P. aeruginosa* infection
2) To determine the safety and cost-effectiveness of *P. aeruginosa* eradication treatment in bronchiectasis patients.
3) To work in partnership with patients to deliver a patient centred clinical trial and to achieve optimal study design, recruitment and dissemination

3.3. Table of endpoints/outcomes

Primary Objective		
Objective	**Outcome Measures**	**Timepoint(s)**
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on rate of exacerbations	Frequency of pulmonary exacerbations (EMBARC definition)	Day 0 to week 104
Secondary Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To evaluate the cost-effectiveness of *P. aeruginosa* eradication treatment compared with standard care	Frequency of pulmonary exacerbations (EMBARC definition)	Day 0 to week 104
	Incremental cost per exacerbation prevented	
	Incremental cost per quality adjusted life year (QALY) gained.	
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on eradication of *aeruginosa*	Frequency of *P. aeruginosa* isolation in sputum samples	Day 0, weeks 12, 52, 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on hospitalisation	Hospitalisations for severe exacerbations	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on quality of life	Quality of life-bronchiectasis (QOL-B) respiratory symptom scale	Day 0, weeks 12, 52, 104
	Chronic Airways Assessment Test (CAAT)	
	Quality of life using the EQ-5D-5L	
	Bronchiectasis exacerbation and symptom tool (BEST) diary	Daily day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with	Time to reinfection (isolation of *P. aeruginosa* after a first negative sputum sample)	Day 0 to week 104

standard care excluding inhaled antibiotics on reinfection rates		
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on antibiotic use	Total days of antibiotic use	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on antibiotic resistance	*P. aeruginosa* antibiotic resistance	Day 0, weeks 12, 52, 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on healthcare usage	All-cause healthcare contacts	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on death	All-cause mortality	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on adherence to treatment	Treatment adherence	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on safety	Frequency of adverse events (AEs) and serious adverse events (SAEs)	Day 0 to week 104
To evaluate the effect of *P. aeruginosa* eradication treatment compared with standard care excluding inhaled antibiotics on use of long term inhaled antibiotic treatment	Time to commencement of long term inhaled antibiotic treatment	Day 0 to week 104
Exploratory Objectives		
Objective	**Outcome Measures**	**Timepoint(s)**

To evaluate the detection of *P. aeruginosa* using molecular laboratory methods	*P. aeruginosa* abundance measured by molecular laboratory tests	Day 0, weeks 12, 52, 104

4. TRIAL DESIGN

Parallel group design. Randomised, open-label, multicentre.

The current care pathway is highly variable across the UK (32). The trial has been designed to fit into the current clinical care pathway for bronchiectasis in the UK where different systemic and inhaled antibiotics may be used as eradication therapy.

5. TRIAL SETTING

The trial will be conducted in approximately 50 primary or secondary care sites across the UK.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

1. Adults (18 years or older)
2. Able to provide informed consent.
3. Capable of complying with all trial procedures and of completing the trial, in the opinion of the investigator.
4. Bronchiectasis, confirmed by computed tomography (CT), showing bronchiectasis in 1 or more lobes (a historical radiology report or report from the investigator confirming bronchiectasis is sufficient for enrolment) and the appropriate clinical syndrome (symptoms of cough, sputum production and/or respiratory tract infections).
5. Able to be prescribed one of the inhaled antibiotics defined in the intervention arm, in the opinion of the investigator.
6. *P. aeruginosa* infection confirmed by:
   6.1) New isolation of *P. aeruginosa*, defined as the first documented sputum or other respiratory tract sample e.g. bronchoalveolar lavage samples) positive for *P. aeruginosa* within the 6 months prior to randomisation
   OR
   6.2) New isolation of *P. aeruginosa*, within the 6 months prior to randomisation, following previous clearance of *P. aeruginosa* defined as a minimum of 12 months without a positive *P. aeruginosa* culture and at least 2 intervening cultures negative for *P. aeruginosa*.

Notes

The investigator will take into account contraindications when determining both participant eligibility and the choice of antibiotic for each individual participant.

If a participant does not have a positive sputum sample within 6 months prior to randomisation but otherwise meets inclusion criteria 1 to 5, the investigator may send a sputum sample at the screening visit. If the participant is positive for *P. aeruginosa* then the inclusion criteria are met.

6.2. Exclusion criteria

1. Current treatment with inhaled antibiotics or treatment with inhaled antibiotics within the previous 6 months
2. Chronic *P. aeruginosa* infection defined as isolation of *P. aeruginosa* persistently in sputum, or the absence of negative sputum samples for *P. aeruginosa* so that inclusion criteria (6) above cannot be met
3. Cystic fibrosis
4. Use of any investigational drugs within five times of the elimination half-life after the last dose or within 30 days, whichever is longer. Current enrolment in non-interventional, observational studies will be allowed
5. Currently pregnant or breast-feeding
6. Unstable co-morbidities (e.g., cardiovascular disease, active malignancy) which in the opinion of the investigator would make participation in the trial not in the participant's best interest
7. Estimate eGFR<30 or abnormal liver function tests that in the opinion of the investigator make antibiotic treatment inappropriate (note that the trial is designed to be pragmatic and embedded within normal practice therefore testing is at the discretion of the managing clinician)
8. A strong preference, either from the managing clinician or the participant, for one of the two trial arms such that in the opinion of the investigator adherence to the trial protocol would not be possible.

Notes

Previous intolerance to inhaled antibiotics is not an exclusion from the trial, but participants should be prescribed a different inhaled antibiotic to one that was previously not tolerated. If no antibiotic treatment options for the active arm are available/possible, then the participant should be excluded.

Coexisting asthma, COPD or other respiratory diseases are allowed as long as the participant also meets the inclusion criteria related to radiological and clinically significant bronchiectasis.

Participants may have received antibiotic treatment (including antibiotic treatment against *P. aeruginosa*) in the previous 6 months as long as this antibiotic treatment did not include an inhaled antibiotic.

7. TRIAL PROCEDURES

7.1. Recruitment

Anonymised information on participants, who are not randomised, for CONSORT reporting will include:

- age
- gender
- ethnicity
- the reason not eligible for trial participation, or if they are eligible but declined

7.1.1. Participant identification

Identification of potentially eligible trial participants by the research or clinical teams may make use of any or all of the following:

- With appropriate local Caldicott Guardian approval and arrangements with microbiology laboratories investigators may make use of notification from local microbiology laboratories of individuals who have recently tested positive for *P. aeruginosa* in a respiratory tract sample.
- From secondary care via contact with participants at specialist respiratory clinics or pulmonary rehabilitation classes. Clinic lists and rehabilitation class participant lists will be reviewed by a member of the clinical care team or research team, if delegated by the clinical care team, and medical records checked to identify suitable participants. Potential participants will then either be approached and given the brief Participant Information Sheet (bPIS) when they attend clinic or class or will be posted an invite letter and bPIS. Contact at clinic or class will be by a member of the clinical care team or local clinician. Postage of invitation letters and bPIS will be carried out by the clinical care team or a member of the trial team on delegation from the clinical care team.
- From local Bronchiectasis databases where participants have given prior consent to be contacted for future research projects, e.g. EMBARC registry, or local registers such as TAYBRIDGE, BRONCH-UK, or similar databases with appropriate approval in other NHS facilities as defined locally. Local Principal Investigator (PI) or delegated member of the clinical care or research teams will send out invite letters with bPIS to individuals who may be suitable to take part.
- Recruitment of participants registered via the Scottish Health Research Register (SHARE)
- From primary care practices or via the Primary Care Networks. These participants will be sent an invitation letter and bPIS from the GP practice or Primary Care Network. GP practices will also be asked to display bPIS in their waiting rooms.

When first contact is via letter a bPIS will be sent which gives a general overview of the trial. Participants will be asked to contact the research team if they are interested in the trial. When first contact is in a hospital clinic they will be given a bPIS and will be asked to either return an expression of interest in a stamped addressed envelope or to contact a member of the research team by telephone or email; trial staff may also arrange a convenient time to call the participant. Contact details will be provided on the bPIS. Where a participant does not contact the research team, the research team may contact them once via telephone, email or post to determine their interest in the trial.

Should individuals express an interest in taking part in the trial, the PI or delegate will contact the individual and ask for permission to check their medical notes. Individuals who returned a reply slip may have provided this permission on the slip in which case further contact with them would not be required prior to accessing their medical notes. Participants will receive a full Participant Information Sheet (PIS).

Recruitment may also utilise publicity materials including posters, information leaflets and advertisements.

The local PI will be responsible for recruitment but may delegate to other named individuals within the trial team.

7.1.2. Screening

At the screening visit (Visit 1) the procedures as detailed in the Schedule of Procedures, Appendix 4, will be carried out.

Assessment of eligibility will be carried out by the PI or other medically qualified delegate. Eligibility will be assessed at Visit 2, randomisation/baseline once all results have been reviewed.

Details of all participants consented to the trial and screened for eligibility will be recorded on the Enrolment and Randomisation Log, this will detail if a participant fails screening or goes on to be randomised.

Where an ineligible participant's medical condition or concomitant medications change sufficiently so that they are deemed potentially eligible for the trial they may be rescreened one further time. All screening procedures will be repeated, including informed consent, and eligibility checked.

7.1.3. Ineligible participants

Where an individual is found to be ineligible for trial participation, they will be thanked and the reasons for the ineligibility fully explained. Any queries or questions will be answered by an appropriate member of the research team. If ineligibility is related to an incidental finding (IF) which is considered to be clinically significant, it will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the individual.

7.1.4. Payment

Participants will not receive payment for participation, but reasonable travel expenses will be reimbursed.

7.2. Consent

The PI retains overall responsibility for the recording of informed consent of participants at their site. They will ensure that any person delegated the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding, and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the participant's legal representative, or if not contactable, a professional legal representative will be asked for their consent.

In all cases the PI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where

appropriate, the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

7.2.1. Additional consent provisions for collection and use of participant data in ancillary studies

Consent from participants will be gained for:

- use of their data in future research
- use of sputum samples in future research
- contact by trial staff for further ethically approved future research (optional)

Anonymised trial data will be kept under the control of the CI for future research use within the University of Dundee (UoD) and with other research collaborators (commercial and non-commercial).

Any data collected to the point of withdrawal will be retained for reasons of public interest in the area of public health (Article 9(2)(i) General Data Protection Regulation (EU) 2016/679 GDPR).

7.3. The randomisation scheme

Participants will be assigned in a 1:1 ratio to receive eradication treatment plus background therapy or background therapy only. Participants will be allocated to an arm using a minimisation algorithm, with factors for centre, long-term use of macrolides, and first isolation vs new isolation following previous clearance.

7.3.1. Method of implementing the randomisation/allocation sequence

After successful completion of screening the participant will be assessed for eligibility for each treatment arm. This will be documented in the participant's medical notes and electronic Case Report Form (eCRF).

Participants will be randomised by the PI or delegate using a centrally controlled web-based GCP compliant randomisation system, Tayside Randomisation System (TRuST), run by the UK Clinical Research Collaboration registered Tayside Clinical Trials Unit (TCTU). TRuST is provided by the Health Informatics Centre, UoD. TCTU use a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation.

The randomisation allocation will be emailed to the person completing the randomisation.

Access to be able to randomise a participant will only be given after completion of appropriate training.

7.4. Blinding

Nil, open label.

7.5. Emergency Unblinding

Not applicable

7.6. Baseline data

Baseline data will be collected at day 0 as per Schedule of Procedures, Appendix 4, and as described below, section 7.7.

7.7. Trial assessments

Trial assessments will be performed according to the Schedule of Procedures, Appendix 4. Where trial assessments identify any clinically significant incidental findings, these will be communicated to the participant's GP, with the participant's consent.

Trial assessments will be carried out according to trial specific guidelines.

Missed trial assessments or visits completed outside the visit window will not be reported as breaches where this is due to participant choice or a clinical decision, excursions will be documented, and trial statistician made of aware of discrepancies.

Medical history: focused medical history, taken from medical records and participant reporting, including the following information:

- History of chronic medical conditions related to inclusion and exclusion criteria
- Medication allergies

Demographics: age, gender and ethnicity will be collected for the trial analysis. Participants will be asked to self-complete optional additional demographic questions (from the DISCTINCT trial question set) to evaluate the inclusivity of the trial population.

Review concomitant medications and therapies: taken from medical records and participant reporting at each visit.

Review of AEs: participants will be asked about the occurrence of any AEs since the previous visit which are related to the background treatment of exacerbations or the eradication treatment, medical records will also be reviewed.

Severity of bronchiectasis: will be evaluated using the Bronchiectasis Severity Index which incorporates the Medical Research Council dyspnoea score. Exacerbation assessment will use the EMBARC definition of exacerbation (Hill et al. 2017).

Physical examination: a detailed physical examination will be performed at screening to exclude participants with co-morbidities or other clinical disorders that would constitute an exclusion from the trial. This will include the following systems:

- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Dermatological

Height & weight: as per trial guidelines.

Vital signs: Blood Pressure, pulse, temperature, oxygen saturation as per trial guidelines.

Electrocardiogram (ECG): as per trial guidelines, will be reviewed by a doctor prior to randomisation.

Questionnaires: as per schedule of procedures.

Sputum sample: two sputum samples will be collected at visits 2, 4, 5 & 6. One clinical sputum sample will be collected for local culture and antimicrobial sensitivity testing. Sites will be

requested to store any excess sample for research purposes. One research sputum sample will be collected for exploratory research analysis.

If required, an additional eligibility sputum sample will be collected at visit 1 and tested locally for *P. aeruginosa*.

Participants will be asked to bring a spontaneous early morning sputum sample with them to visits. Where a participant is unable to produce a sputum sample at a visit a hierarchical approach to obtaining sputum samples will be used:

1. spontaneous sputum sample produced at the visit
2. spontaneous early morning sputum brought from home on the day
3. spontaneous early morning sputum brought in within the following 48 hours after the scheduled visit.
4. Induced sputum at sites able to perform induced sputum according to local protocols.

7.8. Long term follow-up assessments

The trial will link with the EMBARC registry, an international register for patients with bronchiectasis which includes recording of exacerbations and *P. aeruginosa* status. CI Chalmers is also the CI of the EMBARC study (32) After their completion of the trial, all participants will be offered continued participation in the registry allowing the collection of long-term data on whether there is a benefit beyond 24 months.

7.9. Quality of life and symptom assessments

Quality of life will be evaluated using the QOL-B respiratory symptom scale (Quittner et al. 2015a), Chronic airways assessment test (CAAT) and the EQ-5D-5L.

Participants will be issued with an electronic diary through Castor electronic Patient Reported Outcomes (ePRO) to complete the Bronchiectasis Exacerbation and Symptom Tool (BEST) via mobile app or website. BEST captures exacerbations and exacerbation symptoms. If participants are unable to use the ePRO BEST diary for any reason, participants will be issued with a weekly paper diary to record exacerbations. If the participant uses the electronic diary, they will receive daily notifications to complete the diary via email if using the web-based ePRO or via an app notification if using the Castor app.

7.10. Withdrawal criteria

Participants are free to withdraw at any time and are not obliged to give reason(s). The CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights.

The investigator may withdraw a participant at any time if it is in the best interest of the participant and treatment continuation would be detrimental to the participant's well-being. A full explanation will be provided. The trial is being conducted on an intention to treat basis, and once the participant has been randomised, s/he will be asked to complete trial visits as per the protocol, if the CI considers it appropriate. This would allow for an intention to treat analysis - but will be censored in the per-protocol analysis. Participants are free to refuse to do so.

Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

If a participant withdraws or is withdrawn, they have the right to ask for their data held to be removed, changed or deleted. This might not always be possible if it means the data cannot be used to do the research, if this is the case, participants will be informed.

7.11. Storage and analysis of clinical samples

The collection, processing and storage of samples will be detailed in the Laboratory Manual. The analysis of samples will be detailed in the Laboratory Analytical Plan.

Sputum samples will be obtained as per Laboratory Manual. A clinical sputum sample will be collected at visits 2, 4, 5 & 6 for culture in local laboratories to confirm *P. aeruginosa* status and antibiotic resistance. Sputum samples will be transferred to the local NHS Laboratory, where, if possible after testing, any surplus samples will be stored by the NHS microbiology. It is not mandatory for sites to store surplus clinical sputum samples, if the site does not have capacity to do this. Any excess clinical sputum samples will be transferred to UoD, Division of Respiratory Medicine and Gastroenterology, central laboratory for analysis and storage either at the end of site's participation or sooner if site requests for future exploratory research use.

A research sputum sample will be collected at visits 2, 4, 5 & 6 for exploratory analysis, as per Laboratory Manual. The fresh sputum sample will be shipped on the day of the visit from the research site to the central laboratory at Dundee for future exploratory research use. If a participant is unable to produce two sputum samples at the visit, the participant will be provided with a sputum collection pot and shipping box and will be requested to ship a fresh sample to the central laboratory at Dundee within 7 days of the visit.

Access to samples will be limited to members of the CI's laboratory team. Specimens will be registered with NHS Tayside Biorepository. Future use of those specimens will be made available and will be governed by the NHS Tayside Biorepository and access committee. Trial data may be released with samples.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act 2018. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.12. End of trial

The end of trial at all sites is defined as last participant last visit (LPLV). The Sponsor, CI and/or the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA) and National Health Service Research & Development (NHS R&D) Office(s) within 90 days, or 15 days if the trial is

terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A final clinical trial report will be submitted to the MHRA within 1 year of the end of the trial and will also be provided to the Sponsor and REC.

8. TRIAL TREATMENTS

Guidelines from the British Thoracic Society and European Respiratory Society make a conditional recommendation in favour of performing “eradication treatment” against *P. aeruginosa* by providing a combination of systemic (oral or intravenous) and inhaled antibiotics for 3 months.(8,9) however, there are no large randomized controlled trials to prove that this approach is effective.(9)

Most patients in the NHS currently receive background therapy only when they isolate a new *Pseudomonas*. Eradication treatment is used in some hospitals and is conditionally recommended by some guidelines and not recommended by others. Therefore, eradication treatment is variably applied across the NHS and the current standard care is not well defined.

This trial is randomising participants to two treatment strategies (background therapy only vs eradication treatment in addition to background therapy). It is crucial to test the efficacy of the eradication approach compared to background therapy only.

Eradication treatment consists of systemic antibiotics, usually administered for 2 weeks, followed by inhaled antibiotic treatment, in addition to background therapy. Background therapy may consist of their existing bronchiectasis treatments such as airway clearance, bronchodilators, long term macrolide treatment or other symptomatic therapies e.g mucoactive drugs. Background therapy also includes administration of antibiotics if patients have symptoms of an exacerbation.

The comparator arm is background therapy only. Participants should continue to receive their usual background therapies. As noted above, if participants have symptoms of an exacerbation, background therapy may include the administration of systemic antibiotics to treat the exacerbation. Participants in the comparator arm should not receive inhaled antibiotics. This trial is aimed at assessing efficacy, safety and cost effectiveness of *P. aeruginosa* eradication treatment in bronchiectasis in current clinical practice used in the UK. To allow this, trial treatments are not individually specified but will be determined by the individual prescribing clinician following their usual practice and the British Thoracic Society Guidelines.

<u>Example trial treatments</u>

The comparator arm is background treatment only, as defined above. In practice this means that if the participant has no symptoms of an acute exacerbation and the investigator judges that antibiotic treatment is not required, no treatment is offered. If the participant has an acute exacerbation or the investigator feels antibiotic treatment is required for symptomatic reasons, then an example oral antibiotic treatment would be ciprofloxacin 750mg twice daily for 14 days. ERS/BTS guidelines suggest intravenous antibiotics if oral antibiotic treatment is unsuccessful or the organism is resistant. Participants in the comparator arm should not receive inhaled antibiotics during the first 3 months post randomisation. The comparator background therapy is

not defined and will be determined by the individual prescribing clinician following their usual practice and the British Thoracic Society Guidelines

The intervention arm is eradication treatment, consisting of oral or intravenous antibiotics as clinically indicated, plus inhaled anti-pseudomonal antibiotics for 3 months. The two most widely used inhaled antibiotics in the UK are Colistin and Tobramycin (data from the EMBARC registry). Therefore, a typical eradication regimen **may** consist of Ciprofloxacin 750mg twice daily for 14 days plus 3 months of inhaled Colistin. The final eradication treatment will be determined by the investigator with no influence from the trial team. The antibiotics to be prescribed for the eradication treatment are defined in the IMP table 1, no other eradication trial treatments can be prescribed.

It is recommended for the eradication treatment that the systemic antibiotic and the inhaled antibiotic are started at the same time. However, if the prevision of inhaled antibiotics is delayed due to local practices, the systemic antibiotic treatment should be commenced and the inhaled antibiotic treatment commenced as soon as available. The inhaled antibiotic should be continued for 12 weeks. Visit 4 will take place once the treatment period has ended.

8.1. Name and description of investigational medicinal product(s)

Intervention	*P. aeruginosa* eradication treatment consisting of systemic antibiotics (either oral or intravenous as clinically indicated) alongside or followed by inhaled anti-pseudomonal antibiotics for 3 months, in addition to background therapy.
Formulation, Dose, Route of Administration	As per British Thoracic Society Guidelines.
Comparator	Background therapy only.

Medications used in the comparator arm are not defined as IMP, these medications are background therapies applied to both trial arms.

All allocated treatments in the intervention arm for eradication treatment are considered IMP. Only IMPs defined in table 1 can be prescribed for the eradication treatment.

8.1.1. Intervention

The intervention treatment will be prescribed as per British Thoracic Guidelines and following local clinician decision and usual practice. In the British Thoracic Guidelines, *P. aeruginosa* eradication treatment is defined as first line treatment with the oral antibiotic Ciprofloxacin 500 mg or 750 mg twice a day for 2 weeks. Second line treatment of IV antipseudomonal beta-lactam ± an IV aminoglycoside for 2 weeks. This would be followed by a 3-month course of a nebulised antipseudomonal antibiotic. Table 1 defines the IMP prescribing options for eradication treatment. The choice of antibiotic and combination of antibiotics for the eradication treatment will be determined by the local investigator in line with clinical practice.

Table 1: ESCAPE trial IMP: prescribing options for *P. aeruginosa* eradication treatment.

Manufacturer	**Oral antibiotic**	**Dosage**	**Duration**
Aurobindo Pharma - Milpharm Ltd.	Ciprofloxacin	500 mg or 750 mg	14 days, twice daily
	IV antibiotics	**Dosage**	**Duration**
Bowmed Ibisqus Limited	Piperacillin/Tazobactam	4 g / 500 mg	14 days, three or four times daily
Wockhardt UK Ltd	Ceftazidime	2 g	14 days, three times daily
Pfizer Limited	Meropenem	1 g or 2 g	14 days, three times daily
Bristol Myers Squibb Pharmaceuticals Limited	Aztreonam	1 g or 2 g	14 days, four times daily or 14 days, three times daily
Merck Sharp & Dohme (UK) Limited	Ceftolozane / tazobactam	1g / 0.5 g or 2g / 1g	14 days, 3 times daily
ADVANZ Pharma	Gentamicin	Not specified, determined by weight	Not specified
Hospira UK Ltd	Tobramycin	Not specified, determined by weight	Not specified
Hameln Pharma Ltd	Amikacin	Not specified, determined by weight	Not specified
InfectoPharm Ltd	Fosfomycin	12–24 g daily dose	14 days, two to three times daily

Bowmed Ibisqus Limited	Levofloxacin	500 mg	14 days, once or twice daily
	Nebulised antipseudomonal antibiotics		
Teva UK Limited	Colistin	2 MU	3-months, twice daily
ADVANZ Pharma	Gentamicin	80 mg	3-months, twice daily
Sun Pharmaceutical Industries	Tobramycin	300 mg	One month, twice daily or 3-months, twice daily

A representative SmPC has been provided for each IMP . In practice, equivalent licensed brands or different doses of these antibiotics may be used during the trial, depending on clinical need and local availability. The IMPs listed in table 1 includes medications not included in the British Thoracic Guidelines, to reflect prescribing practices in routine care.

8.1.2. Comparator

8.2. The comparator treatment (background therapy) will be prescribed as per usual practice and are not pre-determined. Regulatory status of the drug

All treatments used in this trial are widely used treatments in the NHS and have marketing authorisation in the UK for respiratory disorders. Although they do not have a marketing authorisation specifically for bronchiectasis, each are recommended by British Thoracic Society Guidelines for the treatment of bronchiectasis.

8.3. Product Characteristics

The prescribing clinician will determine the medication to be prescribed for each treatment arm according to their clinical judgement and routine clinical practice.

8.4. Accountability Procedures

As this is a Type A trial, drug accountability will be according to local pharmacy protocols. Treatments will be prescribed by the participants' clinician using local prescriptions and dispensed by their local pharmacies as it is per routine clinical practice. Accountability will follow local pharmacy protocols.

8.5. Preparation and labelling of Investigational Medicinal Product

As this is a Type A trial, with no higher risk to the participant than standard of care, and the trial will use commercially available IMP with no modifications, no additional clinical trial labelling is required.

8.6. Drug storage and supply

Following randomisation, participants will be prescribed and dispensed their allocated treatment through the hospital pharmacy with treatment provided as part of routine NHS care.

All treatments will be stored as per SmPC, any treatment requiring specific storage instructions will be detailed on the NHS clinical dispensing label.

8.7. Dosage schedules

Participants will receive treatment as described in section 7.3. Dosing schedules for allocated treatments will be as per SmPC at the discretion of the prescribing clinician as per routine clinical practice.

8.8. Description and justification of route of administration

This will be as per SmPC at the discretion of the prescribing clinician as per routine clinical practice.

8.9. Frequency of administration

This will be as per SmPC at the discretion of the prescribing clinician as per routine clinical practice.

8.10. Missed doses

If a participant misses a treatment dose, they will continue with further treatment doses as per routine clinical practice.

8.11. Dosage modifications

Dosage modifications will be at the discretion of the prescribing clinician as per routine clinical practice. Any other chronic treatment for the management of bronchiectasis can be continued and there will be no restrictions to how participants can be managed.

8.12. Known drug reactions and interaction with other therapies

Known drug reactions and interaction with other therapies are described in the SmPC for individual medications.

8.13. Concomitant medication

Details of all concomitant medications will be recorded on the trial Case Report Form (CRF) on a concomitant-medications log.

There are no prohibited medications.

8.14. Trial restrictions

Certain treatments may not be appropriate for women of childbearing potential. Prescribing clinicians should follow the guidelines on the medication SmPC they choose to prescribe. A woman is considered of childbearing potential 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 for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

A pregnancy test must be performed for women of childbearing potential at screening to confirm eligibility. The use of a highly sensitive urine test, performed at home and communicated to the investigators, is acceptable.

Participants in the comparator arm should not receive inhaled antibiotics during the first 3 months post randomisation. However, if inhaled antibiotics are required clinically as part of usual care these will not be withheld and the participant would crossover from control arm to eradication arm.

8.15. Assessment of compliance with treatment

Trial drug compliance will be assessed by trial personnel verbally at visit 3 & visit 4. Trial drug compliance will be assessed from the information provided by the participant.

8.16. Name and description of each Non-Investigational Medicinal Product (NIMP)

Nil

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a consented participant which is not necessarily caused by or related to a medical product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity

	• consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within it's licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Causality assessment

Unrelated	Where the AE is not considered to be related to the study drug: more likely. Information on drug withdrawal may be lacking or unclear
Possibly	Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication, or temporal relationship make other explanations
Probably	The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Information on drug withdrawal may be available and if so the observed response to study drug withdrawal is considered clinically reasonable
Definitely	The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. Information on drug withdrawal is usually available and the observed response to study drug withdrawal is considered clinically reasonable and has a plausible temporal relationship to study drug exposure

9.2. Operational definitions for (S)AEs

The treatments used are routinely used in NHS clinical practice. In clinical practice it would not be normal practice to report AEs unrelated to drug treatment or those expected as part of the normal course of the disease e.g. exacerbations of bronchiectasis.

AEs will only be reported where, in the opinion of the investigator these are:

- Events related to the background treatment of exacerbations
- Events related to eradication treatment
- Trial treatment overdose
- Events leading to treatment discontinuation
- Events related to trial procedures

9.3. Recording and reporting of SAEs, SARs AND SUSARs

All AEs will be recorded on the AE Log in the eCRF. Details of AEs will be recorded in the medical record. AEs will be assessed for severity by the PI. AEs will be recorded from the time a participant consents to join the trial until the participant's last trial visit. Any SUSAR, that the investigator becomes aware of, will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Assessment of severity of AEs:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE may be classified as a SAE or AR.

Participants with unresolved AEs/SAEs at end of trial will be followed up until 30 days after participant's last visit. SUSARS will be followed until resolution, where a participant agrees to this.

The CI, PI or delegate will ask about the occurrence of AEs and hospitalisations at every visit during the trial. SAEs will be submitted on an SAE form to the Sponsor Pharmacovigilance Section via the online Tayside Pharmacovigilance System within 24 hours of becoming aware of the SAE. Site PIs will also notify the CI when submitting an SAE.

The evaluation of expectedness will be made based on the knowledge of the reaction and the RSI held within the medication's SMPC. The Sponsor will make the definitive assessment on expectedness for the purposes of SUSAR reporting.

The Sponsor is responsible for reporting SUSARs to the Competent Authority, and the REC. Fatal or life-threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

Reporting of safety data to the funders will be as detailed in the funding agreement.

9.4. Reference Safety Information

A representative SmPC for each antibiotic in the active treatment arm has been submitted to the Competent Authority and will serve as the Reference Safety Information (RSI) for this trial. In the event that other equivalent licensed brands are used at trial sites, the submitted SmPCs will remain the RSI for consistency of safety reporting.

The individual medication's SmPC section 4.8 will be used as the RSI for that medication. Events listed in the SmPC as undesirable effects will be treated as expected. SmPCs will be reviewed annually for updates. Responsibilities

CI/PI or delegated staff:

- Checking for AEs and ARs at all visits.

CI/PI or medically qualified delegate:

- Confirmation of eligibility criteria.
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was related.
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

CI:

- Central data collection of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
- Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.
- Clinical oversight of trial participant safety, including an ongoing review of the risk/ benefit.
- Immediate review of all SUSARs.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report.
- Reporting safety information to funder as per contract.

Sponsor (UoD/NHS Tayside):

- Expedited reporting of SUSARs to the MHRA within required timelines.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA.

Trial Steering Committee (TSC):

In accordance with the TSC Charter, the TSC will periodically consider recommendations from the DMC following their review of safety data and make decisions on early termination or continuation of recruitment to individual treatment arms and the overall trial.

Data Monitoring Committee (DMC):
In accordance with the DMC Charter, the DMC will periodically review overall safety data to determine patterns and trends of events, and identify potential safety issues, making recommendations to the TSC.

9.5. Notification of deaths

All deaths occurring during the trial, will be reported to the sponsor irrespective of whether the death is related to disease progression, the trial drug or an unrelated event. Deaths will be reported to Sponsor as SAEs as per Section 9.3.

9.6. Pregnancy reporting

Pregnancy itself is not considered an AE or SAE, unless there is a congenital abnormality or birth defect. Any unexpected pregnancy occurring during the trial and the outcome of the pregnancy, will be recorded on a TASC Pregnancy Notification Form, and submitted to the Sponsor Pharmacovigilance Section within 14 days of becoming aware of the pregnancy and the outcome of the pregnancy. The pregnancy will be followed up until the end of the pregnancy. If the trial participant is a male, informed consent for follow up will be sought from his female partner.

9.7. Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE section in the eCRF. Any dose administered other than prescribed dose for that participant will be reported to the Sponsor as a protocol breach.

If an overdose of trial drug occurs during the trial, then the Investigator or other site personnel will inform the appropriate sponsor representatives immediately, or no later than 24 hours after becoming aware of it. The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided to the sponsor's Pharmacovigilance Committee.

9.8. Reporting urgent safety measures

The PI or other trial physician will take appropriate immediate urgent safety measures to protect the participants against any immediate hazard to their health or safety. On discovering a safety issue, the PI or delegate must contact the Sponsor immediately to discuss further action by emailing tay.pharmacovigilance@nhs.scot marking it "Urgent safety measure". The initial notification of urgent safety measures to the MHRA will be via telephone (immediately, within 24 hours of measures being taken and no later than 3 days from the date the measures are taken). After discussing the urgent safety measures with the MHRA assessor via phone, the MHRA will be notified in writing of the measures taken and discussed with the medical assessor within 3 days from the date the measures were taken. The written notification will be made via Integrated Research Application System (IRAS), no additional notification is required to the REC.

9.9. The type and duration of the follow-up of participants after adverse reactions.
All ARs will be recorded as per section 9.3. Where ARs occur, assessment of clinical condition and appropriate treatment will be instigated by a delegated doctor and will continue until the symptoms resolve or the condition stabilises.

9.10. Development safety update reports

The DSUR will be prepared jointly by the Sponsor Pharmacovigilance Section and CI and submitted by the Sponsor to the MHRA on the anniversary of date of Clinical Trial Authorisation.

Any other safety reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

The primary endpoint is frequency of exacerbations in 24 months. The comparison of exacerbation rates between arms will be performed using a negative binomial regression model; see section 10.3 for details. The sample size estimate has been developed based on the recent PROMIS trials of inhaled colistin vs placebo and other previous inhaled antibiotic trials in patients with *P. aeruginosa* infection. A control exacerbation rate of 1.4 exacerbations per patient per year was estimated over 24 months and based on feedback from experts in the field as well as effect estimates used in prior trials, that a 35% reduction in exacerbations would be clinically relevant. Based on analysis of the PROMIS and ORBIT trials (25,26) conducted in a similar population (patients infected with *P. aeruginosa)* a negative binomial dispersion parameter of 0.7 has been estimated. With these assumptions for 90% power at the 2-sided 5% significance level, a sample size of 260 participants is required, inflated to 326 participants (163 per arm) to account for up to 20% of participants dropping out (with no data beyond this), and/or control arm participants “crossing over”.

Table 1 illustrates the power achieved for the primary analysis under various dropout and “crossover” assumptions. Power is still approximately 90% for a reasonably large proportion dropping out early (20%) and a large “crossover” from control to eradication arm (20%). The table also illustrates power available under the same scenarios with this sample size, assuming the “true” reduction in 2-year exacerbation rates is only 30%; even with 10% dropout and up to 20% of control arm participants “crossing over” to commence treatment with long-term inhaled anti-pseudomonal antibiotics, power to detect this smaller effect size should be close to 80%. Note that the simulations have not adjusted for prognostic factors or sites, so in reality, power may be greater than stated (27).

Table 1. *Simulated power* for the primary analysis approach under various dropout and crossover (control to treatment arm) assumptions with the chosen total sample size of 326 participants, assuming the "true" reduction in 2-year exacerbation rate is 30% and 35%.*

Scenario		"True" reduction in exacerbation rate	
		30%	**35%**
No dropout, no crossover		86.1%	95.2%
Dropout (uniformly distributed over 2 years), but no crossover – MAR analysis for dropout ("hypothetical" strategy, i.e. estimand reflects no participants dropping out)			
10% dropout		84.4%	95.1%
20% dropout		83.8%	93.8%
30% dropout		81.9%	93.1%
Crossover (uniformly distributed over 2 years), but no dropout – "treatment policy" strategy for data beyond "crossover" point (a strict ITT approach)**			
10% crossover from control to eradication		82.8%	94.0%
20% crossover from control to eradication		79.4%	92.0%
30% crossover from control to eradication		76.4%	89.0%
Dropout and crossover* (both uniformly distributed over 2 years) – MAR analysis for dropout ("hypothetical" strategy) and "treatment policy" strategy for data beyond "crossover" point (a strict ITT approach)**			
10% dropout	10% crossover from control to eradication	81.2%	92.6%
	20% crossover from control to eradication	78.2%	91.1%
	30% crossover from control to eradication	74.7%	87.6%
20% dropout	10% crossover from control to eradication	80.4%	91.8%
	20% crossover from control to eradication	77.2%	89.6%
	30% crossover from control to eradication	72.6%	86.3%
30% dropout	10% crossover from control to eradication	78.8%	90.8%
	20% crossover from control to eradication	74.5%	88.7%
	30% crossover from control to eradication	70.5%	84.6%

** Distribution of dropout and control arm "crossover" times is assumed to be uniform over the 2-year follow-up period. "Crossover" assumed to occur in a random sample of control arm participants, not necessarily those experiencing the most exacerbations. Results are based on a control arm rate of 1.4 exacerbations per year, dispersion parameter 0.7, and 2-sided 5% significance level. Power for each scenario is estimated using 10000 simulations.*
*** Assumes that exacerbation rate for control arm participants who "crossover" is the same as the treatment arm, from the point of crossover onwards.*
**** A small proportion of control arm participants (0.5% to 5%, so ≤8 participants) dropout after crossover. For simplicity of simulations, a simple MAR approach has been used for these cases (using the offset term). In reality, the methods of Keene et al (2004) (28) or Roger et al (2019) (29)would be used, which may result in a slightly lower power than stated (e.g. with a Jump-to-Reference imputation approach). Given the proportion of control arm participants affected is very small, we expect the impact to be minimal.*

10.2. Planned recruitment rate

Overall recruitment is expected to take 3 years. The projection for recruitment is 82 participants (25%) to be randomised by month 20, 163 (50%) by month 25, 245 (75%) by month 29 and 326 (100%) by month 36.

10.3. Statistical analysis plan

The primary analysis will be intention-to-treat (ITT). The frequency of exacerbation endpoint will be analysed using negative binomial regression as recommended by the US Food and Drug Administration for analysis of exacerbation endpoints in bronchiectasis trials. The model will be adjusted for known prognostic factors and site. For participants lost to follow-up, subsequent exacerbation data will be implicitly imputed under a missing at random (MAR) assumption by the inclusion of the logarithm of follow-up time as an offset term (a “hypothetical” strategy as per ICH E9 (R1) (24)). In line with the pragmatic nature of the trial, data will be collected until the end of the trial for all participants, including control arm participants who “crossover” to eradication treatment; “crossover” will be analysed using a “treatment policy” strategy (29). Where little or no post-crossover data is available, reference-based imputation will be considered; results using the Jump-to-Reference (J2R) and Copy Reference (CR) approaches will be presented (28). A sensitivity analysis for the primary endpoint will be performed using GP records to minimise the impact of participant dropout/loss-to-follow-up.

P. aeruginosa eradication rates will be compared between the arms, separately at 12 and 24 months, using a logistic regression model, adjusted for known prognostic factors and site. Missing data will be dealt with using a similar approach as described for the primary endpoint above, consistent with the “treatment policy” approach to control arm participants “crossing over”. Full details of all primary and secondary analyses, including approaches to deal with missing data and sensitivity analyses, will be provided in a Statistical Analysis Plan.

10.4. Interim analysis and criteria for the premature termination of the trial

There will be no interim analyses considering early stopping for efficacy or futility.

Termination criteria will be the set-up of an inadequate number of sites and inadequate recruitment per centre over the first 18 months of the trial (the pilot phase). Feasibility of participant retention and cross-over will be assessed once 36 participants have been followed up for 12 months. The duration of the assessment may be modified according to the needs of the trial.

Pilot phase review (18 months) termination criteria:

	Proceed/Green	**Amend/Amber**	**Stop/Red**
Feasibility of site recruitment At 18 months	If ≥24 sites open to recruitment	If 12-23 sites are open to recruitment	If ≤11 sites are open to recruitment
Feasibility of participant recruitment At 18 months	If ≥62 participants recruited	If 31-61 participants recruited	If ≤30 participants recruited

Retention review termination criteria:

	Proceed/Green	**Amend/Amber**	**Stop/Red**
Feasibility of participant retention After 36 participants followed-up for 12 months or dropped-out	If ≤6 of 36 participants (both arms) drop-out (≤16.7%)	If 7-17 out of 36 participants (both arms) drop-out	If ≥18 of 36 participants (both arms) drop-out (≥50%)
Feasibility of adherence to control arm After 18 control arm participants followed-up for 12 months or crossed-over	If ≤3 of 18 control arm participants cross-over (≤16.7%)	If 4-8 out of 18 control arm participants crossover	If ≥9 of 18 control arm participants cross-over (≥50%)

10.5. Economic evaluation

An economic evaluation will be integral to the main RCT adhering to gold standard economic evaluation practice (30,31). The cost effectiveness of *P. aeruginosa* eradication treatment will be estimated in comparison to standard care from the perspective of NHS health and social care. A within trial analysis will include a cost-effectiveness analysis and cost-utility analysis, reporting the incremental cost per exacerbation prevented and incremental cost per quality adjusted life year (QALY) at 24 months (to align with the primary efficacy outcome). Quality of life will be measured using the EQ-5D-5L collected at baseline and all study follow-up points (3, 12 & 24 months) to estimate within trial QALYs.

Participant level resource use data will be collected during the trial including medication, treatment administration and delivery costs such as attendance at day case treatment facilities specialised nurse appointments and hospitalisation for severe exacerbations. The analysis will take into consideration variation across the NHS in delivery methods for eradication treatment. Bespoke questionnaires will be administered at baseline, 12 months and 24 months to collect additional primary care resource use, and participant out of pocket expenses to enable a secondary analysis incorporating the participant perspective. A lifetime model will be developed, extrapolating within trial outcomes in order to estimate the longer terms costs and consequences related to treatment, bronchiectasis and chronic infection, reporting incremental cost per QALYs over a lifetime horizon. Model parameter uncertainty will be addressed using probabilistic sensitivity analysis, undertaken using Monte Carlo simulation techniques and summarised using the cost-effectiveness acceptability curve at differing willingness to pay thresholds.

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

The PI or delegate will maintain source documents for each participant in the trial, consisting of hospital medical records containing demographic and medical information, laboratory data, electrocardiograms, trial questionnaires and the results of any other tests or assessments. The questionnaires will be completed by the participants and act as source data, the completed form will be filed in the ISF. All trial data relevant to a participant's general medical history will be recorded in the medical record. The medical record will be flagged to state that the participant is participating in the ESCAPE trial.

An eCRF, using Castor Electronic Data Capture (EDC) system, will be provided by TCTU. The trial system will be based on the protocol for the trial. Development and validation of the trial database and quality control will be done according to TCTU procedures. The eCRF will not collect more information than is required to meet the aims of the trial and to ensure the eligibility and safety of the participant.

Participants will be requested to input daily BEST diary data directly into Castor electronic Patient Reported Outcomes, either via an email weblink or the Castor Connect App which can be downloaded and installed in the participants mobile or tablet devices. The electronic BEST diary will be completed daily throughout the trial duration. To capture any exacerbations between visits, a monthly question will be added alongside the BEST diary to record any commencement of new antibiotics. Electronic Patient Reported Outcomes data collected via Web email and Castor Connect App will automatically be stored and synced to the Castor EDC. If a participant is unable to complete the electronic diary, they will be issued with a weekly paper diary to report any new exacerbations or commencement of antibiotics.

The PI may delegate eCRF data entry but is responsible for completeness, plausibility, and consistency of the eCRF. Delegated trial staff will enter the data required by the protocol into the eCRFs following training in the definitions and methods used in completing the eCRF. Any queries will be resolved by the PI or delegated member of the trial team. On completion of data collection, the PI must certify that the data entered are complete and accurate.

Data verification, cleaning and data extraction will be performed as per TCTU local procedures and detailed in the Data Management Plan.

All electronic data will be stored on secure UoD or cloud-based servers which have restricted access and have disaster recovery systems in place.

11.2. Data handling and record keeping

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 2018. The Data Controller will be the UoD and the Data Custodian will be the CI.

Development and validation of the trial database, quality control and data extraction will be managed by TCTU. Details will be documented in the Data Management Plan.

11.3. Access to Data

The CI, PIs and all institutions involved in the trial will permit trial related-monitoring, audits, REC review, and regulatory inspection. In the event of an audit or inspection, the CI and/or PI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

Anonymised trial data will be kept under the control of the CI for future research use within the UoD and with other research collaborators (commercial and non-commercial). Access to the data will be as described in section 13.7.

11.4. Archiving

Archiving of trial documents will be in compliance with Sponsor Standard Operating Procedures. Medical records will be maintained in compliance with local NHS policy on retention of medical records. The CI will be responsible for arranging the archiving of the TMF and ensuring that research data is archived in a way that will permit accurate reconstruction of the research. Sites will be responsible for archiving local trial records including the ISF and Pharmacy Site File. Sponsor will be responsible for archiving the Sponsor file.

12. MONITORING

12.1. Monitoring

A trial risk assessment will be carried out by the Sponsor prior to Sponsorship approval being granted. The Sponsor will determine the appropriate extent and nature of monitoring for the trial and will delegate monitoring to appropriately qualified and trained monitors. A Monitoring Plan will be developed by the Sponsor based on the trial risk assessment which will include on site and/or remote monitoring. The Monitoring Plan will be reviewed regularly using a risk-based approach and updated as required. The Monitoring Plan will detail the procedures and anticipated frequency of monitoring and processes reviewed. Sites must have access to source data for purposes of remote monitoring and assist the Sponsor in monitoring of the trial. In recognition that source data may come from different sources at each site, sites shall ensure that a source data identification list is supplied to the Monitoring Team in advance of any monitoring review and ensure this data is available on the agreed date and time to facilitate the review.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from an independent REC for the trial Protocol, Informed Consent Form, and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the TMF.

A progress reports will be submitted to the REC according to REC approval conditions. It is the CI's responsibility to produce the REC reports as required.

The CI will notify the REC of the end of the trial. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. The CI will submit a final report with the results, including any publications/abstracts, according to REC approval conditions.

A copy of all REC reports will be submitted to the Sponsor.

13.2. Peer review

This trial has been funded by NIHR Health Technology Assessment Programme who have extensively reviewed the grant application. The trial has also been peer reviewed by EMBARC. The protocol has been reviewed and approved by the Sponsor Committee.

Resulting publications will be reviewed by the referees of the journal to which the paper will be submitted.

13.3. Public and Patient Involvement

Patients and the public have been involved at every stage of the development of this proposal. PPI has been co-ordinated by the European Lung Foundation, a European patient organisation based on Sheffield and part of the European Respiratory Society.(36) They run a patient advisory group consisting of people with bronchiectasis and their carers. The research question was determined through a priority setting exercise that was conducted by the applicants involving a survey of 711 patients with bronchiectasis from across Europe and more than 100 bronchiectasis specialist clinicians. This determined that the effectiveness of *Pseudomonas* eradication treatment was the top research priority as judged by patients and clinicians. This survey has been published (Aliberti et al, European Respiratory Journal 2017). Consultation with the patient advisory group in August 2023 during the development of the outline proposal confirmed that this remained a highly relevant research question.

PPI input was sought during the design stage on several aspects of study design. Firstly, in view of the existing guideline recommendations to offer *Pseudomonas* eradication treatment to patients with bronchiectasis we sought PPI input on whether patients felt it was ethical to randomize and whether randomisation would be acceptable. This was gathered through an online meeting with the European Lung Foundation patient advisory group (approximately 12 patients and carers attended). Patients felt that randomisation was ethical and would be acceptable to patients as long as they were fully informed. Feedback was gathered on whether we should propose a particular antibiotic regimen or use a placebo design. Patient feedback was that patients receive a wide range of different antibiotic treatments and have antibiotic allergies and intolerances that would make this not feasible and therefore a pragmatic design with the antibiotic choice left to the clinical team was selected. Patient feedback on the patient reported outcome measures used in the trial was also received.

Patients felt that exacerbations are important events in the natural history of bronchiectasis which have a major effect on health status and progression of disease and therefore PPI input agreed on selection of exacerbations as the primary endpoint. PPI input informed the selection of the questionnaires used to measure health status. The St Georges Respiratory Questionnaire was felt to be long, more difficult to complete than other questionnaires and not specific to

bronchiectasis. Three patient reported outcomes which are shorter and were judged to be acceptable to patients are therefore being used.

Patients have reviewed the plain English summary of the research proposal and provided feedback to make it more accessible. The lay summary has also been reviewed by a broader PPI group, without lived experience of bronchiectasis, with positive feedback.

Funding is included for the European Lung Foundation patient advisory group representatives who have agreed to input into the study. Members of the European Lung Foundation patient advisory group, who are UK patients with bronchiectasis, have agreed to participate in the TMG, which oversees the running of the trial, and we will also include two patient representatives in an independent TSC.

The involvement of the European Lung Foundation provides training and support to patient representatives as they have extensive experience of facilitating the input of patient representatives into research projects. Facilitated by the European Lung Foundation, patient representatives will feedback on trial related issues during monthly teleconferences with the wider patient advisory group which includes >30 European patients with bronchiectasis allowing us to gather a broader range of views and input.

Through involvement in these groups patient representatives have been involved in protocol development/trial design and will be actively involved in the conduct of the trial. In partnership with the European Lung Foundation there is an annual patient conference which is attended by more than 1000 patients and carers with bronchiectasis. Updates on the progress and outputs from the research to the wider patient community will be provided through this medium.

At the completion of the trial, patient representatives will be involved in dissemination of the results which will include trial publications, presentation of results at the patient conference, and creating a lay summary of the research for publication on the patient facing European Lung Foundation Patient Priorities Website.

13.4. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation is obtained from the MHRA and favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the CI, PI, or delegate will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the CI, PI, or delegate, in agreement with the sponsor, will submit information to the appropriate body for them to review and issue approval for the amendment. The CI, PI or delegate will work with sites so they can put the necessary approvals and arrangements in place to implement the amendment to confirm their support for the trial as amended.

13.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed, e.g., it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified

in the trial protocol. Trial staff will not implement deviations to the protocol except where necessary to eliminate an immediate hazard to trial participants.

Accidental protocol breaches can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor using the TASC Breach Reporting Form. If there is a breach of the protocol, the nature of and reasons for the breach will be documented in the trial Breach Log. Breaches from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to affect 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

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

a) the conditions and principles of GCP in connection with that trial; or
b) the protocol relating to that trial, as amended from time to time.

If a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the Breach Reporting Form and will be recorded in the eCRF and documented in the trial Breach Log.

If a breach necessitates a subsequent protocol amendment, this will be submitted as per section 13.10.

13.7. Data protection and patient confidentiality

The CI and trial staff will comply with the requirements of GDPR and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

All trial records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate data will have limited access measures via usernames and passwords. Age, gender, and ethnicity will be the only personal identifiable details held on Castor EDC system.

Personal data or data concerning health will not be released without the existence of a legal basis for processing under Articles 6 and 9 of GDPR, such as official authority 6(1)e or substantial public interest 9(2)g. The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to the CI and appropriate delegated trial staff. In the event that data are shared with collaborators or groups wishing to undertake further analysis, collaborators will not have access to personal identifiable details other than those held on the EDC system. Pseudonymised participant data will also be available to interested parties after publication of the final report upon reasonable written request to the CI and subsequent approval.

The transfer of data to collaborators or for use in further research will be as described in the Clinical Research Agreement.

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

13.8. Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

Additional disclosure information, if any, will be collected at site initiation and documented in the site file. Members of the TSC and DMC will complete a competing interest form, which will be held in the TMF

13.9. Indemnity

The UoD and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The UoD will obtain and hold Clinical Trials indemnity cover for legal liabilities arising from the trial.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Tayside in relation to the trial.

Where the trial involves UoD staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Co-Sponsors do not provide trial participants with indemnity in relation to participation in the Trial but have insurance for legal liability as described above.

Where other Scottish Health Boards are participating as trial sites, those other Scottish Health Boards will maintain membership of CNORIS to cover their liability in relation to their conduct of the trial.

Other participating sites will maintain membership of a scheme similar to CNORIS.

13.10. Amendments

Amendments to the protocol will be conducted in compliance with Sponsor Standard Operating Procedures. The decision to amend the protocol will lie with the CI after consultation with the TMG, and trial statistician. The TSC will also be consulted on any major amendments. The CI will seek Sponsor approval for any amendments to the Protocol or other approved trial documents. The Sponsor will decide whether an amendment is substantial or non-substantial. The CI will be responsible for submitting the amendment to the appropriate regulatory authorities and communicating amendments to sites. Amendments to the protocol or other trial documents will not be implemented without approval from the Sponsor and subsequent

approval from the appropriate REC and/or MHRA, as appropriate, and appropriate site approvals. The amendment history will be detailed in an Amendment Log.

13.11. Post trial care

Following the end of trial, participants should be continued, started, or restarted on the appropriate treatment for their bronchiectasis. No provision for continuation of trial drug will be made by the trial team or Sponsor.

13.12. Access to the final trial dataset

The CI and Trial Statistician will have access to the final trial dataset. Access to the final trial dataset to others will be approved by the CI. See also section 13.7.

14. DISSEMINIATION POLICY

14.1. Dissemination policy

Details of the trial and clinical trial final report will be published on ISCTRN Registry, no later than 12 months after the end of trial. Trial results will be available to the public via the ISCTRN registry. The report will be made available to the Funder. The report can be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial. The participant representatives will be invited to suggest further dissemination activities for patients.

Participants in the trial will be notified of the results via a Results Letter.

14.2. Authorship eligibility guidelines and any intended use of professional writers

The data arising from this trial resides with the trial team and ownership with the UoD. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial final report will be prepared.

Authorship and the publication will be defined and developed by the TSC and the site investigators. An inclusive approach will be taken with either named or group authorship (e.g., “on behalf the ESCAPE Investigators”). In the case of group authorship all contributing participants will be named in (for example) a supplementary appendix. Named authors will be expected to meet authorship criteria set out by the International Committee of Medical Journal Editors.

15. REFERENCES

1. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Prim. 2018 Nov;4(1):45.

2. Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon T, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Vol. 50, The European respiratory journal. England; 2017.

3. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet (London, England). 2018 Sep;392(10150):880–90.

4. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc. 2015;12(11).

5. Martinez-Garcia MA, Soler-Cataluna J-J, Perpina-Tordera M, Roman-Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest. 2007 Nov;132(5):1565–72.

6. Hilliam Y, Moore MP, Lamont IL, Bilton D, Haworth CS, Foweraker J, et al. Pseudomonas aeruginosa adaptation and diversification in the non-cystic fibrosis bronchiectasis lung. EurRespir J. 2017 Apr;49(4).

7. Wilson R, Aksamit T, Aliberti S, De Soyza A, Elborn JS, Goeminne P, et al. Challenges in managing Pseudomonas aeruginosa in non-cystic fibrosis bronchiectasis. Respir Med. 2016 Aug;117:179–89.

8. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Stuart Elborn J, Andres Floto R, et al. British thoracic society guideline for bronchiectasis in adults. Thorax. 2019;74.

9. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50(3).

10. Goeminne PC, Hernandez F, Diel R, Filonenko A, Hughes R, Juelich F, et al. The economic burden of bronchiectasis - known and unknown: a systematic review. BMC Pulm Med. 2019 Feb;19(1):54.

11. Blanchette CM, Noone JM, Stone G, Zacherle E, Patel RP, Howden R, et al. Healthcare Cost and Utilization before and after Diagnosis of Pseudomonas aeruginosa among Patients with Non-Cystic Fibrosis Bronchiectasis in the U.S. Med Sci (Basel, Switzerland). 2017 Sep;5(4).

12. Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, et al. Research priorities in bronchiectasis: A consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J. 2016;48(3).

13. Pieters A, Bakker M, Hoek RAS, Altenburg J, van Westreenen M, Aerts JGJ V, et al. The clinical impact of Pseudomonas aeruginosa eradication in bronchiectasis in a Dutch referral centre. Vol. 53, The European respiratory journal. England; 2019.

14. White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis. Respir Med. 2012;106(3):356–60.

15. Vallieres E, Tumelty K, Tunney MM, Hannah R, Hewitt O, Elborn JS, et al. Efficacy of Pseudomonas aeruginosa eradication regimens in bronchiectasis. Vol. 49, The European respiratory journal. England; 2017.

16. Blanco-Aparicio M, Saleta Canosa JL, Valiño López P, Martín Egaña MT, Vidal García I, Montero Martínez C. Eradication of Pseudomonas aeruginosa with inhaled colistin in adults with non-cystic fibrosis bronchiectasis. Chron Respir Dis. 2019;16.

17. Suarez-Cuartin G, Smith A, Abo-Leyah H, Rodrigo-Troyano A, Perea L, Vidal S, et al. Anti-Pseudomonas aeruginosa IgG antibodies and chronic airway infection in bronchiectasis. Respir Med. 2017 Jul;128:1–6.

18. Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration. 2015;90(4):299–305.

19. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, Montgomery AB, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015 Jan;70(1):12–20.

20. Finch S, Laska IF, Abo-Leyah H, Fardon TC, Chalmers JD. Validation of the COPD Assessment Test (CAT) as an Outcome Measure in Bronchiectasis. Chest. 2020;157(4).

21. Crichton ML, Dudgeon EK, Shoemark A, Chalmers JD. Validation of the Bronchiectasis Impact Measure (BIM) - a novel patient reported outcome measure. Eur Respir J. 2020 Nov;

22. Spargo M, Ryan C, Downey D, Hughes C. Development of a core outcome set for trials investigating the long-term management of bronchiectasis. Chron Respir Dis. 2019;16:1479972318804167.

23. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J. 2017 Jun;49(6).

24. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.2020.

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

25. Haworth CS, Bilton D, Chalmers JD, Davis AM, Froehlich J, Gonda I, et al. Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. Lancet Respir Med. 2019 Mar;7(3):213–26.

26. Haworth CS, Shteinberg M, Winthrop KL, Blasi F, Dimakou K, Morgan L, et al. RCT Abstract - The efficacy and safety of colistimethate sodium delivered via the I-neb in bronchiectasis: the PROMIS-I randomized controlled trial. Eur Respir J [Internet]. 2021 Sep 5;58(suppl 65):RCT4267. Available from: http://erj.ersjournals.com/content/58/suppl_65/RCT4267.abstract

27. Kahan et al.: The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. Trials 2014 15:139.

28. Keene, O. N., Roger, J. H., Hartley, B. F., & Kenward, M. G. (2014). Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical statistics, 13(4), 258–264. https://doi.org/10.1002/pst.1624

29. Roger JH, Bratton DJ, Mayer B, Abellan JJ, Keene ON. Treatment policy estimands for recurrent event data using data collected after cessation of randomised treatment. Pharmaceutical Statistics. 2019;18:85–95. https://doi.org/10.1002/pst.1910

30. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMC Med. 2022 Jan;20(1):23.

31. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. BMJ. 2011 Apr;342:d1548.

32. Chalmers JD, Polverino E, Crichton ML, Ringshausen, FC, De Soyza A, Vendrell M, Regis Burgel, P, Haworth CS, Loebinger MR, Dimakou K, Murris M, Wilson R, Hill AT, Menendez R, Torres A, Welte T, Blasi F, Altenburg J, Shteinberg M, Boersma W, Elborn JS, Aliberti S. Bronchiectasis in Europe: Data from the European Bronchiectasis Registry (EMBARC). Lancet Respir Med. 2023;

33. Chalmers JD, Haworth CS, Metersky ML, Loebinger MR, Blasi F, Sibila O, et al. Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med. 2020 Sep;

34. Keir HR, Long MB, Abo-Leyah H, Giam YH, Vadiveloo T, Pembridge T, et al. Dipeptidylpeptidase-1 inhibition in patients hospitalised with COVID-19: a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial. Lancet Respir Med. 2022 Sep;

35. De Soyza A, Aksamit T, Bandel T-J, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J. 2018 Jan;51(1).

36. Chalmers JD, Timothy A, Polverino E, Almagro M, Ruddy T, Powell P, et al. Patient participation in ERS guidelines and research projects: The EMBARC experience. Breathe. 2017;13(3).

16. APPENDIX 1-RISK

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: This trial is testing different treatment approaches which are already used in standard medical care. The monitoring in the trial setting will be at least as good as in routine medical practice and all normal medical care will continue therefore arguably the risk to participants here is lower to standard medical care.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?	How will these risks be minimised?
Risks for individual medications are detailed in the SmPC.	The prescribing clinician will follow the guidelines described within the SmPC when prescribing the medications. The eligibility criteria will exclude participants not suitable to be randomised

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

There will be an independent data monitoring committee responsible for reviewing safety data.

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.

IMP labelling:
As this is a Type A trial, with no higher risk to the participant than standard of care, and the trial will use commercially available IMP with no modifications, no additional clinical trial labelling is required.

Accountability:
As this is a Type A trial, drug accountability will be according to local pharmacy protocols. Treatments will be prescribed by the participants' clinician using local prescriptions and dispensed by their local pharmacies as it is per routine clinical practice. Accountability will follow local pharmacy protocols.

17. APPENDIX 2 - TRIAL MANAGEMENT / RESPONSIBILITIES

Responsibilities will be detailed in the co-sponsorship and participating site agreements.

17.1. Participant registration/randomisation procedure

TCTU TRuST web-based randomisation system will be used.

Sites will be provided with a randomisation guide detailing the web-based randomisation system process. Prior to recruitment, individuals delegated this task will be given an individual username and password upon completion of training.

17.2. Data management

Data management will be overseen by TCTU Data Management Team.

Local sites will be expected to enter data directly on to the eCRF. Worksheets will be provided to facilitate this process, but their use is not mandatory. Worksheets, where used, will not be used for monitoring purposes.

All data from participants should be entered on the eCRF within 7 days of the last data collection point for that participant.

Data queries will be generated by the Data Management Team and should be addressed within 2 weeks.

17.3. Preparation and submission of amendments

TCTU Trial Management Team will be responsible for working with the CI to submit any amendments.

17.4. Preparation and submission of Annual Safety Report/Annual

TCTU Trial Management Team will be responsible for liaising with the CI to submit REC annual reports. The Sponsor Pharmacovigilance Team will be responsible for liaising with the CI to submit DSURs.

17.5. Data protection/confidentiality

The CI and trial staff will comply with the requirements of the Data Protection Act 2018, GDPR and the Data Protection Act 2018, or any subsequent amendment or replacement thereof regarding the collection, storage, processing and disclosure of personal data. The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

17.6. Trial documentation and archiving

Archiving trial site data will be the responsibility of individual sites. Payment for archiving will be provided as per site agreement.

18. APPENDIX 3 – AUTHORISATION OF PARTICIPATING SITES

18.1. Required documentation

The following data should be made available to TCTU Trial Management Team prior to site initiation:

- PI CV, signed and dated within the last 2 years
- PI GCP certificate
- Protocol signature page, signed and dated by PI
- Copy of signed Participating Site Agreement
- Copy of NHS R&D confirmation of capacity and capability
- Copy of the Delegation Log.

The following data should be made available and held within the ISF/Pharmacy Site File prior to site initiation:

- CV, signed and dated for all trial staff listed on Delegation Log
- GCP certificate for all trial staff listed on Delegation Log

18.2. Procedure for initiating/opening a new site

Site Initiation will be performed by Monitors and TCTU Trial Management Team and may be on site and/or remote.

18.3. Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement. A summary is given below:

- Attendance at the site initiation meeting
- Training of new members of trial staff in the protocol and its procedures,
- Ensuring that the ISF is accurately maintained
- Dissemination of important safety or trial related information to all stakeholders within their site
- Safety reporting within the required timelines
- Ensuring data entry to eCRF and responses to data clarification queries are completed within the required timelines
- Certify data entered on eCRF is correct and complete
- Ensuring any trial staff coming into contact with participants have the appropriate Personal Protective Equipment and training in its use
- Archiving of site trial data

19. APPENDIX 4 – SCHEDULE OF PROCEDURES

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	**Randomisation**	**Phone call**	**Follow-up assessments**	**Follow-up assessments**	**Final Assessments**
	Day -35 to 0	**Day 0**	**Week 2 (+/- 3 days)**	**† Week 12 - 14 (+ 7 days)**	**Week 52 (+/- 14 days)**	**Week 104 (+/- 14 days)**
Informed consent	X					
Eligibility check	X	X				
Medical history	X					
Demographics	X					
Concomitant medications	X	X	X	X	X	X
Pregnancy test, if required	X					
ECG	X					
Weight & Height	X					
Temp, BP, Pulse O_2 sats	X	X		X	X	X
Physical examination	X					
Bronchiectasis severity index score	X					
Clinical sputum sample	X*	X		X	X	X
Research sputum sample		X		X	X	X
QoL-B		X		X	X	X
CAAT		X		X	X	X
EQ-5D-5L		X		X	X	X
BEST diary ** (continuous throughout the trial)		X				
Review of routine sputum culture results for *P. aeruginosa*		X	X	X	X	X
Randomisation		X				
Prescription for trial		X				
Exacerbation recording		X	X	X	X	X
Review/reporting of participant AEs/SAEs		X	X	X	X	X
Drug compliance			X	X		

*A clinical sputum sample is only required for eligibility at visit 1 if a participant has not had a new infection of *P. aeruginosa* in a routine respiratory sample within the previous 6 months. If a participant has had a positive sample for *P. aeruginosa* within the previous 6 months, then a separate screening visit and an eligibility sputum sample is not required, and screening & randomisation assessments can take place during the same visit.

** The electronic BEST diary will be activated by the site team on Castor. The diary will be scheduled to be sent to the participant daily throughout the trial. If a participant is unable to complete the electronic diary, they will be issued with a weekly paper diary to report any new exacerbations.

† For participants randomised to receive eradication treatment, visit 4 should take place within 7 days of the completion of inhaled antibiotic treatment. Those randomised to standard care, visit 4 should take place at 12 weeks (+7) days.

Missed trial assessments or trial medication, or visits completed outside the visit window, will not be reported as breaches, where this is due to participant choice or a clinical decision.

20. APPENDIX 5 – SAFETY REPORTING FLOW CHART

Activity	Responsibility	Timing	Comments
Review medical records and questioning of participant for evidence of AEs at all visits.	Trial staff	All visits	Recorded on eCRF system.
Review of recorded AEs for causality and seriousness	PI (or delegate)	Within 7 days of recording	Recorded on eCRF and/or medical records.
Reporting SAEs - All SAEs need to be assessed and signed off by the PI or delegated doctor.	PI (or delegate)	Within 24 hours of becoming aware of SAE	Reported via the online Tayside Pharmacovigilance system
Reviewing of SAEs	Sponsor	Following receipt	Pharmacovigilance Committee
Reporting of SUSARs to MHRA	Sponsor	Within 7 days if life threatening or fatal. Within 15 days for others	Senior Research Governance Manager or delegate

21. APPENDIX 6 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1	30/10/25	Gillian Martin	Initial protocol for regulatory review
N/A	2		Gillian Martin	Protocol updates from MHRA review: Table of contents, updated page numbers Updated trial flow chart with background therapy terminology 6.1 Inclusion criteria point 5 added Addition & clarification of inclusion criteria notes Inclusion & exclusion criteria numbered 8. Trial treatment clarified & background therapy defined

				Throughout, “symptomatic treatment” terminology replaced with “background therapy” 8.14 updated & pregnancy test added 9.8 reporting of urgent safety measures clarified Appendix 4 pregnancy test added