Value of inhaled treatment with aztreonam lysine in bronchiectasis

VitalBE Trial Operations Manual

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Author: Margaret Band / Clare Clarke

CHANGES

VERSION	DATE	Details of changes
V2.0	28-04-20	Further clarification in section 3 table and sections 4.7, 4.9, 4.11, 4.15, 4.16, 5.10, 5.17, 6.3, 6.4, 8.2, 8.3,12.4, 14.1. Typographical errors amended.
V3.0	28-10-20	Sputum induction removed Change in TASC website and PV address
V4	17-05-23	Changes to visit schedule Changes to data management system

Contents

Abbreviations/Terms Used

AE	Adverse Event
AR	Adverse Reaction
BP	Blood Pressure
bPIS	BPIS
CI	Chief Investigator
CRF	Case Report Form
CTP	Clinical Trial Pharmacy
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
mmHG	millimetres of Mercury
mmol/L	millimols per litre
P	Pulse
PCRN	Primary Care Research Network
PI	Principal investigator
PIS	Participant Information Sheet
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPCRN	Scottish Primary Care Research Network
SUAR	Suspected Unexpected Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TP	Tayside Pharmaceuticals
TRuST	Tayside Randomisation System

1. Recruiting Participants

1.1 Identifying Participants

Principal Investigator (PI) and research staff at each site should use their local knowledge to identify the appropriate clinics, rehabilitation classes, registries and networks from which to identify participants and target advertising.

Secondary Care:

After obtaining the permission from the patients' doctor the patients' medical notes should be checked prior to clinics by a member of the clinical team. Where appropriate a Clinic Invitation with Reply Slip and bPIS should be posted prior to their attendance at clinic. Alternatively, potentially suitable participants may be approached directly in clinic by a member of the clinical team.

Where local patient registries are kept where patients have given prior consent to being contacted for research these should be used to search for potentially suitable participants.

Targeted local advertising may also be used. The Trial Manager should be contacted for approved adverts.

Primary Care:

Primary care recruitment may be carried out with the assistance of the NRS Primary Care Network in Scotland and the Clinical Research Networks (CRN) in England and Wales.

Approval to use the CRN will require an amendment to add Participate Identifying Centres and the TM should be contacted regarding this.

Participants identified from GP practices will be sent a GP Network Invitation Letter and a bPIS.

1.2 Recruiting Participants

The research staff should discuss the trial with the potential trial participants when they attend their clinic appointment and provide a bPIS.

Where the research staff receives a reply slip from a participant indicating their interest in the trial the research staff should phone them to discuss the trial further.

The research staff should ascertain if the participant has any contraindications to taking part in the trial.

Participants should be made aware that a taxi can be provided to bring them to the appointment and return them home or if they prefer, travel costs to the research visits will be reimbursed. This has been proven to help recruitment and retention of trial participants.

If participants decline to participate in the trial thank them for their time and make them aware that this will not affect their future medical care.

If participants agree to take part in the trial a screening appointment should be arranged. Details of this along with a Participant Information Sheet (PIS) should be sent to the

participant. Participants MUST always have a minimum of 24 hours to read over the PIS before attending a screening visit.

1.3 Recording Participant Invites

The research staff should record how many participants were given BPISs in clinics, via GPs and from other sources on the Pre-Screening Log.

2. Informed Consent

2.1 Responsibility for taking informed consent

The PI has responsibility for obtaining informed consent at each recruiting centre. The PI can delegate obtaining consent to research staff, on the condition that they have received training in the informed consent process (GCP training) and protocol specific training to ensure that they are sufficiently knowledgeable about the trial. This must also comply with the local Trust's Research Governance Policy. The delegation of taking consent by the research staff must be entered in the Delegation Log and filed in the Investigator Site File (ISF).

2.2 Taking Informed Consent

Informed consent should only be taken once participants have had ample time (at least more than 24 hours) to read over the PIS.

The person taking informed consent should satisfy themselves as to the identity of participants. This should be noted in the medical notes.

Give participants an opportunity to ask any questions they may have regarding their participation in the trial. 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.

Once satisfied that participants fully understand the nature of the trial, participants should complete the Informed Consent Form (ICF) by entering their initials if they agree to each of the consent conditions.

The ICF should be signed and dated by the participant and the person taking the consent (PI or research staff). The research staff should write the participant's Participant ID number and date and version of the PIS provided to the participant at the top of the consent form.

If a participant refuses to enter their initials to any of the statements, then the participant is **not eligible** to start the trial, with the exception of question 9 regarding future contact.

2.3 Circulation of PIS & Informed Consent Form:

One copy of the PIS and ICF should be given to the participant for their records.

One copy of the PIS and ICF should be stored in the participant's medical notes.

The original ICF should be filed in the ISF.

Complete the Enrolment and Randomisation Log in the ISF when you enrol participants into the trial. Every participant consented to the trial should be included on the Enrolment and Randomisation Log, i.e. all participants who have completed an ICF including those who do not go on to be randomised.

If there are significant changes to the PIS during the period participants are enrolled in the trial, participants must receive a copy of the new PIS and re-consent. This should be filed as per circulation list above.

If consent is taken on a separate day from screening, the research staff should go through consent again at the screening visit to check the participant is still happy to participate.

The maximum time between taking consent and performing the screening visit is 1 month.

In all cases where participants fail screening for a reason that is modifiable, rescreening will be permitted. See Section 4.14

3. Visit Schedule

Type of visit	Screening V1	Baseline and randomization V2	Follow-up phone call V3	Follow-up phone call V4	Follow-Up Assessments V5	Final visit Assessments V6	Unscheduled visit Assessments
Timeline	Month -1 to 0	Up to 35 days after screening	Month 1 (4 weeks) (+/- 2 Weeks)@	Month 3 (12 weeks) (+/- 2 Weeks)@	Month 6 (24 weeks) (+/-2 Weeks)@	Month 12 (48 weeks) (+/- 2 weeks)@	As Required
Informed Consent	X						
Inclusion/Exclusion Criteria Check	X	X					
Medical History	X						
Record Concomitant Medications	X	X	X	X	X	X	X
Physical Examination	X						X
Height	X						
Weight	X						
Check Vital Signs^	X	X			X	X	X
ECG	X						
Full blood count	X						
Urea and electrolytes	X						
Liver function tests	X						
Sputum	X				**X**	X	**X**
Research Blood Sample *		X			X	X	X
Sputum sample for storage		X			X	X	X
Standard Spirometry	X	X			X	X	X
Quality of life bronchiectasis questionnaire &		X	X&	X&	X&	X	X
SGRQ		X	X	X	X	X	
BHQ		X	X	X	X	X	X
Exacerbation recording		X	X	X	X	X	X

Type of visit	Screening V1	Baseline and randomization V2	Follow-up phone call V3	Follow-up phone call V4	Follow-Up Assessments V5	Final visit Assessments V6	Unscheduled visit Assessments
Timeline	Month -1 to 0	Up to 35 days after screening	Month 1 (4 weeks) (+/- 2 Weeks)@	Month 3 (12 weeks) (+/- 2 Weeks)@	Month 6 (24 weeks) (+/-2 Weeks)@	Month 12 (48 weeks) (+/- 2 weeks)@	As Required
Viral nasal swab		X				X	X
Supervised first dose of IMP		X					
Safety Spirometry Post trial medication		X					
Bronchiectasis severity index and components eg MRC dyspnoea score	**X**						
Pregnancy Testing If Applicable	X	X			X	X	X
Record Adverse Events		X	X	X	X	X	X
Randomisation		X					
Dispense Trial Drugs		X[a]	**X**[a]	X[a]	X[a]		
Drug Return And Compliance Check					X	X	

Under exceptional circumstances (*which may include: in the event of another lockdown, it is felt unsafe for the patient to come in as they should be self-isolating, patient declines visit due to COVID risk*) visits 5, 6 and unscheduled visits can be performed remotely e.g over the telephone.

^ Vital Signs: Blood Pressure, pulse, temperature, oxygen saturation

Where rapid PCR using the Biofire PCR system is available (e.g. Tayside site) this may be used to confirm the presence of protocol defined Gram negative pathogens to allow combined screening and randomization in the same day (the Biofire system takes approximately 1 hour to obtain a result). If there is sufficient sputum an aliquot will still be send for culture and sensitivity testing but the PCR is sufficient to confirm eligibility

@trial visits will be delayed after an unscheduled visit; they will be rescheduled for 7 days following the participant's recovery from the exacerbation

*Research blood samples will be stored and analysed at the end of the trial

a Trial drugs may be dispensed on a monthly basis depending on the preference of the participant.

**The 28-day off trial drug cycle maybe amended by the appropriate number of days to get a patient back on track for the 28-day treatment cycle. This may occur in situations such as participant going on a planned holiday. Trial teams to discuss with CI in such situations.

4. & Quality of life bronchiectasis questionnaire will be completed each month

5. Visit 1 - Screening Visit (approx. 2-3 hours)

5.1 Participant Transport

When arranging participant visits, participants should be offered a taxi to bring them to the appointment and return them home. This has been proven to help recruitment and retention of trial participants.

An account should be set up with a local taxi company for this as per local practice.

Alternatively, participants wishing to use public transport should have their cost reimbursed or petrol paid as per local practice. This should be done as per local procedure e.g. from petty cash or by completing a travel expense form.

5.2 Participant identity

Participant identity should be checked. Some examples of identification are listed below:

- Current passport
- Current photographic identification driving licence
- Current matriculation card
- Young person's or senior citizen's railcard
- Proof of Address
- National Insurance Card
- CHI Number/Medical Card

5.3 Informed Consent

See Section 2.

5.4 Participant ID

All participants consented to the trial should be allocated a participant ID number.

Participant ID numbers are made up of five numbers the first to indicate the site and the last three indicate the participant number at that site. E.g. 01-001 is the first participant at site one.

Please use participant ID numbers in order and ensure site ID is correct for your site.

The Participant ID allocated will remain as the participant's participant ID for the duration of their time in the trial. If participant IDs are used out of sequence a file note should be entered in the ISF, this will not disrupt the randomisation process.

If participant fails screening and do not go on to randomisation their participant ID number should not be re-used.

5.5 Recording Participant Data

Once participants have consented to the trial, their data needs to be entered in the eCRF. All trial data should be documented in the participant's medical notes as source data, along with all test results. There are Vital BE medical notes recording sheets for each visit which can be used for this purpose if wished. There is a worksheet which can also be used to record data prior to it being entered into the DMS and medical notes. The worksheet should not to be used as source data.

Demographic Details

Please ensure participants are 18 years or over on date of screening visit to comply with the inclusion criteria.

5.6 Concomitant Medications

Please ask participants to bring their current prescription. Please go through this with them and ensure it is accurate for what the participant is taking at the time of the visit, scoring off medications that the participant is not actively taking on a copy of the prescription, which should be retained as source data and filed in the medical notes. At screening, the medication that the participant is taking should be ticked ongoing at start of study on the eCRF. Any new medications during the course of the trial should have a start date entered.

5.7 History of Bronchiectasis

Participants should have CT evidence of bronchiectasis in at least one lobe, if not they are not eligible for the trial.

5.8 Pulmonary Exacerbations

Participants should have had at least 3 pulmonary exacerbations in the last 12 months, if not they are not eligible for the trial. Please ensure that evidence of 3 exacerbations is documented in the medical notes and signed off by the delegated doctor.
Participants who have had a pulmonary exacerbation within 28 days are not eligible and should be withdrawn. Participants may be rescreened after 28 days has elapsed since symptoms have resolved.

5.9 Medical History – Other Relevant Medical Conditions

The Medical History section should be completed as fully as possible and should be as diagnosed by a doctor.

The “other relevant medical conditions” should include:

- Medical conditions for which the participant is receiving concomitant medications.
- Past medical conditions may impact on the participants’ Activities of Daily Living or ability to complete the trial assessments.

Abbreviations should not be used.

Date of diagnosis is not required.

The participant should be assessed by a delegated doctor as to whether they have and unstable co-morbidities which in their opinion would make the participant unsuitable to be enrolled in the trial.

5.10 Smoking Status

A participant’s pack year history should be calculated using the following website:

www.smokingpackyears.com

Please document the figures used for the pack years calculation in the medical notes. Participants who have a primary diagnosis of COPD and have a pack year history of more than 20 years are not eligible.

5.11 Trial Assessments

All trial assessments should be completed as per the appropriate Working Practice Guidelines (WPG)

5.11.1 Vital signs

Height should be carried out as per WPG.

Weight should be carried out as per WPG.

Blood pressure and pulse should be carried out as per WPG.

Oxygen saturation should be carried out as per WPG.

Tympanic temperature should be carried out as per WPG.

5.11.1 Pregnancy test

Should be carried out as per WPG.

5.11.1 Spirometry

Spirometry should be performed post bronchodilation (reversibility) as per WPG.

Ensure the height and weight entered into the spirometer is the height and weight recorded at the visit and not historical values.

If spirometry is not performed the participant should be withdrawn from the trial.

5.11.2 Bronchiectasis Severity Index

The Bronchiectasis Severity Index (BSI) should be calculated from the following website:

http://www.bronchiectasisseverity.com/15-2/

The Bronchiectasis Severity Score given by the BSI website should be entered in the eCRF.

All results for the above assessments should be entered in the medical notes as source data to confirm the answers to each of the questions.

5.11.3 ECG

ECG should be carried out as per WPG.

The ECG is mandatory and if not performed the participant should be withdrawn from the trial.

The ECG must be assessed by a delegated doctor. Any abnormalities should be documented in the participant's medical notes. The delegated doctor should assess where there are abnormalities if it is appropriate for the participant to continue in the trial, this should be documented in the participant's medical notes.

The doctor assessing the ECG. should sign and date the ECGto confirm review.

The ECG recording should be filed in the participant's medical notes.

5.11.4 Physical examination

The physical examination is mandatory and if not performed the participant should be withdrawn from the trial.

This should be completed by a delegated doctor and documented in the participant's medical notes/

5.11.1 Inclusion/Exclusion Criteria

All participants MUST meet the inclusion and exclusion criteria.

If any of the inclusion criteria is answered NO, or exclusion criteria answered YES participants are NOT eligible for the trial and should be withdrawn. Please list reason(s) for ineligibility for screen failure on Completion of Trial Early/Withdrawal Form

Participants cannot enrol into the trial if they are participating in another drug trial, or less than 30 days since completing another drug trial. Observational trials would not exclude a participant but the research staff must confirm with the other research team that this would not cause any contraindications with their trial. This confirmation should be recorded in the participant's medical notes.

5.11.2 Sputum samples

Sputum samples should be obtained as per Laboratory Manual.

If no sputum sample is obtained prior to randomisation the participant should be withdrawn.

Results

Results should be reviewed by a doctor on the delegation log and a signed and dated copy filed in the participant's medical notes.

If the sputum culture and sensitivity is not positive for Gram-negative respiratory pathogens the participant may provide more samples. A positive result must be obtained and participant attend for baseline visit within 35 days of screening visit.

Pre-specified eligible organisms include *P. aeruginosa*, *Eschericia coli, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella pneumoniae, Proteus mirabilis, Serratia marcescens, Achromobacter, Enterobacter and Stenotrophomonas maltophilia*

5.11.3 Bloods

Blood samples should be obtained as per Laboratory Manual.

Results should be reviewed by a doctor on the Delegation Log in a timely manner. A copy of the results signed and dated by a delegated doctor should be filed in the participant's medical notes.

5.12 Data Entry

Data shouldbe entered into Castor Data management system, either from Participant notes or worksheet, if used. see Section 13.

Data entry should be completed within 2 weeks of the visit.

Participants who fail screening and do not go on to be randomised should also be entered into Castor

5.13 Enrolment and Randomisation Log

The participant's details should be entered into the Enrolment and Randomisation Log, filed in the ISF.

All participants consented to the trial must be entered in the Enrolment and randomisation Log, including screen fails.

5.14 Failed Screening

If a participant fails screening the "Completion of Trial Early Withdrawal Form" form. In addition, all screening assessments, excluding taking blood samples, should be completed in the event of a screen fail visit. The eCRF should still be fully completed for this visit.

Where participants fail screening due to a reason which is modifiable can be rescreened. Examples:

- Participants who have had a pulmonary exacerbation within 28 days can be rescreened after 28 days from last symptoms have elapsed
- Participants with recent use of an investigational drug can be rescreened after 30 days or five times of the elimination half-life after the last trial dose if longer than 30 days.
- Participants with unstable co-morbidities can be rescreened if, in the opinion of the investigator, the co-morbidity becomes stable or resolves such that the participant could be included.
- Participants who fail to isolate *P. aeruginosa* or other Gram-negative pathogens at the screening visit may send further sputum samples between screening and randomization, until sputum cultures are positive. Once 35 days has elapsed, however, the participant should be regarded as a screen failure and would require to be rescreened in full.

Participants attending for rescreening should be given a new PIS, re-consented and given a new participant ID number.

5.15 Documenting the Screening Visit in Medical Notes

The Screening Visit should be documented in the participants' medical notes and should include the following information for source data verification.

VitalBE Medical Notes Recording Sheets can be used if wished.

- Front coloured card/sheet/sticker to state they are a research participant
- Copy of signed ICF.
- Copy of PIS participant has consented to.
- Copy of GP letter informing GP of participation
- Date of visit
- Confirmation that the participant has had the PIS for at least 24 hours.
- Confirmation of how participant identity was verified.
- Details of any notable findings at the visit and any action taken.
- Details of concomitant medications at time of visit, this may be a copy of the participant's repeat prescription form, updated with any changes required.
- History of bronchiectasis details if source data not elsewhere in medical notes.
- Medical & smoking history if source data not elsewhere in medical notes.
- Height and weight
- Vital signs

- For women who were deemed not WOCBP document how this was confirmed. Result of pregnancy test if appropriate.
- Spirometry results and how bronchodilation was achieved. Spirometry results should be signed and dated on day of visit by doctor on the delegation log. To be filed in medical notes with Pt ID and visit number on them.
- Evidence for questions asked for Bronchiectasis Severity Index if source data not elsewhere in medical notes.
- Copy of ECG signed and dated by doctor on Delegation Log. Result of ECG i.e. normal/abnormal and any action taken if appropriate.
- Physical exam normal/abnormal and action taken if appropriate.
- Record blood samples taken.
- Confirmation that the visit was carried out as per protocol.
- Name and Signature of Research staff completing the visit.
- Copy of blood and sputum results signed and dated by delegated doctor to be added when obtained.
- Please document any changes to con meds or any AE's (*even if there were none*) in the continuation sheets of the medical notes at every visit.
-

5.16 **Arranging next visit**

Visit 2, randomisation, must occur within 35 days of visit 1 screening.

Ensure a sputum sample that is culture positive for *P. aeruginosa* or other Gram-negative respiratory pathogens within 35 days of visit 2 is available. Pre-specified eligible organisms include *Eschericia coli, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella pneumoniae, Proteus mirabilis, Serratia marcescens, Achromobacter, Enterobacter and Stenotrophomonas maltophilia*

When arranging visit 2 ensure that the following timelines will be met on the day of the visit:

Inclusion

- A history of at least 3 exacerbations in the previous 12 months
- *Pseudomonas aeruginosa* or other Gram-negative respiratory pathogen detected in sputum or bronchoalveolar lavage on at least 1 occasion in the previous 12 months

Exclusion

- Recent significant haemoptysis (a volume requiring clinical intervention, within the previous 4 weeks).
- Treatment with inhaled, systemic or nebulized anti-Pseudomonal antibiotics in the 35 days prior to randomization
- Oral macrolides which have been taken for a period of less than 3 months prior to the start of the trial.
- Treatment of an exacerbation and receiving antibiotic treatment within 4 weeks of randomization
- Use of any investigational drugs within five times of the elimination half-life after the last trial dose or within 30 days, whichever is longer.

6. Visit 2 - Randomisation (approx. 2 hours)

The Visit 2 - Randomisation must be completed within 35 days of Visit 1 - Screening.

6.1 Participant identity

Participant identity should be checked.

6.2 Informed consent

The participant should be asked if they still wish to take part in the trial.

6.3 Adverse events

Participants should be asked if they have experienced any adverse event(s) (AE) since attending the Screening Visit. If they have had an AE the AE Log should be completed, if the AE is assessed to be a reportable Serious AE, a SAE form should be completed and submitted, see section 12.

6.4 Concomitant medications

Any changes to concomitant medications should be updated in the participants medical notes and on the Concomitant Medications pages of the eCRF

6.5 Pulmonary exacerbations

If the participant has had any signs or symptoms of pulmonary exacerbation since the last visit a Pulmonary Exacerbation Repeating Data Form should be completed in the eCRF.

A separate Pulmonary Exacerbation Repeating Data Form should be completed for each distinct exacerbation.

If symptoms have resolved for at least 48 hours before more symptoms develop then this should be classified as a new exacerbation.

Castor will calculate if the exacerbation is a protocol defined exacerbation, non-protocol defined exacerbation or, not an exacerbation

6.6 Visit 2 assessments

These should be carried out according to the appropriate Working Practice Guidelines.(WPG)

6.7 Eligibility checked

All inclusion and exclusion criteria which were either not known or may have changed since the last visit must be rechecked.

The PI or delegated doctor **MUST** sign the participant's medical notes to confirm eligibility. The eligibility pages of the worksheet can be used for this but must be filed in the participant's medical notes.

6.8 Randomisation

Randomisation should only take place **AFTER**:

- Informed consent has been obtained
- The participant is present at the visit i.e. randomisation should not be carried out prior to visit.

- The participants' eligibility against the inclusion/exclusion criteria has been checked by the PI or delegated doctor.
- The Participant Eligibility has been signed off by the PI or other doctor delegated to do this as entered on Delegation Log.

If the randomisation visit is more than 35 days since screening the **CI** must confirm it is still ok to randomise and reason for allowing this must be given. This must also be documented in the participant's medical notes.

Further information on the randomisation process can be found in Section 10.

6.9 Trial samples

Should be collected as per Laboratory Manual.

6.10 Questionnaires

Should be completed by the participant. Help may be given if required although prompting of answers should be avoided.

Quality of Life – Bronchiectasis Questionnaire (QoL-B)

This should be completed by the participant on the last day of their treatment and the last day of their off period, i.e. day before they restart treatment for the duration of the trial.

Where this coincides with a trial visit the questionnaire should be given to the participant to complete at the visit. Please ensure all questionnaires have ID, visit number and date completed fully documented on each page. When questionnaires are to be completed between trial visits the questionnaire(s) should be provided to the participant at the visit to complete in the following months, with and provided with a stamped addressed envelope to return the completed questionnaire to research staff. A member of the research staff should phone the participant when the questionnaire is due to be completed to remind them to complete and return it. If the questionnaire has not been returned within one week the research staff should phone the participant and ask them to complete and return the questionnaire. If the questionnaire is still not returned then this should be recorded in the medical notes, and documented on the eCRF.

Completed QoL-B should be held securely at site until transferred to TCTU.

Bronchiectasis Health Questionnaire (BHQ)

- The BHQ should be completed on the day of the visit.
- When the questionnaire has been returned,check for completeness and if any questions are missed or answered incorrectly e.g. 2 answers ticked instead of one, go through the questionnaire with the participant.
- Enter questionnaire data in eCRF

St Georges Respiratory Questionnaire (SGRQ)

- The SGRQ should be completed on the day of the visit.
- When the questionnaire has been returned,check for completeness and if any questions are missed or answered incorrectly e.g. 2 answers ticked instead of one, go through the questionnaire with the participant.

- Enter questionnaire data in eCRF

6.11 Trial Medication

See Section 12

6.12 Participant Pack

When randomised participants should be given the following to take away:

Trial bag

Trial Medication – 28 days' supply, (3 packs)

Nebuliser controller unit

Nebuliser handset

Trial Medication Guide

Contact Card

Participant Appointment Sheet

Copy of Informed Consent Form

Questionnaires – QoL-B to complete between Visits 2 and 5

6.13 Travel Expenses

Where a taxi was not provided participants should be offered travel expenses for each trial visit. These should be reimbursed according to local practice e.g. from petty cash, completing travel expense form.

6.14 Informing Participants' GP

Once participants have been randomised, please inform his/her GP by completing the details in the GP letter and sending it to the GP. A copy of this letter should be filed in the participants' medical notes.

6.15 Data Entry

Data from the visit should be entered into eCRF. see Section 13.

Data entry should be completed within 2 weeks of the participant's visit.

6.16 Enrolment and Randomisation Log

The Enrolment and Randomisation Log should be updated with the participant's randomisation date, filed in the ISF.

6.17 Documenting Visit 2 in Medical Notes

Visit 2 should be documented in the participants' medical notes and should include the following information for source data verification.

- Date of visit.
- Confirmation that participant identity was checked
- Confirmation that the participant was willing to continue in the trial.
- Details of any adverse events since visit 1 (document 'no AEs since last visit' if none)

- Details of any changes to concomitant medications since visit 1. (document 'no changes to con meds since last visit' if none)
- Details of any exacerbations since visit 1
- Height and weight
- Vital signs
- Result of pregnancy test if appropriate.
- Confirmation that eligibility checks were met.
- Pre and post-dose spirometry results and how bronchodilation was achieved.
- Confirmation of change in post dose FEV1
- Confirmation that trial medication was dispensed.
- Confirmation that preparation of trial medication and use of nebuliser was demonstrated.
- Confirmation that participant received trial medication, nebuliser, handset, Preparation of Trial Medication leaflet, Contact Card, Participant Appointment Sheet.
- Details of any notable findings at the visit and any action taken.
- Copy of GP letter– participants being randomised only.
- Confirmation that the visit was carried out as per protocol.
- Name and Signature of research staff completing the visit.

7. Visits 3 & 4 Telephone visits

7.1 Participant identity

Participant identity should be checked.

7.2 Informed consent

The participant should be asked if they still wish to take part in the trial.

7.3 Adverse events

Participants should be asked if they have experienced any adverse event(s) (AE) since attending the Screening Visit. If they have had an AE the AE Log should be completed, if the AE is assessed to be a reportable Serious AE, a SAE form should be completed and submitted, see section 12. Please record that this question was asked and participant did not report any if this was the case in the participant's medical notes

7.4 Concomitant medications

Any changes to concomitant medications should be updated on the Concomitant Medications form in the eCRF. Please record that this question was asked and that the participant did not report any changes to con meds if this was the case in the participant's medical notes

7.5 Pulmonary exacerbations

If the participant has had any signs or symptoms of pulmonary exacerbation since the last visit a Pulmonary Exacerbation Repeating Data Form should be completed in the eCRF.

A separate Pulmonary Exacerbation Repeating Data Form should be completed for each distinct exacerbation.

If symptoms have resolved for at least 48 hours before more symptoms develop then this should be classified as a new exacerbation.

6.6 Questionnaires SGRQ and BHQ should be completed over the telephone at these visits. QoL-B should continue to be completed at home by the participant and completed questionnaires brought to Visit 5.

8. Follow-up Visits (approx. 1½ hours)

8.1 Participant identity

Participant identity should be checked.

8.2 Informed consent

The participant should be asked if they still wish to take part in the trial.

8.3 Adverse events

Participants should be asked if they have experienced any adverse event(s) (AE) since attending the Screening Visit. If they have had an AE the AE Log should be completed, if the AE is assessed to be a reportable Serious AE, a SAE form should be completed and

submitted, see section 12. Please record that this question was asked and participant did not report any if this was the case.

8.4 Concomitant medications

Any changes to concomitant medications should be updated on the Concomitant Medications pages of the CRF. Please record that this question was asked and that the participant did not report any changes to con meds if this was the case.

8.5 Pulmonary exacerbations

If the participant has had any signs or symptoms of pulmonary exacerbation since the last visit a Pulmonary Exacerbation Record Form should be completed in the CRF.

A separate Pulmonary Exacerbation Record Form should be completed for each distinct exacerbation.

If symptoms have resolved for at least 48 hours before more symptoms develop then this should be classified as a new exacerbation.

8.6 Trial Assessments

Should be completed as per WPG

8.7 Sputum samples

Sputum samples should be obtained as per Laboratory Manual.

8.8 Bloods

Should be collected for the visit as per Laboratory Manual.

8.9 Questionnaires

Should be completed by the participant. Help may be given if required although prompting of answers should be avoided.

8.10 Trial Medication

See Section 12

8.11 Significant Clinical Finding

If participants are found to have another significant clinical finding at any of the research visits then the PI/delegated doctor should be informed and they should take the appropriate action according to their clinical opinion.

A letter with details of the finding and any actions taken should be completed and sent to the participant's GP and a copy filed in participants' medical notes.

8.12 Data Entry

Data should be entered into Castor see Section 14.

Data entry should be completed within 2 weeks of the participant's visit.

8.13 Documenting the Follow-up Visits in Medical Notes

Follow-up Visits should be documented in the participants' medical notes and should include the following information, where appropriate for that visit, for source data verification.

- Date of visit.
- Confirmation that participant identity was checked

- Confirmation that the participant was willing to continue in the trial.
- Details of any adverse events since last visit.
- Details of any changes to concomitant medications since last visit.
- Details of any exacerbations since last visit
- Vital signs
- Result of pregnancy test if appropriate.
- Confirmation that trial medication was dispensed and new handset given for each 28 day supply
- Details of any notable findings at the visit and any action taken.
- Confirmation that the visit was carried out as per protocol.
- Name and Signature of research staff completing the visit.

9. Randomisation

Randomisation should only take place AFTER:

- Informed consent has been obtained
- The participant is present at the visit i.e. randomisation should not be carried out prior to visit.
- The participants' eligibility against the inclusion/exclusion criteria have been checked by a doctor on the Delegation Log.
- The Participant Eligibility page has been signed off by the PI or other doctor delegated to do this on their behalf as entered on the Delegation Log.
- It must be a doctor of medicine who signs off the eligibility page.

9.1 Tayside Randomisation System (TRuST)

Randomisation is carried out via the web-based Tayside Randomisation System (TRuST). Only those on the Delegation Log who are delegated to perform randomisation should complete randomisation and they should ensure that they only use their own login details for this.

See TRuST User guide for detailed guidance on use of the system.

The TRuST will allocate the appropriate trial medication treatment arm.

9.2 Inability to Access TRuST for Randomisation

If research staff are unable to access TRuST they should complete an Emergency Randomisation Form and phone the CTM (or delegate). The CTM will access TRuST and randomise the participant using the information provided from the Research staff on the Emergency Randomisation Form and inform the Research staff of the allocated treatment arm.

See full procedure in the 'VitalBE Emergency TRuST Access' document, a copy can be found in the ISF section 9.1 o

10. Trial Medication

Participants will be randomised to one of the following two treatments:

- Aztreonam 75mg three times per day
- Placebo 75mg three times per day

Trial medication is given in 28 day cycles with participants taking 28 days of trial medication followed by 28 days not taking trial medication for the 12 months of the trial.

10.1 Preparation

Each dose of IMP consists of one vial of Aztreonam/placebo 75mg mixed with one ampoule of saline prior to being inhaled through the Altera handset.

See Trial Medication Guide for mixing Aztreonam/placebo 75mg with the saline.

10.2 Nebuliser and handset

Each participant will be given an eFlow nebuliser machine and Altera nebuliser handset which must be used with the trial medication.

The nebuliser machine and handsets must only be used with the trial medication and must not be used for other inhaled medications. The trial medication must only be taken via the supplied nebuliser and handset and not with any other nebuliser machine.

The nebuliser machine will be supplied to the research team and should be given to the participant after randomisation.

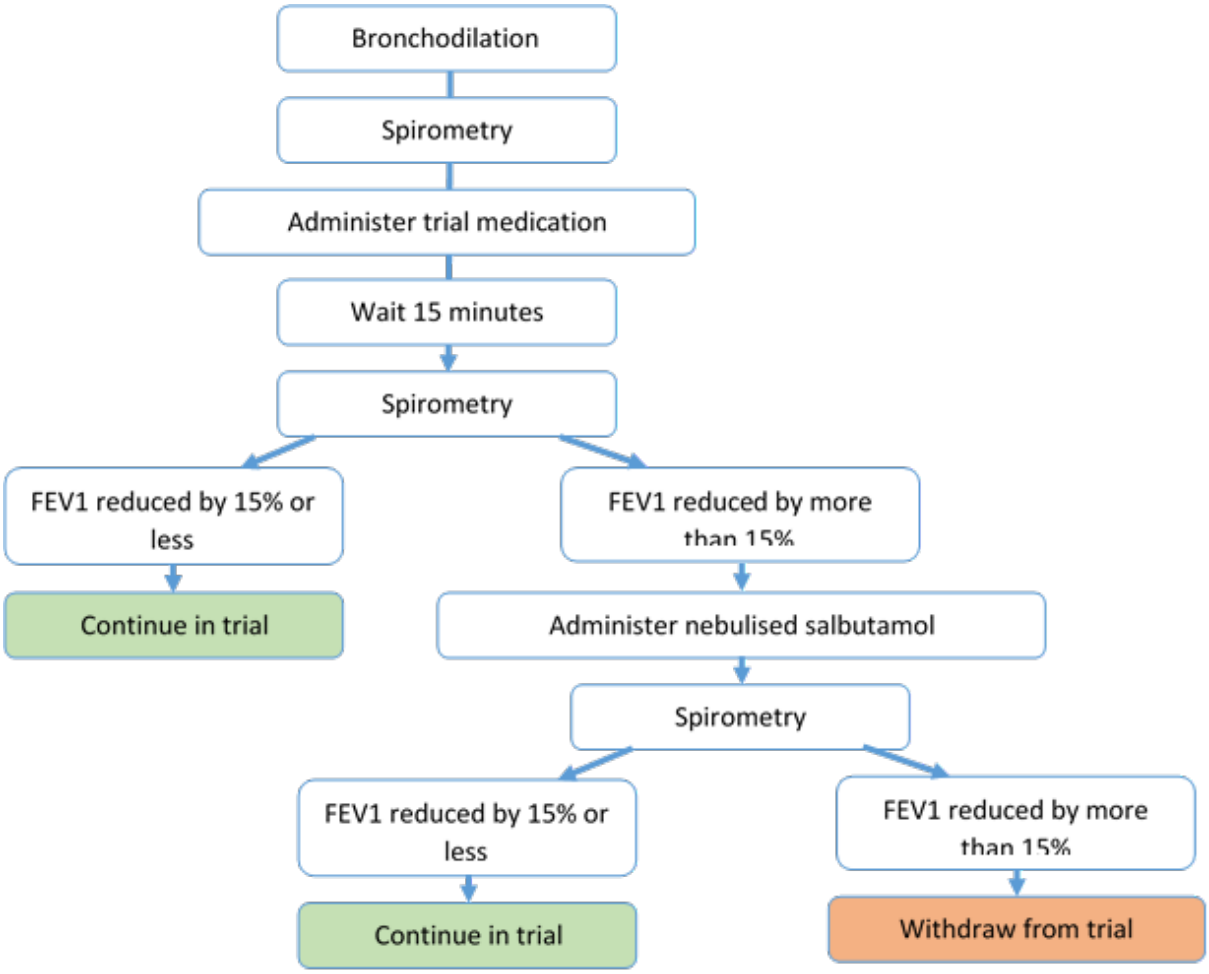
A new nebuliser handset should be used for each 28-day cycle of treatment, these will be supplied along with their trial medication from pharmacy. Handsets should be disposed of at home by the participant or in clinical waste at the hospital via the research team. They should not be returned to pharmacy.

Participants must be shown how to use the nebuliser and handset during the administration of the first dose of trial medication at visit 2 see Trial Medication Guide.

10.3 First dose of trial medication

It is possible that participants may experience bronchospasm with the trial medication therefore participants will receive their first dose of trial medication at visit 2. Research staff could keep the empty vial from the first dose in the box for accountability purposes.

The first dose of trial medication should be given to the participant at visit 2. The process should follow the flow diagram below:



- After randomisation collect allocated trial medication from Clinical Trial Pharmacy.

Show the participant the video “Setting up your Altera nebuliser system for use with Cayston” (from 28 sec to 2 mins 49 sec only)

- Ask the participant to set up their nebuliser system as per video and Trial Medication Guide.

Show the participant the video “Mixing and storing your Cayston” (From 1 min 11 secs to 2 min 46 secs only)

- Ask the participant to prepare their first dose of trial medication as per video and Trial Medication Guide.

Show the participant the video “Using Cayston in your Nebuliser” (from 28 secs to 3 min 11 secs only)

- Perform bronchodilation and spirometry as per WPG
- Ask the participant to take their trial medication as per video and Trial Medication Guide.
- After their nebuliser is finished wait 15 minutes

- Perform spirometry.

Post bronchodilation and post dosing spirometry should be recorded in the CRF and participant's medical notes.

If the change in FEV1 from pre-dosing spirometry is greater than 15% the participant can continue in the trial.

If the change in FEV1 from pre-dosing spirometry is less than or equal to 15% spirometry should be repeated.

If the change in the second FEV1 from pre-dosing spirometry is less than or equal to 15% the participant should be withdrawn from the trial.

Explain storage of trial medication to participant. Trial medication should be kept in the fridge but may be out of the fridge for up to 28 days at room temperature, less than 25C.

Show participant the video "Cleaning and disinfecting your Altera nebuliser handset" (from 28 secs to 3min 17 secs only).

Video links:

https://www.cayston.com/resources/forms-videos-links

Scroll down to video links and click on: How Cayston and the Altera nebuliser work.

10.4 **Storage**

The trial medication should be stored in a fridge; however, it can be stored out of the fridge for up to 28 days at temperatures less than 25C. The participant should store it in their own domestic fridge, no temperature monitoring is required.

Discuss trial medication storage with the participant. Where a participant is taking home trial medication which will not be used within the next 28 days e.g. next treatment cycle, or given enough trial medication for several treatment cycles confirm if they have sufficient fridge storage space for the trial medication.

If a participant does not have enough storage space for their trial medication their trial medication should be kept in the Clinical Trial Pharmacy and they should receive the trial medication on the first day of their next treatment cycle. The trial medication can be collected by the participant in person, or couriered to them

Where a participant is not able to receive the trial medication at the time of their research visit or is not able to collect the trial medication in person it is acceptable for the trial medication to be delivered to the participant's home provided there is a local SOP in place for this and this is followed. Temperature monitoring during delivery is not required, however, delivery to a participant must be same day delivery and the time from removal from the pharmacy fridge to delivery to participant must be minimized.

10.5 **Requesting trial medication**

Once a participant has been randomised the Clinical Trial Request Form should be generated and printed from TRuST. The Request Form should be completed by filling in the participant's name, participant ID number and hospital/CHI number.

The Clinical Trial Request Form should then be signed by the PI (or delegated doctor) and dated. The Clinical Trial Request Form should only be signed by those doctors delegated on the Delegation Log to sign the request forms.

The request form should then be taken to the Clinical Trial Pharmacy and trial drugs collected as per usual local practice. The request form should be filed in the PSF.

10.6 Further supplies

A Clinical Trial Request form should be generated from TRuST, see TRuST User Guide, and appropriate packs given to participant.

A new handset should be provided for each 28-day supply, this will be supplied with trial medication from pharmacy.

The participant should be reminded of how the trial medication should be stored and when they should start their trial medication.

Participants should be phoned before they are due to start their next treatment cycle to remind them.

10.7 Trial medication Compliance

The research staff should reinforce the need for continuing with the trial medication at each visit.

All participants should be asked to return all trial medication vials including empty vials.

Returned trial medication vials should be taken to the Clinical Trial Pharmacy where they will be counted by the Clinical Trial Pharmacy team. Research staff are not required to count returns.

Participants should be asked about compliance at each visit and encouraged to continue with the trial medications as required.

10.8 Loss of trial medication

If a participant loses any of their trial medication this can be reordered using TRuST and a new supply requested, see TRuST user guide.

10.9 Discontinuation of trial medication

See section 8.10.

11. Concomitant Medications

11.1 Concomitant medication pages

All current medication at visit 1 should be recorded on the Concomitant Medications Page of the CRF. Participants should be asked at each visit about concomitant medications and the Concomitant Medications Page updated as necessary.

Abbreviations should not be used.

11.1.1 Respiratory Medications

Medications should be recorded using the **brand** name.

Include the name, dose, number of puffs (if applicable) and frequency of administration. Indicate if the medication was ongoing at the start of the trial or if commenced during the trial period add a start date. Indicate if medication was ongoing at the end of the trial or if stopped during the trial then enter the date stopped.

11.1.2 Other medications

Medications should be recorded using the **generic** name.

Indicate if the medication was ongoing at the start of the trial or if commenced during the trial period add a start date. Indicate if medication was ongoing at the end of the trial or if stopped during the trial then enter the date stopped.

Ingredients of combined medications should be listed separately e.g. for Codydramol list separately as codeine, paracetamol.

11.2 At Visit 1

11.2.1 Excluded medications

If participants are taking the following medications they should not be enrolled into the trial.

- Antibiotics within the past 28 days, apart from oral macrolides which are permitted if they have been used for at least 3 months prior to randomization.
- Inhaled, systemic or nebulized anti-Pseudomonal antibiotics in the 28 days prior to randomization
- Replacement immunoglobulin
- Use of any investigational drugs within five times of the elimination half-life after the last trial dose or within 30 days, whichever is longer.

If the participant agrees they may be re-screened for the trial after a period of 28 days free from receiving antibiotics.

12. Trial Samples

12.1 Trial samples

Trial samples should be obtained and processed according to the Laboratory Manual.

13. Pulmonary exacerbations

If a participant experiences a pulmonary exacerbation the following needs to be completed:

- Unscheduled visit
- Exacerbation record form
- Number of exacerbations since last visit

Pulmonary exacerbations do not need to be recorded as adverse events unless they are classified as serious adverse events. Serious adverse events due to pulmonary exacerbation do not need reporting to Sponsor unless they are thought to be caused by the trial medication.

Admitted to hospital	Related to trial medication	Record on exacerbation record form	Complete unscheduled visit	Record on AE Log	Complete SAE form
NO	NO/YES	YES	YES	NO	NO
YES	NO	YES	YES	YES	NO
YES	YES	YES	YES	YES	YES

13.1 Unscheduled visits

Unscheduled visits should be arranged when a participant informs the research staff of a pulmonary exacerbation, change in symptoms or requires clinical review.

Where a participant is unable to attend for an unscheduled visit, the research staff should complete as much information on the unscheduled visit pages of the CRF and an exacerbation form if appropriate by phone.

Where a participant attends for an unscheduled visit and their next scheduled visit is within 7 days the scheduled visit will be rearranged for 7 days following the participant's recovery from the exacerbation. The participant should continue to take their trial medication according to their treatment regimen.

13.2 Exacerbation record form

Every time a participant has a pulmonary exacerbation an Exacerbation Record Form should be completed. This is to identify whether the event is classified as a protocol defined exacerbation, non-protocol defined exacerbation or not an exacerbation.

13.3 Number of exacerbations

The number of exacerbations that a participant has between scheduled visits should be entered in the scheduled visit eCRF.

14. Adverse Events (AE) / Serious Adverse Events (SAE)

The research staff are responsible for the documentation of all AEs and SAEs.

It is the PI or delegated doctor's responsibility to assess the seriousness, causality, severity and expectedness of AEs and SAEs.

All SAE forms must be signed by the PI. If the PI is not immediately available these can be signed by a delegated doctor although the PI should counter sign at the soonest possible time.

All observed or volunteered SAE and AE must be recorded.

Participants should be instructed to contact the research staff after consenting to join the trial if any symptoms develop.

14.1 Defining AEs & SAEs

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this 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.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious
Serious Adverse Reaction (SAR)	An adverse reaction, defined in the RSI, which is serious, as defined above.
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.

Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs.

Pulmonary exacerbations do not need to be recorded as adverse events unless they are classified as serious adverse events. Serious adverse events due to pulmonary exacerbation do not need reporting to Sponsor unless they are thought to be caused by the trial medication.

14.2 Detecting AEs and SAEs

The research staff should ask about the occurrence of AE/SAE at every visit during the trial.

Open-ended and non-leading verbal questioning of the participant should be used to enquire about AE/SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens.

If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

14.3 Evaluating & Recording AEs & SAEs

All AEs must be recorded from the time a participant consents to join the trial until the last trial visit.

The research staff should record each AE individually on the AE Log of the CRF.

The research staff should pursue and obtain information adequate to confirm whether it meets the criteria for classification as a SAE. If unsure as to whether an AE should be classified as a SAE the Research staff should consult the PI or delegate.

Unless resolved every AE should be reviewed at each visit:

- Assess if still ongoing or now resolved
- Assess if action taken has been changed
- Assess if diagnosis has been made/changed

Participants with unresolved AEs at the last trial visit must be followed up until resolution or 30 days after last visit of that participant whichever is sooner. If a participant has an ongoing AE at the last visit let them know that you will phone them in 30 days, can be sooner if you expect the AE to be resolved sooner.

SUSARS will be must be followed up until resolved.

Details of any AE and any consequential treatment implemented or changes to trial medication must be recorded in the participants' medical notes.

The participant's GP should be informed if it is felt necessary, ask the participant's permission.

Seriousness, causality, severity and expectedness should be evaluated by the PI or delegated doctor.

Seriousness, causality, severity and expectedness should be evaluated as though the participant is taking active drug.

14.4 Evaluating, Recording & Reporting of SAE/SAR/SUSAR

All SAEs should be recorded in the AE Log.

Once any member of research staff becomes aware that a potential reportable SAE has occurred, they must report the information to the CI and TASC Pharmacovigilance Section within 24 hours as per TASC SOP 11.

SAE reporting

The SAE form and reporting procedure (TASC SOP 11) is available via this link TASC SOPs and templates: Pharmacovigilance and Investigational Medicinal Products | University of Dundee

The SAE reporting system: https://hicservices.dundee.ac.uk/Pharmacovigilance/

Always go to the link provided to access the SAE form as it could be that a new version of the form has been added and this would be the most current version of the form that the SAE would need reporting on. Research staff should complete the SAE form as thoroughly as possible with all available details of the event. The completed from should be printed, reviewed and signed by the PI or delegated doctor and **must be e-mailed to** TAY.pharmacovigilance@nhs.scot **j.chalmers@dundee.ac.uk and the Clinical Trial Manager via respiratorytrials@dundee.ac.uk within 24 hours.** The signed form should be filed in the ISF.

The link to the SAE form is also available via the Staff Portal of the VitalBE website (www.vitalBE.org.uk) where it can be completed electronically.

When a SAE occurs, the research staff should ensure that all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event is reviewed. The research staff should then record all relevant information in the AE log and on the SAE form.

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

Where the PI delegate signs the SAE form the PI should be informed of the SAE when available and the PI should counter sign the SAE form.

If all the required information is not available at the time of reporting, the research staff must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

Assessment of Causality

The PI or delegated doctor must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

Unrelated: where an event is not considered to be related to the trial drug.

Possibly: although a relationship to the trial drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug.

Definitely: The known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that trial drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the trial drug will be considered as ARs/SARs.

All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the trial drug and another drug will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Severity

The PI or delegated doctor should make an assessment of severity for each AE/SAE and record this on the AE Log/SAE Form according to one of the following categories:

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

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

Severe: an event that prevents normal everyday activities.

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

Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and relevant Summary of Product Characteristics (SmPC). A copy of the SmPC can be found in the ISF.

Data Entry

Data from the paper AE Logs should be entered into OpenClinica or uploaded to LabKey as appropriate.

Data on the AE Log **must** match the details on the SAE form.

Adverse Events / Serious Adverse Events Associate Documents

The latest versions of all documents including WPGs can be found your ISF.

Link to the TASC SOP 11 Identifying, recording and reporting adverse events for clinical research:
https://www.dundee.ac.uk/tasc/researchers/policies-sops-templates/sopstemplates/pv-imp/

SOPs should not be printed out to ensure the most up-to-date version is used.

15. Discontinuation of trial medication, withdrawal from trial and completion of trial activities

15.1 Visit 1 - Screening

Participants must meet the inclusion and exclusion criteria stated in the CRF to allow them to continue in the trial and attend Visit 2 – randomisation.

Participants who fail screening should be withdrawn from the trial.

15.2 Prior to randomisation

If the participant has a pulmonary exacerbation requiring treatment with antibiotics the participant should be withdrawn. The PI or delegated doctor should assess if there is a clinical need for the participant to attend for an unscheduled visit at this point.

The randomisation visit must occur within 35 days of the screening visit. If the randomisation visit is more than 35 days after the screening visit the CI must confirm it is still ok for the participant to be randomised and this must be recorded in the CRF and participant's medical notes. The reason for allowing randomisation in this situation must be documented.

The inclusion and exclusion criteria stated in the CRF must be checked again. Ensure that the timelines within the inclusion and exclusion criteria are calculated from the day of visit 2, randomisation not visit 1, screening.

15.3 Re-screening

Where participants fail screening due to a reason which is modifiable can be rescreened. Examples:

- Participants who have had a pulmonary exacerbation within 28 days can be rescreened after 28 days from day of last symptom
- Participants with recent use of an investigational drug can be rescreened after 30 days or five times of the elimination half-life after the last trial dose if longer than 30 days.
- Participants with unstable co-morbidities can be rescreened if, in the opinion of the investigator, the co-morbidity becomes stable or resolves such that the participant could be included.
- Participants who fail to isolate *P. aeruginosa* or other Gram-negative pathogens at the screening visit may send further sputum samples between screening and randomization, until sputum cultures are positive. Once 35 days has elapsed, however, the participant should be regarded as a screen failure and would require to be rescreened in full.

If participants attend for a re-screening visit, they should be treated as new participants and given a new PIS, re-consented, given a new participant ID number and new CRF.

Once randomised if a participant is withdrawn or withdraws themselves from the trial, they **cannot** be re-screened.

15.4 After randomisation

After receiving their first dose of trial medication if a participant's change in FEV_1 from pre-dosing result is 15% or less nebulised salbutamol should be given and their FEV_1repeated. If their change in FEV_1 from pre-dosing result remains 15% or less the participant should be withdrawn from the trial.

15.5 During follow up

15.5.1 Adverse events

Side effects of Aztreonam are likely to be minor and expected in the majority of cases.

Participants may report cough, dyspnoea or wheezing post dose and should be told to take their bronchodilator prior to taking their trial medication.

Symptom management may include temporary discontinuation of the trial drug, which will be allowed in order to try to maintain participants in the trial. The drug may be discontinued for up to a total of 28 days during the year long course of treatment. Withdrawal from the trial will only be recommended when symptoms are severe, persistent, are determined by the investigator to be treatment related and cannot be managed with appropriate measures.

Lung function changes, other than after first treatment dose, are not an indication for discontinuation of trial treatment unless associated with severe and persistent symptoms which are treatment related and cannot be managed by the site.

The Investigator will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's discontinuation of treatment either temporarily or permanently. A participant may also voluntarily discontinuation of treatment either temporarily or permanently due to what he or she perceives as an intolerable AE.

15.5.2 Concomitant medications

Corticosteriods and mucoactive drugs:
Participants should not be started on corticosteroids (inhaled and systemic) or mucoactive drugs during the trial. However, if this is required clinically, the participant should continue in the trial and continue to take their trial medication.

Long-term antibiotics:
Participants should not be started on long-term antibiotics including macrolide treatment during the trial. If this is required clinically, the participant should continue in the trial but their trial medication should be discontinued permanently.

15.5.3 Pregnancy

Female participants:
All women of child-bearing potential will have a serum pregnancy test performed at the screening visit and a urine pregnancy test at each follow-up trial visit, if positive the participant should continue in the trial but their trial medication should be discontinued permanently. A Pregnancy Notification form should be completed and emailed to the Sponsor's pharmacovigilance team and copied to the CTM. Find the Pregnancy Notification Form and Pregnancy Follow-up forms here https://www.dundee.ac.uk/tasc/researchers/policies-sops-templates/sopstemplates/pv-imp/

The pregnancy will be followed up until the end of the pregnancy.

Male participants:
If a partner of a male participant becomes pregnant a Pregnancy Notification form should be completed and emailed to the Sponsor's pharmacovigilance team and copied to the CTM. Consent from the female partner should be sought and the pregnancy will be followed up until the end of the pregnancy

15.5.4 **Participant's choice**

Participants are free to withdraw from the trial at any time.

Where possible participants should be encouraged to carry on with trial visits even if they discontinue their trial medication.

15.5.5 **Loss of capacity**

For adults who lose capacity their previous wishes will be followed, 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, an appropriate person will be asked for their consent. This will be fully documented in the participant's notes.

In all cases the CI 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.

15.6 **Temporary discontinuation of trial medication**

The trial medication may be discontinued for clinical reasons for up to a total of 28 days during the year long course of treatment.

Record the number of days the trial medication has been discontinued since last visit and in total in the CRF.

Reasons for temporary discontinuation of trial medication other than clinical reasons e.g. participant forgets should not be entered in the eCRF and does not count to towards the maximum discontinuation of 28 days.

The reason and duration of temporary discontinuation should be noted in the participant's medical notes.

15.7 **Permanent discontinuation of trial medication**

Where a participant is either instructed to or chooses to discontinue their trial medication they should be encouraged to attend for all follow-up visits.

When participants permanently discontinue their trial medication but continue in the trial the Discontinuation Trial Meds page should be completed in the CRF.

Once permanently discontinued from trial medication participants cannot re-start it.

15.8 **Withdrawal from trial**

Where a participant withdraws from the trial early, they will be offered an end of trial assessment.

The trial the Completion of Trial page should be completed in the CRF.

If participants withdraw from the trial and do not wish to return for trial visits, contact with them will be maintained by the research staff for 30 days after the participant's last visit if required to follow up on-going AEs.

15.9 **Completion of trial**

The participant must be assessed by a doctor on the delegation log.

Changes to participant's medications and any other actions must be documented in the participant's medical notes and their GP informed, with consent from the participant.

The Completion of Trial page should be completed in the CRF.

If participants have on-going AEs/SAEs contact with them will be maintained by the research staff for 30 days after the participant's last visit. SUSARS will be followed to resolution.

16. Data Entry

Castor Data Management System (DMS)

Castpr is the data DMS for the VitalBE trial. It is the responsibility of research staff at each site to ensure all participant data is entered to the data base. Data should be entered into Castor within 2 weeks of the participant's visit.

Castor training for all staff delegated this role on the Delegation Log must be completed prior to having access to the live DMS. Completion of this training should be entered into the Site Specific Training Log.

See Castor Users Guide for detailed use of the system.

17. Trial monitoring

Trial monitoring will be carried out by the sponsor: University of Dundee/NHS Tayside

Monitoring will be a combination of site visits and remote monitoring, but most will take place as a remote visit. Monitoring visits will be carried out at regular intervals to maintain oversight of sites. Higher recruiting sites may be asked to undertake monitoring visits more frequently.

The Sponsor Monitoring Team will contact sites to arrange the visit.

17.1 Monitoring Visit Schedule

Site initiation – prior to first participant first visit at each site.

After recruitment of 1-5 participants, at 12 months and 24 months depending on the number of participants recruited at site and performance of the site.

Additional on-site monitoring visits may be arranged if it is felt that this is necessary.

Close out – after the last participant last visit at each site and all data queries have been resolved.

See Monitoring Plan, a copy can be found in the ISF Section 14.

If any issues are raised during the remote monitoring review, discussion with the site and the Clinical Trial Manager will take place to resolve these issues.

Any major issues resulting from this process may trigger a site monitoring visit.

Additional monitoring visits will be performed if required throughout the trial.

17.2 Documents to be monitored

Investigator Site File.

Informed Consent Forms – 100%.

Source document verification of critical data (endpoint data, dose adjustments, concomitant medications).

Source document verification of adverse event reporting (AE, SAE, SUSAR) – 100%

Source document verification of eligibility

Trial medication management

18. Protocol and GCP Breaches

18.1 Definitions

A protocol breach is an accidental or unintentional change to, or non-compliance with the approved research protocol which may increase risk or decrease benefit or may have a significant effect on the participant's rights, safety or welfare; and/or on the integrity of the data. Breaches may result from the action of the participant, researcher, or research staff. Examples:

A rescheduled trial visit.

Failure to collect an ancillary self-report questionnaire.

Failure to obtain valid informed consent (e.g., obtained informed consent on an incorrect version of the Informed Consent Form).

Loss of laptop computer that contained identifiable, private information about participants.

Accidental distribution of incorrect trial medication or dose.

Not following inclusion/exclusion criteria.

A serious protocol breach is a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or (b) the scientific value of the trial. Examples:

Persistent non-compliance with GCP or protocol.

Fraud relating to clinical trial records or data.

Breach leading to the death, hospitalisation or permanent disability of a trial participant

Failure to report serious adverse events.

Lack of essential approvals.

18.2 Recording & Reporting Breaches

All protocol breaches should be recorded in the Breach Log as soon as a member of the research team is aware of them.

The PI should be informed of all breaches.

The research staff will complete the online breach form.

The report should include a brief description of the breach, reason for the breach and any corrective and preventative actions already taken (Corrective Action and Preventative Action, CAPA).

The Breach Report will be reviewed by Sponsor and if further corrective and preventative actions are required these will be discussed between the site, research team, Sponsor and MHRA (if applicable).

The breach should be added to the site breach log, and the closed report filed in the ISF

19. Standard Operating Procedures and Working Practice Guidelines

As a condition of co-sponsorship by University of Dundee and NHS Tayside all trial sites will use TASC mandatory SOPs (see Table section 17.2 below).

Please review the Sponsor specific SOPs, once the PI and site staff have reviewed the SOPs please sign/date the Trial Training Log (to be filed in the Investigator Site File).

19.1 VitalBE WPGs

All trial assessments should be carried out according to the VitalBE Working Practice Guidelines:

19.2 TASC SOPs

TASC SOP 11	IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR CLINICAL RESEARCH TASC SOPs and templates: Pharmacovigilance and Investigational Medicinal Products | University of Dundee SAE reporting https://hicservices.dundee.ac.uk/Pharmacovigilance/
TASC SOP 59	REPORTING BREACHES IN CLINICAL RESEARCH TASC SOPs and templates: Study in progress | University of Dundee