Introduction

AIR-NET: Testing anti-inflammatories for the treatment of bronchiectasis

A randomised, open-label, multifactorial, multicentre, platform trial using a range of repurposed anti-inflammatory treatments to improve outcomes in patients with bronchiectasis within the EMBARC clinical research network.

CI: Professor James Chalmers, University of Dundee

Trial Management: Tayside Clinical Trials Unit, University of Dundee

Sponsor: University of Dundee & NHS Tayside

BACKGROUND

- Bronchiectasis is a debilitating chronic respiratory disease characterised by cough, sputum production and associated with a vicious cycle of lung inflammation and infection
- The dominant mechanism of disease in bronchiectasis is chronic neutrophilic inflammation
- The purpose of this platform trial is to repurposing anti-inflammatory therapies in bronchiectasis to investigate therapeutic targets

PRIMARY OBJECTIVE

- To evaluate the effect of a range of interventions compared to usual care on the activity of neutrophil elastase in sputum

Outcome Measure:
Activity of sputum NE

Timepoint(s)
Day 0 and 28

Secondary Objectives	
Objectives	Outcome Measures
To evaluate the effect of a range of interventions compared to usual care on the activity of NE in sputum	Activity of sputum NE
To evaluate the effect of a range of interventions compared to usual care on time to onset of first bronchiectasis exacerbation	Time to first pulmonary exacerbation (EMBARC definition)
To evaluate the effect of a range of interventions compared to usual care on quality of life	Quality of life-bronchiectasis (QOL-B) respiratory symptom scale, Bronchiectasis Impact Measure (BIM) questionnaire
To evaluate the effect of a range of interventions compared to usual care on walking distance	Distance covered during 6-minute walk
To evaluate the safety of a range of interventions compared with usual care	Frequency of adverse events (AEs) and serious adverse events (SAEs)
To evaluate the effect of a range of interventions on peripheral blood neutrophil function	Phagocytosis of bacteria Reactive oxygen species generation Degranulation Ex-vivo formation of neutrophil extracellular traps Mass cytometry (endpoints may vary depending on the experimental arm)

Sub-Study Objectives	
Objectives	Outcome Measures
To evaluate the effect of a range of interventions compared to usual care on endothelial dysfunction	Change in skin perfusion with iontophoresis of acetylcholine and sodium nitroprusside using laser doppler perfusion imaging
To evaluate the effect of a range of interventions compared to usual care on the cardiovascular system	Change in arterial stiffness index Change in pulse wave velocity

Treatment allocation

Participants will be randomised to one of four treatment arms:

		Dosage, form and strength	
Arm 1	Usual care	N/A	
Arm 2	Disulfiram	Two 200 mg oral tablets, once daily	
Arm 3	Dipyridamole	One 200 mg oral prolonged/modified release capsule, twice daily	
Arm 4	Doxycycline	One 100 mg oral capsule, once daily	

Treatment cycle will be 28 days.

IMPs

- **Disulfiram**

Blocks the body's usual routes to break down alcohol and is currently licensed to treat alcohol dependence. Disulfiram has anti-inflammatory properties.

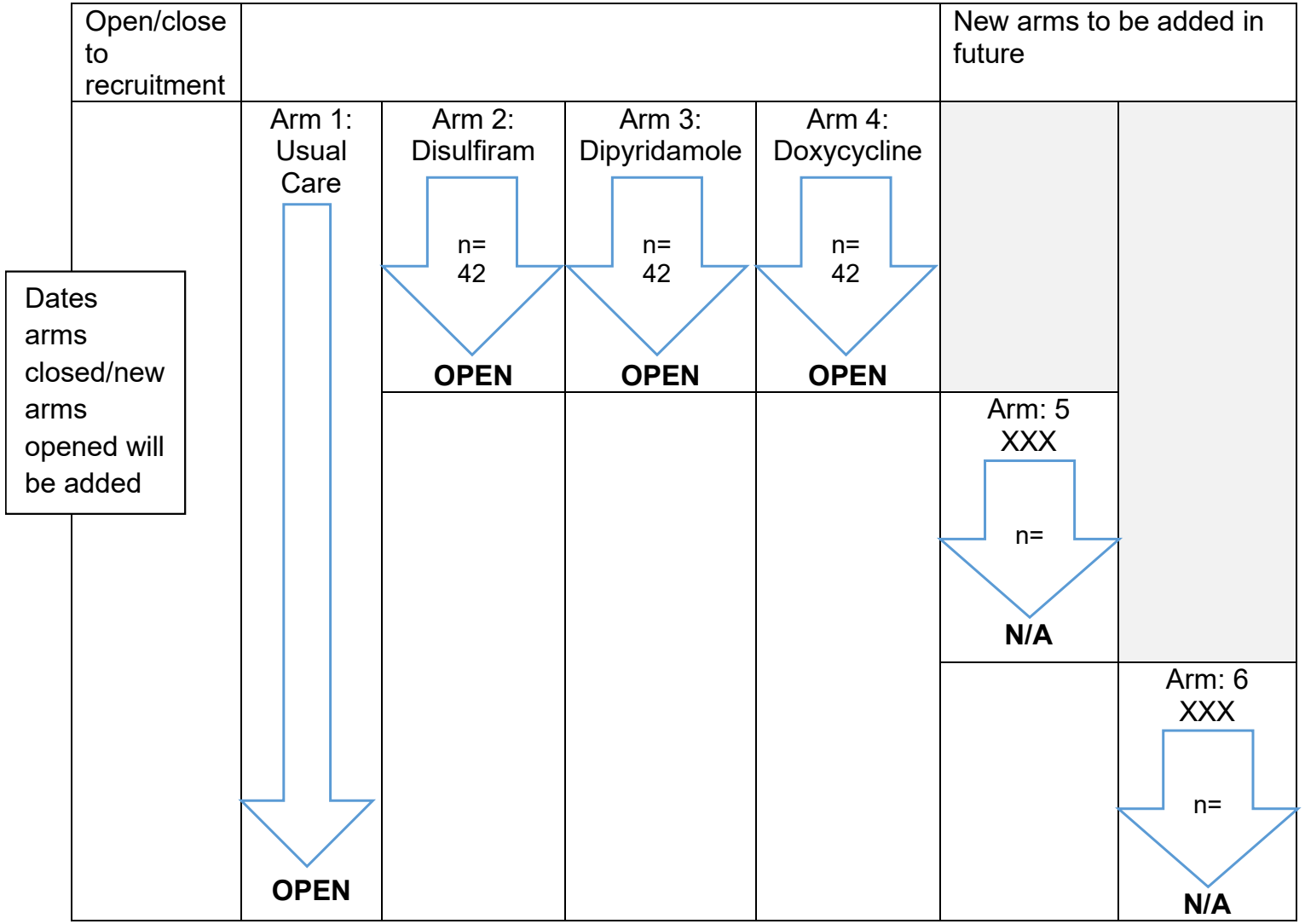
- **Dipyridamole**

Is a blood thinner that is currently licensed to prevent blood clots and strokes. Dipyridamole has anti-inflammatory properties.

- **Doxycycline**

Is an antibiotic with anti-inflammatory properties that is used to treat a range of bacterial infections, including bronchiectasis exacerbations.

Adding new treatment arms



AIR-NET

Identifying participants, pre-screening & eligibility

Participant Identification & Pre-screen

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

- From secondary care via contact with participants at specialist respiratory clinics or pulmonary rehabilitation classes.

- 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.

- Recruitment of participants registered via the Scottish Health Research Register (SHARE)

- From primary care via the Primary Care Networks.

Participant Identification & Pre-screen

Potential participants identified from clinic lists:

- Clinical team will review the patient's medical notes to see if they are potentially eligible (Pre-screen)
- If identified at clinic, a member of the clinical team will give the patient a copy of the brief Participant Information Sheet (bPIS).
- The clinical team will pass on potential participant details to the RNs
- Potential participant details added to pre-screening log

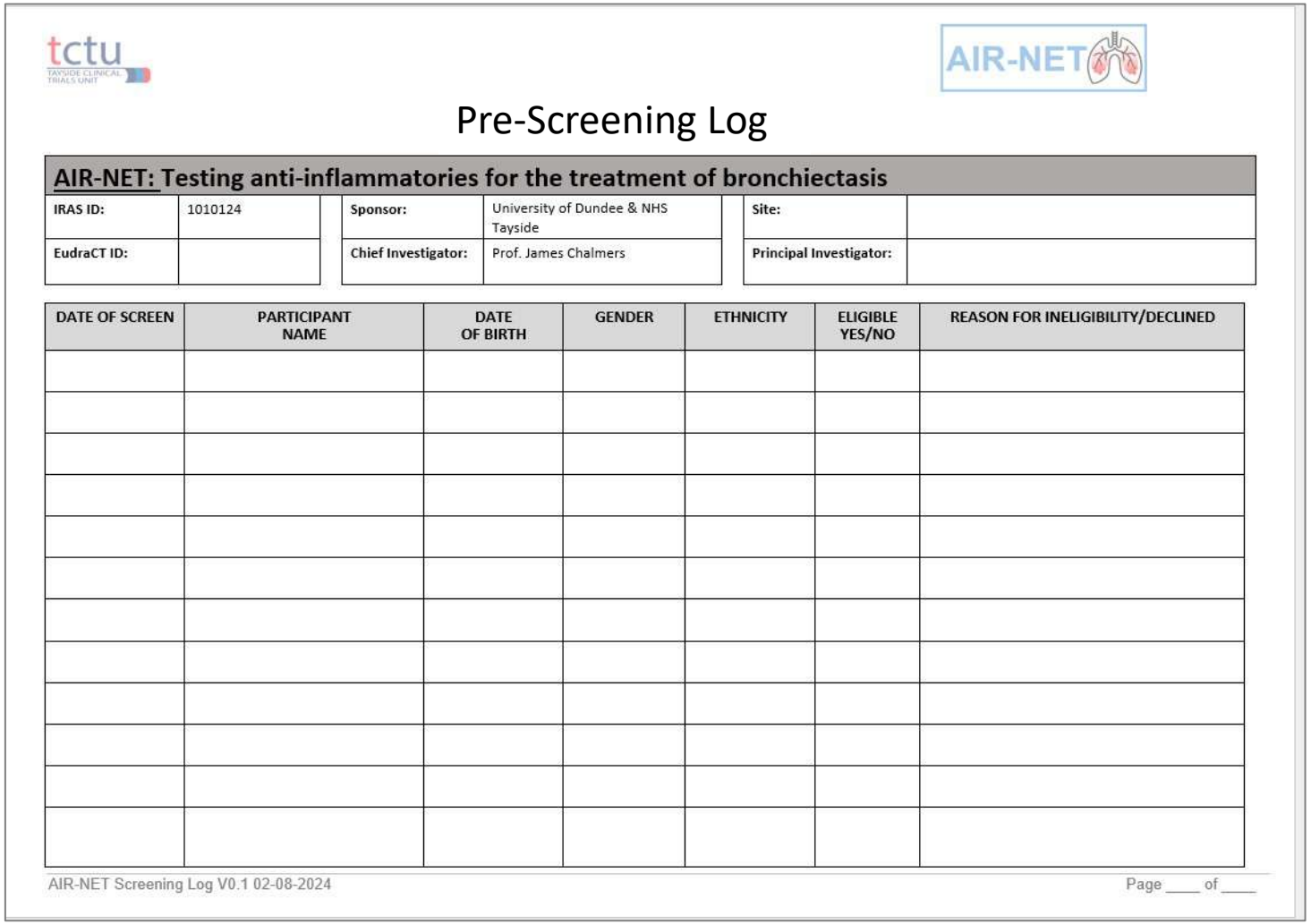
Potential participants identified from locally held databases/SHARE:

- RNs check the potential participants medical notes to see if they meet eligibility criteria
- Check screening log to ensure potential participant has not been approached in clinic
- Database invitation letter and PIS sent to potential participant
- Potential participant details added to pre-screening log

Potential participants identified from primary care via the Primary Care Networks.

- participants will be sent an invitation letter and bPIS from the GP practice. GP practices will also be asked to display bPIS in their waiting rooms

Pre-screening Log



tctu TAYSIDE CLINICAL TRIALS UNIT

AIR-NET

Pre-Screening Log

AIR-NET: Testing anti-inflammatories for the treatment of bronchiectasis

IRAS ID:	1010124	**Sponsor:**	University of Dundee & NHS Tayside	**Site:**	
EudraCT ID:		**Chief Investigator:**	Prof. James Chalmers	**Principal Investigator:**	

DATE OF SCREEN	PARTICIPANT NAME	DATE OF BIRTH	GENDER	ETHNICITY	ELIGIBLE YES/NO	REASON FOR INELIGIBILITY/DECLINED

AIR-NET Screening Log V0.1 02-08-2024 Page ____ of ____

Inclusion Criteria

- ≥ 18 years.
- Able to provide informed consent.
- Capable of complying with all trial procedures and of completing the trial, in the opinion of the investigator.
- Bronchiectasis, confirmed by computed tomography (CT), showing bronchiectasis in 1 or more lobes.
- Normally produces sputum daily.
- Able to provide a sputum sample at the screening visit or between screening and randomisation[a].
- Active neutrophilic inflammation at screening/baseline indicated by a positive NEATstik (Neutrophil Elastase Airways Test) result[b].

[a]Repeat sputum samples may be provided during the screening period, if the sample taken during the screening visit is deemed to be of insufficient quality or quantity by the laboratory.

[b]A positive NEATstik test is equivalent to a NE concentration of 8µg/ml in sputum using the Proaxsis active NE immunoassay. If NEATstik is not available for screening, a frozen sputum sample will be shipped to the central laboratory in Dundee where the immunoassay will be performed and used to confirm eligibility.

Exclusion Criteria

- Enrolled previously in the trial 3 times
- Respiratory infection or bronchiectasis exacerbation 4 weeks prior to screening and/or between screening and randomisation[c]
- Antibiotic or corticosteroid 4 weeks prior to screening and/or between screening and randomisation[c]
- Active allergic bronchopulmonary aspergillosis (defined by International Society for Human and Animal Mycology criteria) on steroids and/or anti-fungals
- Nontuberculous mycobacterial infection on antibiotic therapy
- Immunodeficiency on immunoglobulin replacement
- A primary diagnosis of COPD or asthma (a secondary diagnosis of COPD or asthma is permitted)
- Cystic fibrosis
- Active malignancy except non-melanoma skin cancer
- Currently taking brensocatib
- 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
- Currently pregnant or breast-feeding
- Women of childbearing age and not practicing an acceptable method of birth control

[c] *In the event of a respiratory infection or bronchiectasis exacerbation during the screening period, the screening period may be extended, once only by up to 8 weeks, to ensure that randomisation occurs at least 4 weeks after the last dose of antibiotics is given.*

Treatment Specific Exclusion Criteria

Arm 2: Disulfiram

- Currently on Disulfiram (patients should have a washout period of at least 30 days from last dose if they have previously received this medication)
- Hypersensitivity to Disulfiram
- Participant, or investigator objects to randomisation to Disulfiram
- Does not agree to cease consumption of alcohol during intervention and for 14 days following treatment discontinuation
- Chronic liver disease
- Alanine transaminase (ALT)>135 U/L at screening,
- Bilirubin >30 umol/L at screening.
- Uncompensated cardiac failure
- Coronary artery disease (diagnosis of stable or unstable angina, previous myocardial infarction)
- Previous history of stroke or transient ischaemic attack
- Uncontrolled hypertension
- Hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
- Recent psychiatric exacerbation
- Any significant acute or chronic psychiatric condition, including severe personality disorder, psychotic disorder or suicide risk.
- Hypothyroidism
- Porphyria
- Diabetes Mellitus
- Epilepsy

Treatment Specific Exclusion Criteria

Arm 3: Dipyridamole

- Currently on Dipyridamole (patients should have a washout period of at least 30 days from last dose if they have previously received this medication)
- Hypersensitivity to Dipyridamole
- Participant, or investigator, objects to randomisation to Dipyridamole
- Currently on dual antithrombotic therapy (aspirin or P2Y12 inhibitor plus anticoagulation)
- Current on direct oral anticoagulants (Dabigatran, Rivaroxaban, Edoxaban, Apixaban, Betrixaban or drugs in the same class) or long-term warfarin
- Any major trauma or haemorrhage including gastrointestinal bleeding, operation within the past 30 days
- Coagulation disorder
- Severe coronary artery disease (unstable angina, recent myocardial infarct in 30 days, decompensated/unstable severe left systolic dysfunction, uncontrolled heart failure)
- Myasthenia gravis

Treatment Specific Exclusion Criteria

Arm 4: Doxycycline

- Currently on Doxycycline (patients should have a washout period of at least 30 days from last dose if they have previously received this medication)
- Hypersensitivity to Doxycycline
- Participant, or investigator, objects to randomisation to Doxycycline
- Myasthenia Gravis
- Systemic Lupus Erythematosus
- Chronic Liver Disease
- Porphyria
- Alcohol dependence
- Suspected Syphilis

Enrolment Log

All participants who are consented and randomised should be added to the enrolment log.

Anonymised information on participants who are consented but not randomised will be collected for CONSORT reporting and includes:

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

Enrolment Log

ENROLMENT & RANDOMISATION LOG

AIR-NET: Testing anti-inflammatories for the treatment of bronchiectasis

IRAS ID:	1010124	**Sponsor:**	University of Dundee & NHS Tayside	**Site:**	
EudraCT ID:		**Chief Investigator:**	Prof. James Chalmers	**Principal Investigator:**	

PARTICIPANT NAME	DATE OF BIRTH	ADDRESS	CHI/HOSPITAL NUMBER	PARTICIPANT ID NUMBER	RANDOMISED YES/NO

AIR-NET Enrolment and Randomisation Log V0.1 02-08-2024 Page ____ of ____

Reporting Screening & Enrolment Figures to the Trial Management Team

- TMT will request monthly figures (no identifiable data will be requested, numbers only)
- TMT will compile Screening, Enrolment & Randomisation report for monthly TMG meeting

Trial Visits

All visits

• Participant Transport

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. This should be done as per local procedure e.g. from petty cash or by completing a travel expense form.

• Participant Identity

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

- Passport
- Driving licence
- Current matriculation card
- Young person's or senior citizen's railcard
- Proof of Address
- National Insurance Card
- CHI Number/Medical Card

All visits

Participant trial ID

- All participants consented to the trial should be allocated a participant ID number.
- Participant ID numbers are made up of five numbers:
- First two numbers to indicate the site and
- Last three indicate the participant number at that site.
- E.g. 01001 is the first participant at site one.
- Use participant ID numbers in order
- Ensure site ID is correct for your site.
- If participant fails screening, and does not go on to randomisation, their participant ID number should not be re-used.

Worksheets

- Worksheets are available to facilitate data collection
- Their use is not mandatory
- If worksheets are used to record source data, they must be filed in the medical notes.

Visit 1 Screening (-35 days to day 0)

- Informed Consent
- Eligibility check
- Demographics
- Medical history
- Con meds
- Physical Exam
- Height & weight
- Vital signs
- ECG
- Full blood count & research bloods.
- Sputum sample for eligibility & research
- Post bronchodilation spirometry
- Pregnancy test if applicable
- Questionnaires

Visit 1: BEST diary

Completion of BEST Diary

Participants have 3 options (discuss their preference and record this at visit 1 on the eCRF):

Complete the diary on the paper form
Complete the diary through Castor Connect App
Complete the diary online using a web browser
(participants will receive a daily email reminder via a weblink)

The diary is completed every day from day 0 (visit 2) to day 28 (visit 5)

Important points:
If the participant chooses to complete the diary online (either app or browser, you must collect their email address and add this to Castor **during visit 1**

You must enter visit 2 data (at a minimum the visit date) **on the day of the visit**
This is to allow the email notifications to be set up for the following day (day 1)

Visit 2 Baseline & Randomisation

- Continued Consent
- Eligibility check
- Record Con meds
- Record AEs
- Record any exacerbations
- Vital signs
- 6-minute walk test
- Research blood sample
- Research sputum sample
- Nasal sample
- Pregnancy test if applicable
- Questionnaires
- Randomisation
- Dispensing trial drugs

Visit 3 (day 7)

- Continued Consent
- Record Con meds
- Record AEs
- Record any exacerbations
- Vital signs
- Post bronchodilation spirometry
- Research blood sample
- Research sputum sample
- Pregnancy test if applicable
- Questionnaires

Visit 4 (day 14)

- Continued Consent
- Record Con meds
- Record AEs
- Record any exacerbations
- Vital signs
- Post bronchodilation spirometry
- Full blood count, urea and electrolytes, liver function test
- Research blood sample
- Research sputum sample
- Pregnancy test if applicable
- Questionnaires

Visit 5 (day 28)

- Continued Consent
- Record Con meds
- Record AEs
- Record any exacerbations
- Vital signs
- 6-minute walk test
- Post bronchodilation spirometry
- Full blood count, urea and electrolytes, liver function test
- Research blood sample
- Research sputum sample
- Nasal sample
- Pregnancy test if applicable
- Questionnaires
- Drug accountability

Visit 6 (day 56)

- Continued Consent
- Record Con meds
- Record AEs
- Record any exacerbations
- Vital signs
- Post bronchodilation spirometry
- Full blood count, urea and electrolytes, liver function test
- Research blood sample
- Research sputum sample
- Questionnaires

Safety Visits (as required)

Participants will be requested to attend an unscheduled safety visit if they experience a bronchiectasis exacerbation or any other safety concern

- Concomitant medications check
- Review/recording of adverse events
- Review/recording of exacerbations
- Vital signs
- Post bronchodilation spirometry
- Safety bloods
- Research bloods, as per lab manual
- Research sputum sample collection

Visit windows

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.

Visits 2,3,4 and 5 should be every 7 days. If a participant is unable to attend on the scheduled visit day, then a delay of up to 2 days is acceptable, after which it becomes a missed visit.

AIR-NET

Randomisation & Requesting IMP

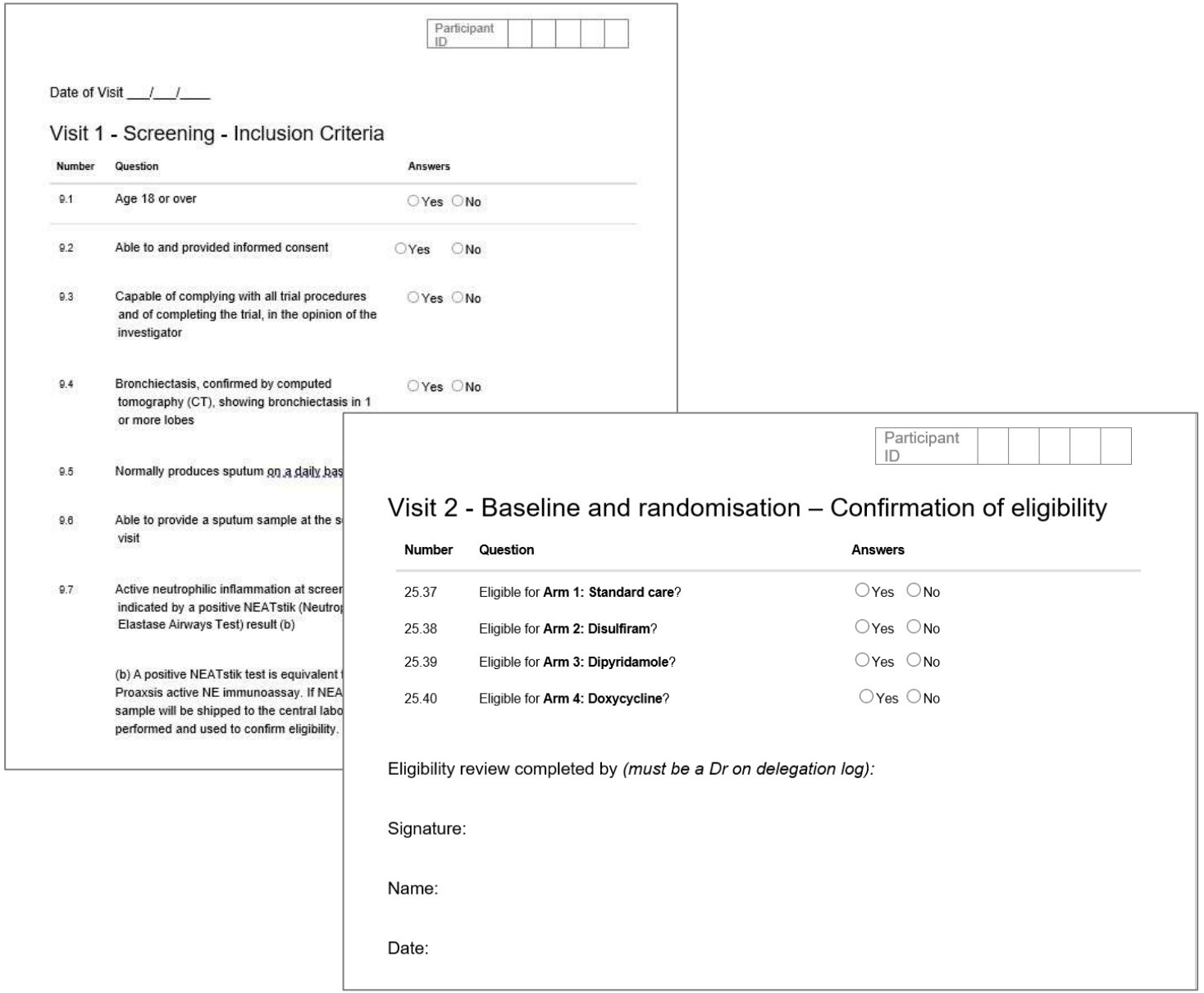
Randomisation Requirements

- Delegated to randomise on Delegation Log
- Randomisation training completed – this presentation documented on Training Log
- Eligibility Form reviewed & signed by PI/delegate
- Internet access
- TRuST log-in
- Participant ID
- Printer

Completion of Eligibility Form

Complete the paper eligibility form to determine which arm(s) the participant is eligible to be randomised to.

This must be reviewed & signed by a delegated doctor **before** randomisation takes place



Participant ID

Date of Visit ___/___/____

Visit 1 - Screening - Inclusion Criteria

Number	Question	Answers
9.1	Age 18 or over	○ Yes ○ No
9.2	Able to and provided informed consent	○ Yes ○ No
9.3	Capable of complying with all trial procedures and of completing the trial, in the opinion of the investigator	○ Yes ○ No
9.4	Bronchiectasis, confirmed by computed tomography (CT), showing bronchiectasis in 1 or more lobes	○ Yes ○ No
9.5	Normally produces sputum on a daily bas	
9.6	Able to provide a sputum sample at the s visit	
9.7	Active neutrophilic inflammation at screer indicated by a positive NEATstik (Neutro Elastase Airways Test) result (b)	

(b) A positive NEATstik test is equivalent Proaxsis active NE immunoassay. If NEA sample will be shipped to the central labo performed and used to confirm eligibility.

Participant ID

Visit 2 - Baseline and randomisation – Confirmation of eligibility

Number	Question	Answers
25.37	Eligible for **Arm 1: Standard care**?	○ Yes ○ No
25.38	Eligible for **Arm 2: Disulfiram**?	○ Yes ○ No
25.39	Eligible for **Arm 3: Dipyridamole**?	○ Yes ○ No
25.40	Eligible for **Arm 4: Doxycycline**?	○ Yes ○ No

Eligibility review completed by *(must be a Dr on delegation log)*:

Signature:

Name:

Date:

TRuST – Tayside Randomisation System

- Web-based randomisation system used by Research Nurses
- TRuST for AIR-NET will be used for randomisation only. Clinical trial pharmacy will perform IMP accountability, this will not be documented on TRuST.
- AIR-NET is unblinded, team members delegated randomisation and clinical trial pharmacy will receive the participant randomisation allocation
- The participant will also be made aware of their treatment allocation

TRuST Access

- TRuST can be accessed directly: https://trust.hicservices.dundee.ac.uk/Account/Login or from the AIR-NET website

- Login details for TRuST will be sent out after training has taken place. If not received, click on “Forgotten Password” and enter your email as your username.

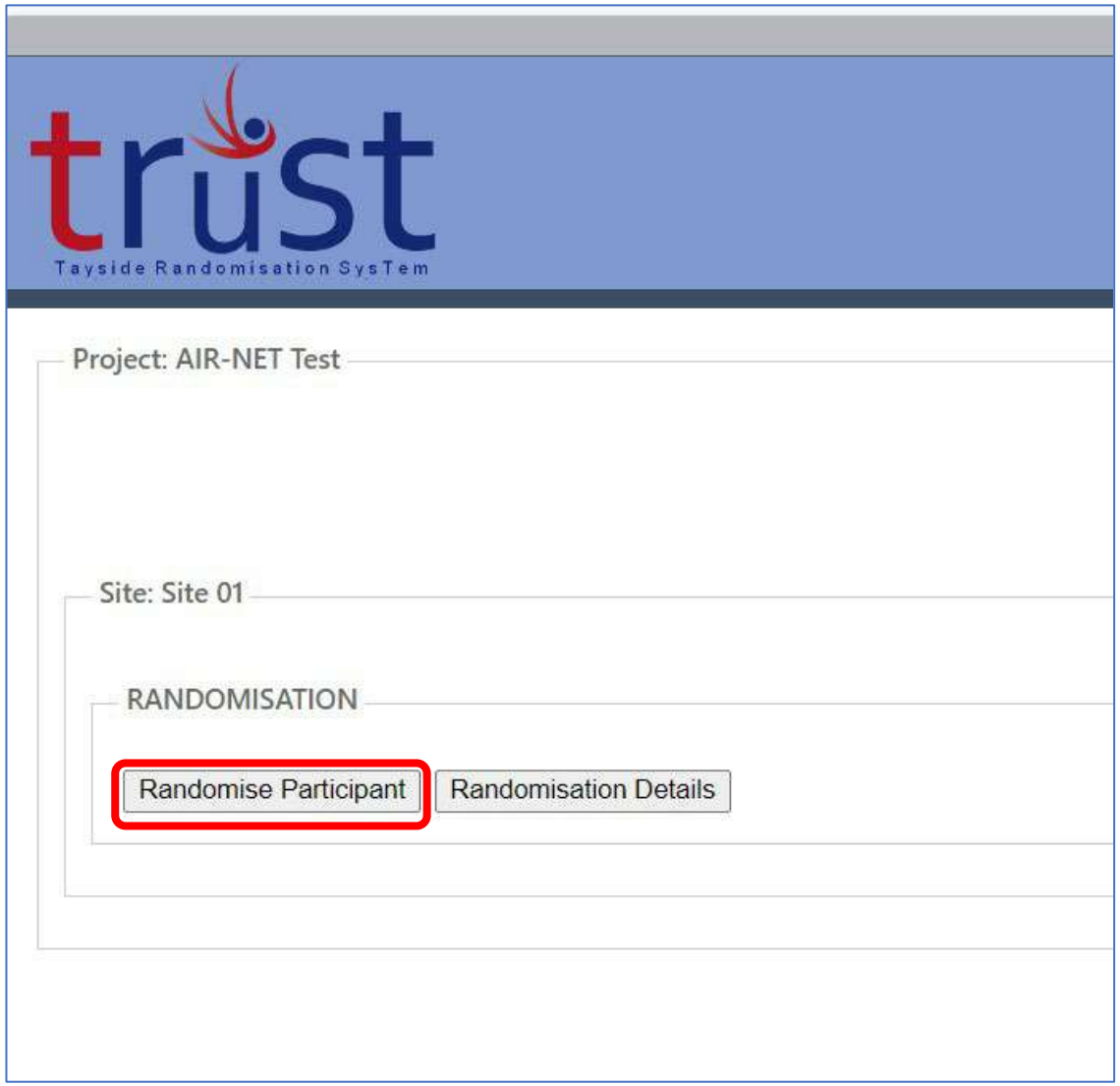
- Log in with your details; on first login you will be asked to change your password

- If you forget your password, click the forgotten password link and your new password will be emailed to you

For staff with multiple projects on TRuST select the AIR-NET trial from the dropdown menu.

Randomising a participant

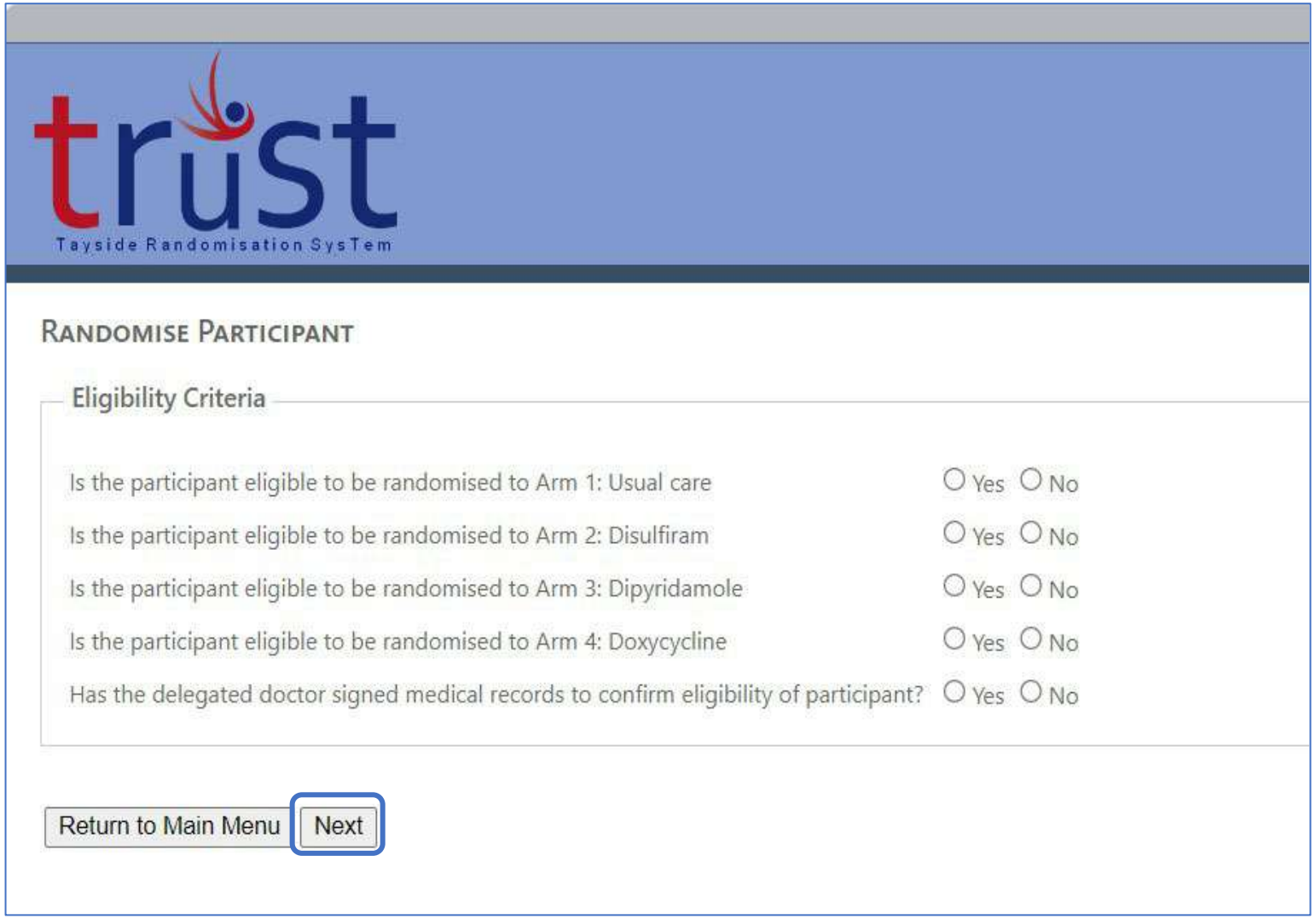
Click “Randomise Participant” button



Randomising a participant

Complete eligibility criteria questions from the paper Eligibility Form, and confirm this has been signed by a DR on the delegation log

Click on “Next” button



Randomising a participant

- Add participant ID (site ID is prepopulated)
- Complete stratification questions
- Completed consent must be “Yes”
- Eligibility must be “Yes”

Randomising a participant

When both consent form and eligibility criteria have been completed as “Yes” the “Randomise” button will appear.

Click on “Randomise” button

Randomising a participant

The screen will now display the randomisation allocation.

IMP Request/Release Form for Pharmacy

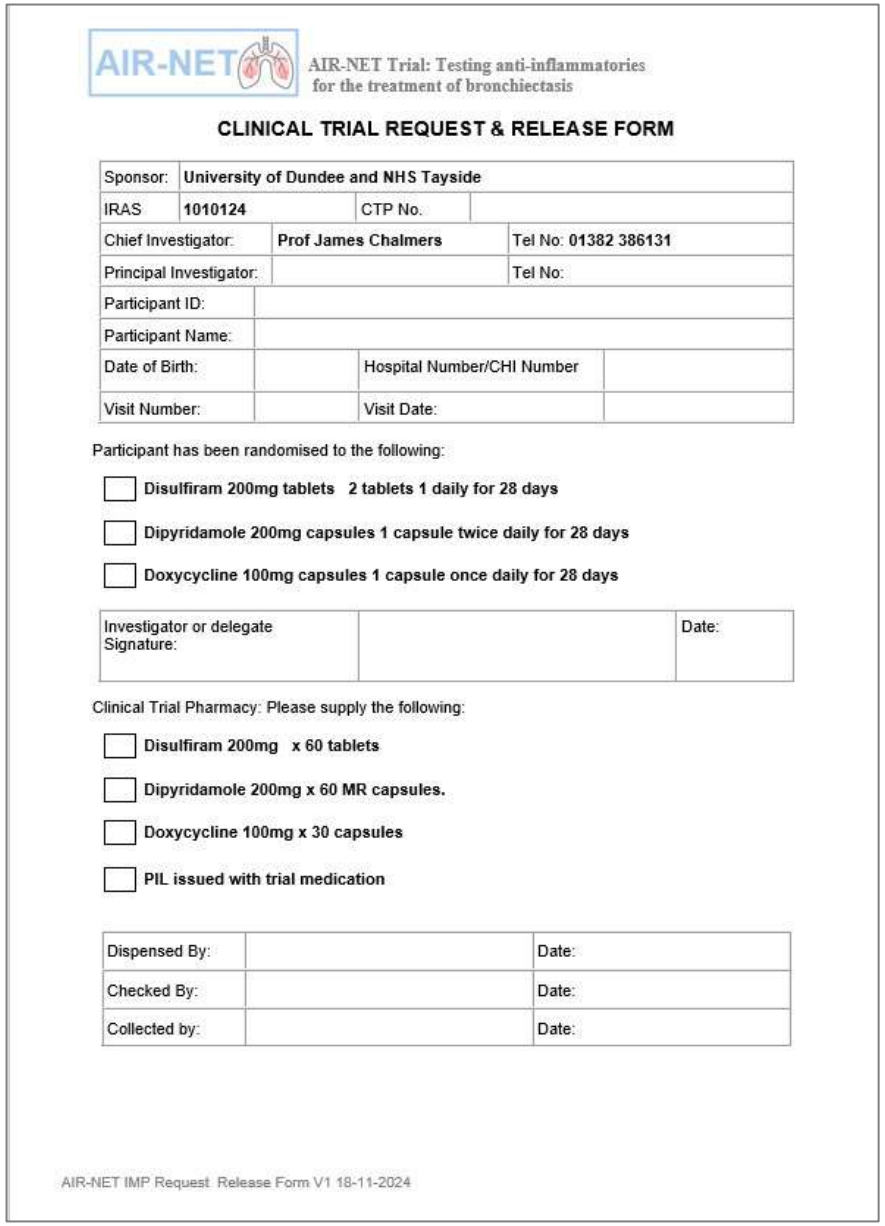
This form is not generated by TRuST

This form should be completed manually after a randomisation takes place. This is not required where a participant has been allocated to “usual care”

Research team to complete:

- PI details
- Participant & visit details
- Randomisation allocation
- PI/delegated doctor to confirm, sign & date

Provide this form to clinical trial pharmacy for dispensing
Document the research team member who collects the trial medication from pharmacy. Print a copy of the randomisation email and attached to the form.



AIR-NET

AIR-NET Trial: Testing anti-inflammatories for the treatment of bronchiectasis

CLINICAL TRIAL REQUEST & RELEASE FORM

Sponsor:	University of Dundee and NHS Tayside		
IRAS	1010124	CTP No.	
Chief Investigator:	Prof James Chalmers	Tel No: 01382 386131	
Principal Investigator:		Tel No:	
Participant ID:			
Participant Name:			
Date of Birth:		Hospital Number/CHI Number	
Visit Number:		Visit Date:	

Participant has been randomised to the following:

- ☐ Disulfiram 200mg tablets 2 tablets 1 daily for 28 days
- ☐ Dipyridamole 200mg capsules 1 capsule twice daily for 28 days
- ☐ Doxycycline 100mg capsules 1 capsule once daily for 28 days

Investigator or delegate Signature:		Date:

Clinical Trial Pharmacy: Please supply the following:

- ☐ Disulfiram 200mg x 60 tablets
- ☐ Dipyridamole 200mg x 60 MR capsules.
- ☐ Doxycycline 100mg x 30 capsules
- ☐ PIL issued with trial medication

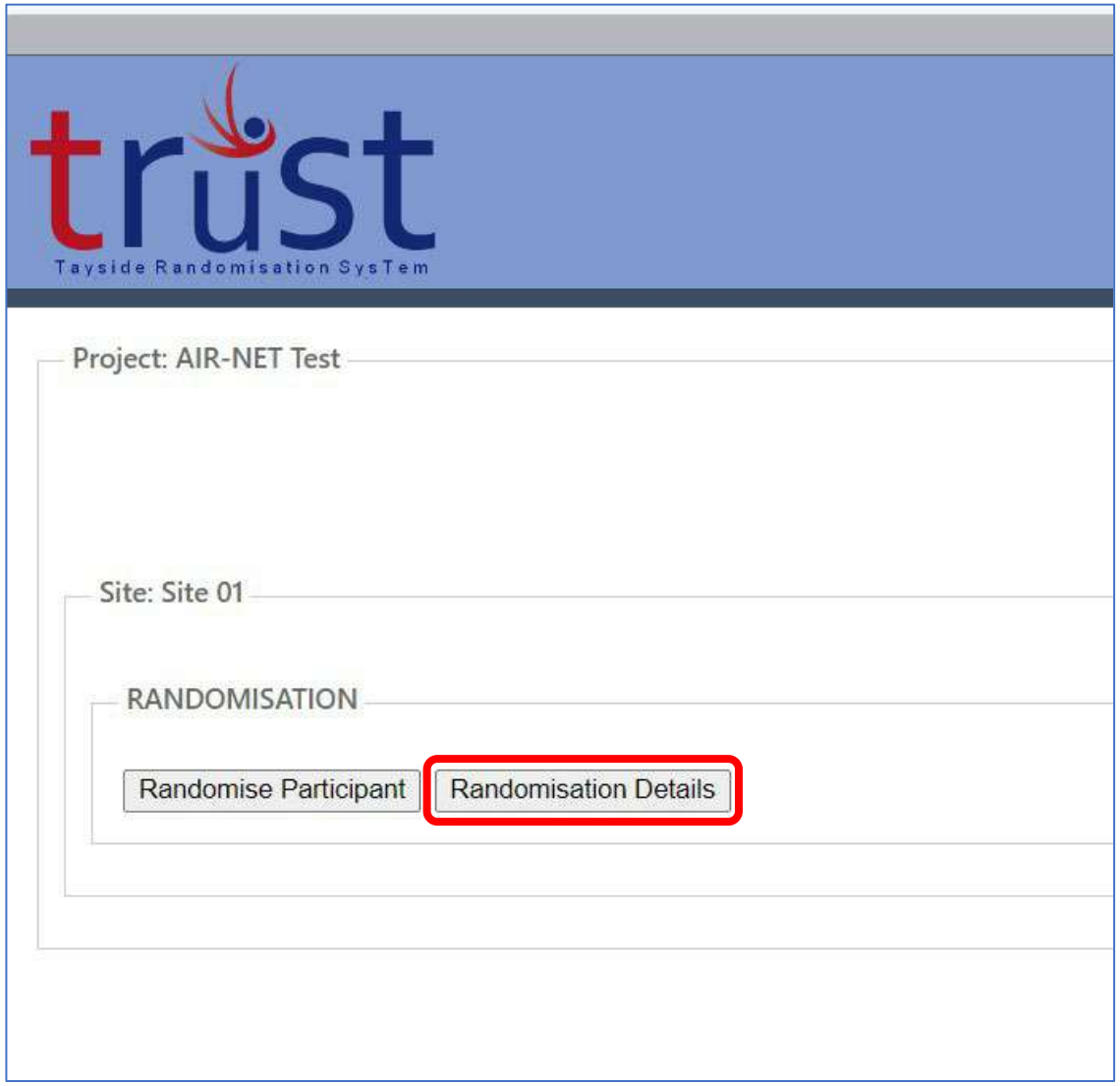
Dispensed By:		Date:
Checked By:		Date:
Collected by:		Date:

AIR-NET IMP Request Release Form V1 18-11-2024

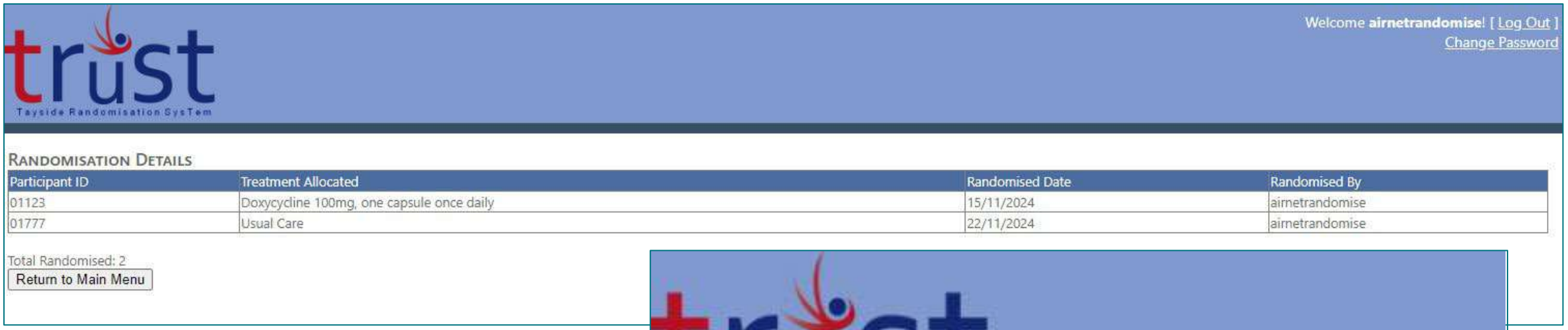
Randomisation Details

Main menu:

Click “Randomisatin Details” button



Randomisation Details



AIR-NET Trial Management Team: AIRNET-TM@dundee.ac.uk
01382 383830

TRuST hicservices-support: hicsupport@dundee.ac.uk

Trial Assessments

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Safety visit
	Days -35 to 0	Day 0	Day 7	Day 14	Day 28	Day 56	If required
Informed consent	X						
Eligibility check	X	X					
Demographics	X						
Medical history	X						
Concomitant medications	X	X	X	X	X	X	X
Physical examination	X						
Height & weight	X						
Record AEs		X	X	X	X	X	X
Record exacerbations		X	X	X	X	X	X
BP, pulse, temp, O_2 stats	X	X	X	X	X	X	X
ECG	X						
6 minute walk test		X			X		
Post bronchodilation spirometry	X	X	X	X	X	X	X
QoL-B	X	X	X	X	X	X	
BIM baseline		X					
BIM follow-up			X	X	X	X	
BEST diary		X	X	X	X		
Full blood count, urea and electrolytes, liver function tests	X			X	X	X	X
Research blood sample for endpoint analyses		X	X	X	X	X	
Sputum sample for screening eligibility (NEATstik)[a]	X						
Research sputum sample for endpoint analyses		X	X	X	X	X	
Nasal sample		X			X		
Pregnancy test, if required	X	X	X	X	X		
Randomisation		X					
Dispensing of trial drugs		X					
Drug accountability					X		
Sub-study only							
Pulse wave velocity		X			X	X	
Laser doppler perfusion imaging		X			X	X	

Demographic details

- Ensure participants are 18 years or over and no more than 85 years old on the date of randomisation

Smoking Status

- A participant's pack year history should be calculated using the following website:
- www.smokingpackyears.com
- Document the figures used for the pack years calculation in the medical notes for source data verification (SDV).
- Participants who have a **primary** diagnosis of COPD and have a pack year history of more than 10 years are not eligible.

History of Bronchiectasis

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

Medical History

- Medical History should be completed as fully as possible and should be as diagnosed by a doctor.
- "Other relevant medical conditions" should include:
  - Medical conditions for which the participant is receiving concomitant medications
  - Medical conditions which impact on the participant's 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 any unstable co-morbidities which in their opinion would make the participant unsuitable to be enrolled in the trial.

Height WPG

Equipment

- Height measure

Procedure

- Ask the patient to remove their shoes and any bulky clothing (e.g., jacket, coat, cardigan).
- Raise the head plate of the height measure and ask the patient to stand with their feet flat on the centre of the base plate, with their feet together and heels against the rod.
- Their back should be as straight as possible, against the rod but not leaning on it and their arms should be hanging loosely by their side.
- The patient's head should be in a horizontal position.
- Ask the patient to look straight ahead, breathe in deeply and stretch to their fullest height.
- Lower the headplate until it is resting on the patient's head, and then ask them to step forward.
- Record the height to the nearest mm, where the arrow points to the measuring scale.

Weight WPG

Equipment

Weighing scales

Procedure

- Ask patients to remove all outer layers of clothing (e.g., jackets, heavy or baggy jumpers, cardigans, or waistcoats) and shoes, and to empty their pockets and remove any heavy jewellery.
- Turn on the scales and wait for the display to read zero.
- Ask the patient to stand on the scales with their feet together in the centre, their weight evenly distributed and their heels against the back edge.
- Their arms should be hanging loosely at their sides and their head facing forwards.
- Once the scales have stabilised, record the reading in kg to the nearest 100 g. Repeat the measurement, and if the reading is different, repeat a third time and take the average of the three readings.

Vital Signs WPG

Equipment

- Blood Pressure Monitor
- Oxygen saturation monitor
- Tympanic thermometer

Procedure: Blood Pressure & Pulse

- Select appropriately sized cuff
- Place the cuff directly against the skin, as clothing may cause a faint heartbeat and result in error
- Ensure that the patient is sitting comfortably for at least 5-10 minutes before measurement is taken
- Ask the patient not to talk or move during blood pressure measurement.
- The blood pressure should be taken twice and the second reading entered in the eCRF.
- Record the readings in the medical records for SDV.

ECG WPG

Equipment

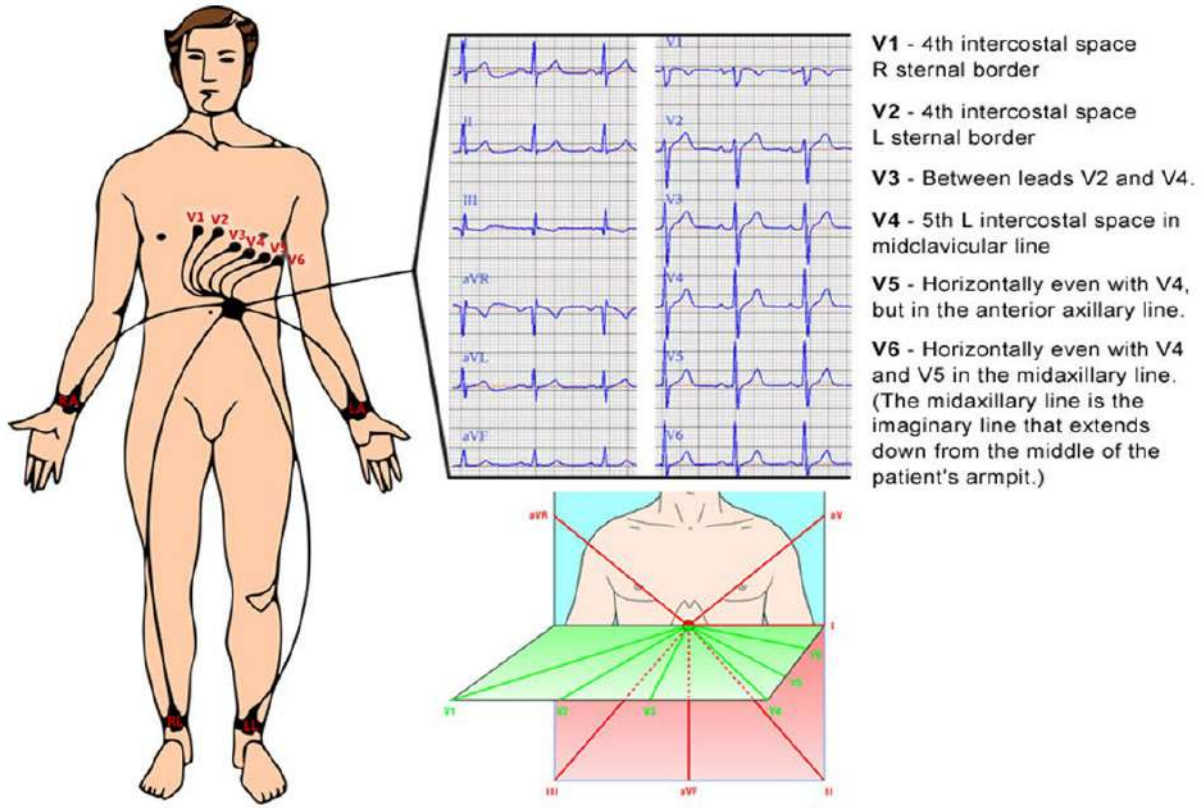
- ECG Machine

Procedure

- Ensure the recorder is in working order and that the annual safety and calibration checks are up to date
- Ensure all sundries are available i.e. razors, skin cleaners, exfoliating tape, adequate supply of ECG paper and electrodes.
- Arrange a room of ambient temperature with privacy/curtains
- Patients should be asked to remove clothing from above the waist and to wear the gown provided.
- Allow the patient to rest supine for 10 minutes.
- Assess the chest area for the need to remove hair and do so if necessary, using a razor.
- If necessary, cleanse the skin, dry, and exfoliate to ensure good adhesion of the electrodes.
- Apply electrode pads (see below)

ECG WPG (cont.)

- Print ECG
- Ensure date, patient name, CHI/hospital number and study ID number are printed or written on the ECG.
- A doctor delegated this task on the Delegation Log should review the ECG before randomisation of participant
- Doctor reviewing ECG should write any abnormal findings and actions taken in patient's medical notes.
- With the patient's consent their GP should be informed of any abnormal findings.
- File ECG in patient's medical notes as source data



Spirometry WPG

Standard spirometry: post bronchodilator spirometry at visits will be carried out as per American Thoracic Society/European Respiratory Society's guidelines.
FEV1 forced vital capacity (FVC) and Forced Expiratory Flow at 25-75% (FEF25-75) will be measured.

Equipment

- As per standard spirometry procedure
- Participant's own salbutamol inhaler or 2.5mg salbutamol for nebulisation

Procedure

- If required by local policy, doctor to prescribe 2.5mg salbutamol for nebulisation if needed.
- Ask the patient to take their salbutamol inhaler or provide salbutamol inhaler and use a single-use spacer. Dose of inhaled salbutamol should be as local policy

  or
- Administer 2.5mg of salbutamol via nebuliser.
- Wait 15 minutes for bronchodilator to take effect.
- Complete spirometry as per standard procedure

Physical Examination

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

Should be completed by a delegated doctor and documented in the participant's medical notes as well as on the eCRF.

Examination to include:

- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Dermatological

Pregnancy test

For women of childbearing potential.

Blood samples

Collected, processed, and stored as per laboratory manual.

Sputum samples

Collected, processed divided and stored as per laboratory manual.
Participants will be asked to bring a spontaneous early morning sputum sample with them to visits, from day 1 visit.

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 in sites able to perform induced sputum according to local protocols.

Exacerbation recording

- 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 eCRF.
- 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.
- Details of any pulmonary exacerbations should be recorded in the medical notes

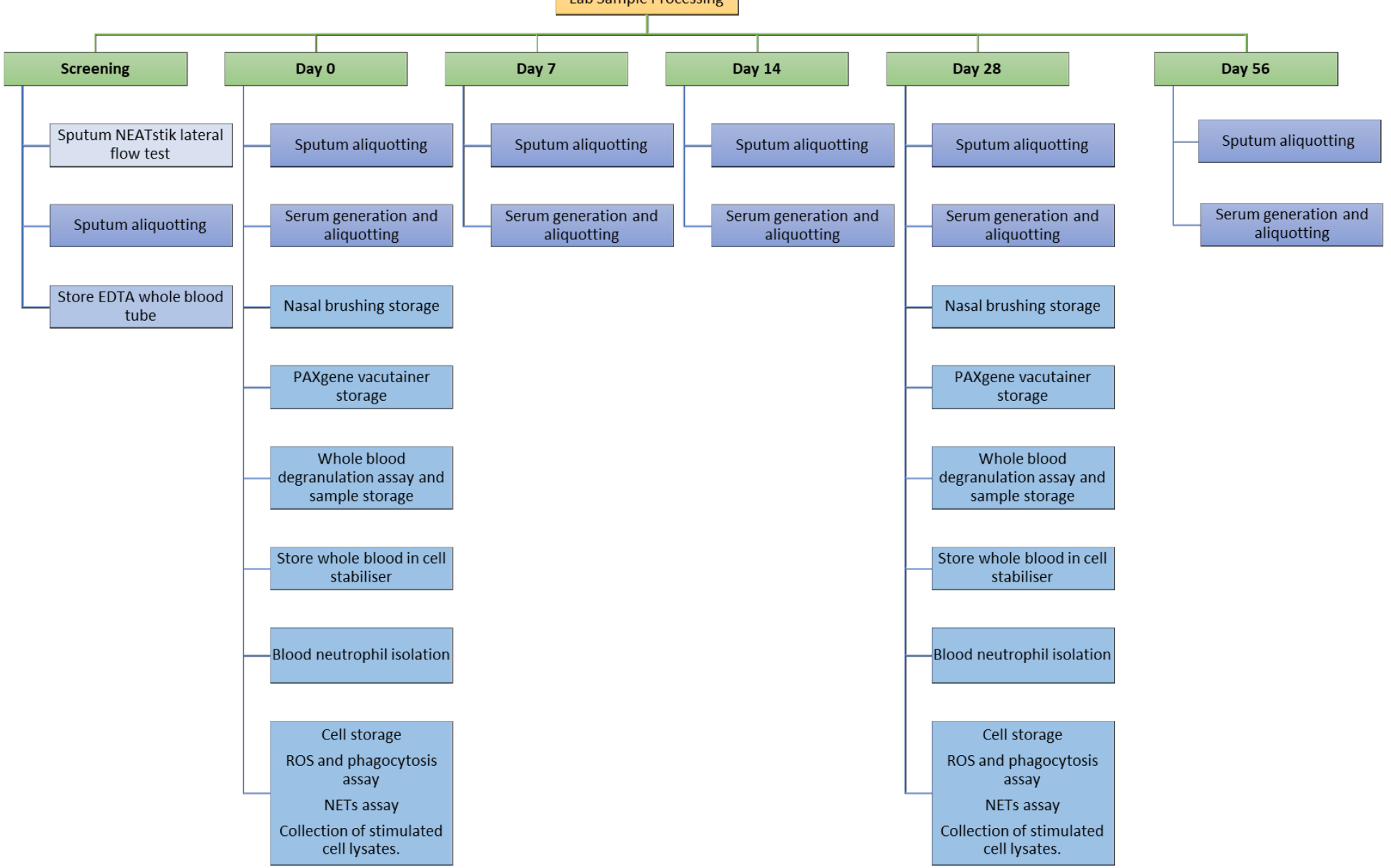
Questionnaires WPG

- The latest approved version of the questionnaires should be used at all times.
- Ensure the patient identification number, the correct visit number and date of visit are entered on each page.
- The questionnaires are intended for self-completion on the day of visit.
- If the respondent is unable to complete the questionnaire by themselves, it may help for the researcher to read aloud the questionnaire. It is acceptable for a third party to record the respondent's replies but care should be taken to avoid prompting.
- If the respondent finds statements too limiting - the researcher should repeat the questionnaire instruction 'to indicate which statements best describe your own health state today' and that there are no right or wrong answers. *NB it is the respondent's own evaluation that is required, and no prompts should be given*.
- If a participant has completed the questionnaire themselves or with the help of a relative/friend the researcher should check the questionnaire for completeness and go through any missing questions or ambiguous answers e.g. 2 answers ticked instead of one, go through the questionnaire with the participant. with the participant.
- If a respondent has ticked 2 statements on a dimension, unless it is possible to clarify, these answers should be treated as missing data.

Laboratory Samples

Samples Required

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Safety visit
	Days -35 to 0	Day 0	Day 7	Day 14	Day 28	Day 56	If required
Full blood count, urea and electrolytes, liver function tests	X			X	X	X	X
Research blood sample for endpoint analyses		X	X	X	X	X	
Sputum sample for screening eligibility (NEATstik)[a]	X						
Research sputum sample for endpoint analyses		X	X	X	X	X	
Nasal sample		X			X		
Pregnancy test, if required	X	X	X	X	X		


Lab Sample Processing
Screening
Day 0
Day 7
Day 14
Day 28
Day 56
Sputum NEATstik lateral flow test
Sputum aliquotting
Store EDTA whole blood tube
Sputum aliquotting
Serum generation and aliquotting
Nasal brushing storage
PAXgene vacutainer storage
Whole blood degranulation assay and sample storage
Store whole blood in cell stabiliser
Blood neutrophil isolation
Cell storage
ROS and phagocytosis assay
NETs assay
Collection of stimulated cell lysates.
Sputum aliquotting
Serum generation and aliquotting
Sputum aliquotting
Serum generation and aliquotting
Sputum aliquotting
Serum generation and aliquotting
Nasal brushing storage
PAXgene vacutainer storage
Whole blood degranulation assay and sample storage
Store whole blood in cell stabiliser
Blood neutrophil isolation
Cell storage
ROS and phagocytosis assay
NETs assay
Collection of stimulated cell lysates.
Sputum aliquotting
Serum generation and aliquotting

Equipment

Bloods:

- Blood tubes as per visit
- Venepuncture equipment (e.g. 21G needle and vacutainer adapter provided to sites. Tourniquet, cotton wool, alcohol wipes etc. to be utilised locally)
- *Collection set compatible with vacutainer tubes must be used for PAXgene*
- Research sample pack note

Sputum:

- Sputum sample pots
- NEATstik sputum elastase test and colour grade print-out
- Murray sputum colour chart
- Screening only: camera or camera phone (if permitted locally) to photograph NEATstik result

Nasal Brushing*:

- 3mm brush
- 1.5 ml LoBind Eppendorf tube containing 1 ml RNAlater buffer
- Sample storage box
- Sample Logs

**nasal brushing & sample addition into RNA later buffer should be done during participant visit by clinical team member*

Blood Samples

Blood samples should be obtained as per Laboratory Manual

NHS samples Visit 1, 4, 5, 6 & any unscheduled visit:

- 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 must be filed in the participant's medical notes

Research samples Visits 2, 3,4,5 and 6:

- Processed as per Laboratory Manual
- Stored at site and transferred to University of Dundee at the end of the trial

Pregnancy Test

- Urine pregnancy test should be carried out where applicable.
- A copy of the results signed and dated by a delegated doctor should be filed in the participant's medical notes.

Visit	NHS Labs	Research Blood Samples	Sputum Sample	Other research samples
1 screening	Bloods: • FBC • U&Es • LFT Urine: • Pregnancy test if required	 SST II Advanced 5 ml  EDTA (K2E) 4 ml	 Min 0.4 g	Nil
2 Day 0 (Baseline)	Urine: • Pregnancy test if required	 SST II Advanced 5 ml  Sodium Heparin (NH) 4 ml  Lithium Heparin (LH) 4 ml  EDTA (K2E) 24 ml *(2x10ml, 1x4ml)*  PAXgene RNA tube 2.5 ml	 Min 0.4 g	 Nasal brushing (3mm brush and 1.5ml tube with 1ml RNAlater solution)
3 Day 7	Urine: • Pregnancy test if required	 SST II Advanced 5 ml	 Min 0.4 g	Nil
4 Day 14	Urine: • Pregnancy test if required	 SST II Advanced 5 ml	 Min 0.4 g	Nil

Visit	NHS Labs	Research Blood Samples	Sputum Sample	Other research samples
5 Day 28	Bloods: • FBC • U&Es • LFT Urine: • Pregnancy test if required	 SST II Advanced 5 ml  Sodium Heparin (NH) 4 ml  Lithium Heparin (LH) 4 ml  EDTA (K2E) 24 ml *(2x10ml, 1x4ml)*  PAXgene RNA tube 2.5 ml	 Min 0.4 g	 Nasal brushing (3mm brush and 1.5ml tube with 1ml RNAlater solution)
6 Day 56	Bloods: • FBC • U&Es • LFT	 SST II Advanced 5 ml  Sodium Heparin (NH) 4 ml  Lithium Heparin (LH) 4 ml  PAXgene RNA tube 2.5 ml	 Min 0.4 g	Nil
Unscheduled **NHS bloods as clinically indicated** • FBC • U&Es • LFT		 SST II Advanced 5 ml	 Min 0.4 g	Nil

University of Dundee

tctu TAYSIDE CLINICAL TRIALS UNIT

NHS Tayside

Labelling Research Samples

Sample pack note should be included in the visit pack with sample tubes and should be completed at the visit by clinical team member. Vacutainers need only to be labelled with the sample ID, date and time using the manufacturers label by clinical team.

AIR-NET research samples

Participant ID: NET- __ __ - __ __ __ - __ __

Date: __ __ - __ __ - __ __

Blood and nasal sampling time: __ __ : __ __

Sputum production time: __ __ : __ __

Staff initials: __ __

All research samples (i.e. all samples not for NHS analyses) including vacutainers for storage should be labelled in the lab with the labels provided by the lab team member, with the exception of the Nasal Brushing (refer to lab manual)

Research Sample Log

Sample should be documented in the sample box location. When transferred to lab a copy should be provided with the samples.

Sample Box Location Log Sheet # _____ Site number: _____ AIR-NET

Sample Type	Box number	Date of first storage	Location and temperature	Initials	New location and temperature, if moved	Date of transfer	Initials	Date of sample shipment to Dundee	Initials	Shipment details
e.g. PAXgene tubes	*1*	*30 / 03 / 25*	*Rm. 101, Freezer 1,-80°C*	*JS*	*Rm. 101, Freezer 8, -80°C*	*15 / 08 / 25*	*GT*	*29 / 03/ 26*	*FL*	*Marken, dry ice, tracking ID: GH79355A*
		/ /				/ /		/ /		
		/ /				/ /		/ /		
		/ /				/ /		/ /		

Research samples will be transferred to the University of Dundee labs at the end of the trial.

Concomitant Medications

Review of concomitant medications

- Taken from medical records and participant reporting
- Reported concomitant medications must be recorded in medical records for source data verification

Visit 1

- Ask participants to bring their current prescription.
- Take a copy, clarify if participant is actively taking all their prescription drugs, and score through any on the list which they are not currently taking.
- File a copy of the prescription in the participant's medical notes for SDV.

All other visits

- Ask if there are any changes to medication since previous visit
- Record changes in medical notes and eCRF

Excluded Medications

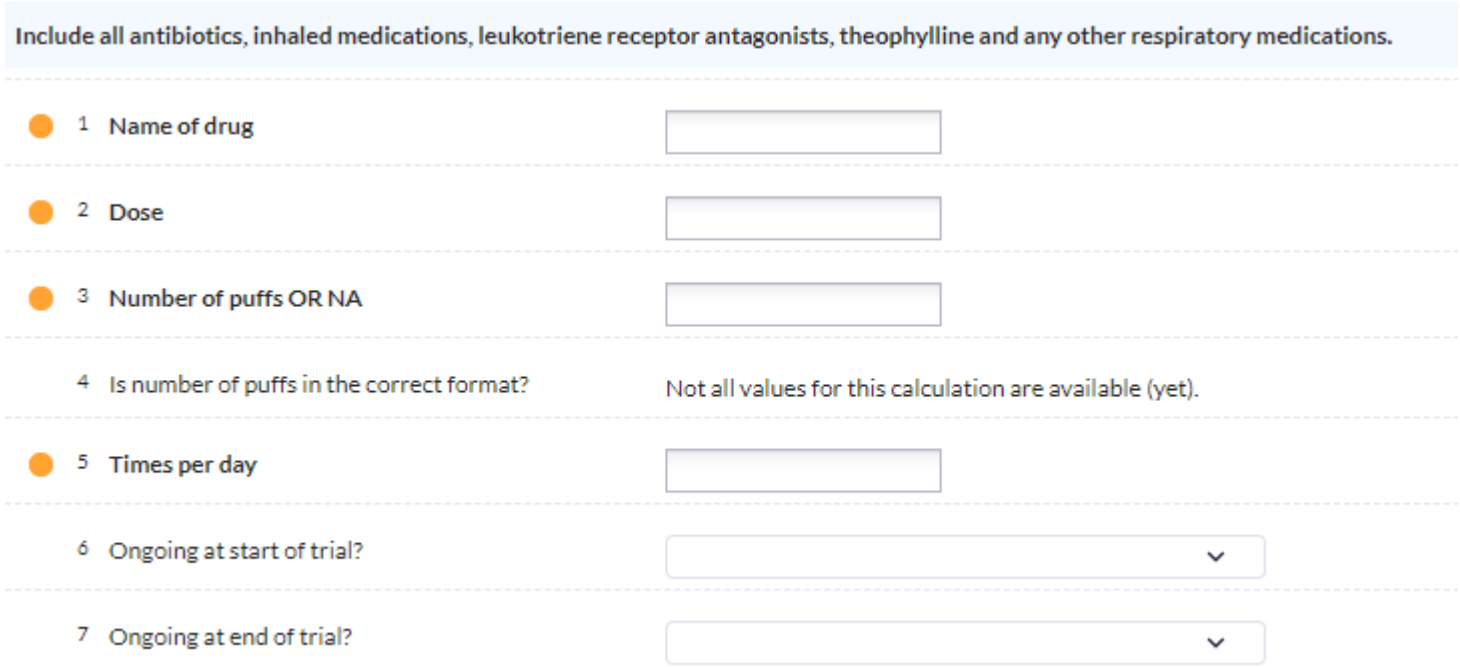
- Please ensure at all visits that the participant is not taking any excluded medicines.

eCRF

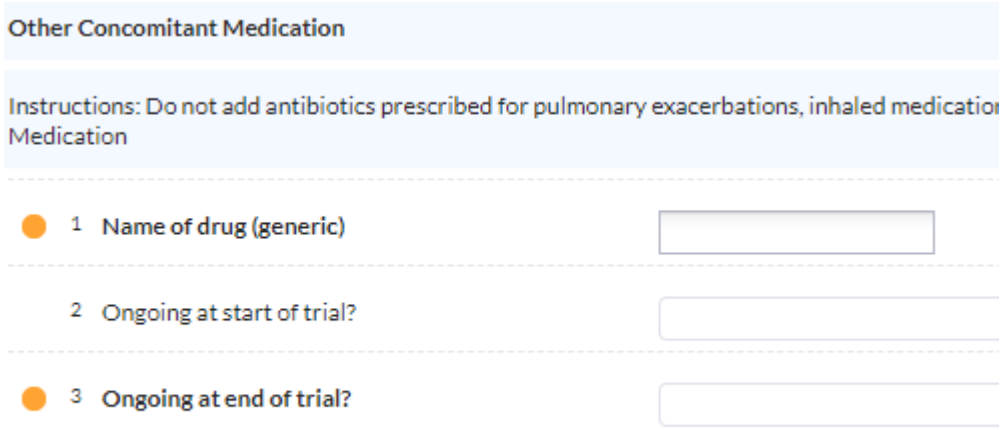
There are 2 con med forms:

Respiratory & antibiotic con meds:

- all antibiotics, inhaled medications, leukotriene receptor antagonists, theophylline and any other respiratory medications
- **Brand name** - no need to list combined medications separately



Other con meds: less information required, **generic name** - ingredients of combined medications should be listed separately e.g. for Co-codamol list separately as codeine, paracetamol.



eCRF

- At Visit 1 all medications should be ticked as ongoing at start of trial.
- Any new medications started during the course of the trial should have a start date.

- Any medications stopped during the participation in the trial should have an end date.
- At the last visit all medications should have either an end date or ticked as “ongoing at end of trial”.

Source Data

Source data

All Visits

- All data collected must have back up source data in the participant's medical record
  - Allows for Source Data Verification (SDV)
  - Allows other healthcare professionals know about the trial and any assessments completed during the visits
  - Eligibility Form is mandatory, and is source data for participant eligibility and Dr signature.

- Template medical note continuation sheets are provided and can be used if wished. These should be filed in the medical notes.

- If worksheets are used to record source data, they must be filed in the medical notes
- The worksheets do not cover everything which is required to be recorded in the medical notes.

Source Data document to be completed for the Monitoring team

Source data

Visit 1

- Front coloured card/sheet/sticker/pop up to state they are a research participant
- Copy of signed Informed Consent Form
- Copy of Participant Information Sheet (PIS) participant has consented to
- Copy of GP letter informing GP of participation
- Confirmation that the participant has had the PIS for at least 24 hours

Visit 2 Eligibility Confirmation Form

- Must be completed **before** randomisation
- Must be dated and signed by a doctor on Delegation Log
- Must be filed in the medical record

Source data

All Visits

- Date of visit
- Confirmation of how participant identity was verified
- Details of any notable findings at the visit and any action taken
- Record of blood, sputum and pregnancy test samples taken
- Copy of blood, sputum and pregnancy test results signed and dated by delegated doctor to be added when obtained
- Changes to con meds (*or state there were no changes*)
- AE's (*or state there were none*)
- Confirmation that the visit was carried out as per protocol
- Name and Signature of Research staff completing the visit

Source data

Assessments

- NEATStix test results (visit 1 only)
- History of bronchiectasis details, if source data not elsewhere in medical notes
- Medical history if not elsewhere in medical notes
- Height and weight
- For women who were deemed not WOCBP document how this was confirmed
- Physical exam normal/abnormal and action taken if appropriate
- Evidence for questions asked for Bronchiectasis Severity Index, if not elsewhere in medical notes
- Copy of ECG signed and dated by a doctor on Delegation Log.
- Result of ECG i.e. normal/abnormal and any action taken if appropriate
- Vital signs results
- Spirometry results and how bronchodilation was achieved
- 6-minute walk test results

Data Collection & Data Entry

Castor eCRF

- Data entry is performed in the electronic case report form (eCRF) using Castor system
- This can be accessed here: https://uk.castoredc.com/
- It is a secure, hosted system that is GCP-compliant

Castor Training

- Inform the Data Manager which site team members need access to Castor
- Access to a test site will be provided
- Castor training will be provided by the Data Management Team
- Castor training consists of:
  - Brief data training sheet to enter test data & become familiar with Castor
  - Supported by a data entry guideline document
  - PI data verification guidelines
  - Additional one-to-one training if required
- Access to the live system will be given once training is completed, and the person is delegated this task on the Delegation Log
- The Data Management Team can be contacted on: air-net-dm@dundee.ac.uk

Paper Worksheets

- Sites will be provided with a paper worksheet for all visits.
- Concomitant Medication Log & AE Log are separate worksheets. These should be reviewed at each visit.
- The use of worksheets is optional. Worksheets will not be monitored and should not be archived at the end of the trial unless they were used to record source data.
- If used to record source data, they must be filed in the medical notes.
- Sites will also be provided with a continuation sheet, to record source data for each visit. Use of this is optional but if not used the information must be documented in the medical records.
- Ensure the correct questionnaires are completed at each visit.

Trial Discontinuation, Withdrawal & Completion

Discontinuation of trial medication

- If a participant has been randomised and given one or more dose of IMP, they will be asked to complete trial visits as per the protocol, to allow for an intention to treat analysis.
- Participants are free to refuse to do so.
- The Investigator may discontinue a participant's trial medication at any time, if it is in the best interest of the participant and continuing treatment would be detrimental to the participant's wellbeing.
- The Investigator will make a clinical judgment as to whether or not an adverse event (AE) is of sufficient severity to require discontinuation of trial medication.
- A participant may also voluntarily discontinue trial medication due to what they perceive as an intolerable AE.
- Participants will be asked to return their medication box/bottle at visit 5, to record trial medication accountability

Withdrawal from trial – stops all trial activity

- Participants are free to withdraw at any time and are not obliged to give reason(s).
- 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.
- If a participant withdraws and does not remain on the study, the Completion of Trial/Early Withdrawal form should be completed on the eCRF.

Completion of Trial