STUDY PROTOCOL

Study acronym	**The BRIDGE study - Bronchiectasis Research Involving Databases, Genomics and Endotyping**
Sponsor	**University of Dundee and NHS Tayside**
Sponsor Ref **R&D number**	**1-008-18** **2017RC11**
Funder	**Asthma and Lung UK/ European Union Innovative Medicines Initiative/ European Respiratory Society**
Chief Investigator	**James D. Chalmers**
REC number	**18/LO/1935**
Version Number	**5**
Date	**24-03-25**

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PROTOCOL APPROVAL

The BRIDGE study - Bronchiectasis Research Involving Databases, Genomics and Endotyping to match the right treatment to the right patient.

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Prof. James D Chalmers		02.04.25
Chief Investigator	Signature	Date

1.0 Summary of Study:

Study Title	**The BRIDGE study - Bronchiectasis Research Involving Databases, Genomics and Endotyping to match the right treatment to the right patient.**	
Study Design	Prospective observational cohort study	
Study Population	Adults with bronchiectasis	
Sample Size	2500 internationally (600 UK)	
Planned study period	8 years	
Clinical phase duration	5 years	
Primary	Objectives To determine molecular endotypes of bronchiectasis which can guide response to treatment.	
Secondary	Objectives 1. To determine molecular endotypes of stable bronchiectasis 2. To determine the causes and inflammatory profiles of bronchiectasis exacerbations 3. To validate candidate biomarkers of stable and exacerbation endotypes to use in stratified medicine 4. To perform in-vivo or in-vitro proof of concept studies using phenotypic data to identify patient populations likely to benefit in future randomized controlled trials	Outcome Measures Detailed endotypes in bronchiectasis which can guide response to treatment.

1.1 Background: Bronchiectasis is a common disabling and heterogeneous disease that has been neglected in terms of basic and clinical research. Recent controlled

trials have failed to achieve their primary end-points, likely because the optimal patient population to benefit from antibiotic, mucoactive and anti-inflammatory drugs has not been identified. This study aims to explore the clinical, microbiological, inflammatory and functional heterogeneity of the disease with the aim of identifying patient endotypes for stratified medicine.

1.2 Study aims and objectives

1. To determine the molecular endotypes of bronchiectasis during stable disease
2. To determine the causes and inflammatory profiles of bronchiectasis exacerbations
3. To validate candidate biomarkers of stable and exacerbation endotypes to use in stratified medicine
4. To perform in-vivo and in-vitro proof of concept studies using phenotypic data to identify patient populations likely to benefit in future randomized controlled trials

1.3 Study Design: Observational Cohort study

1.4 Study methods:

Patients with bronchiectasis will be recruited into an observational study, the objectives of which will be to:

Aim 1 will define and validate endotypes of stable bronchiectasis by studying approximately 2500 patients with bronchiectasis. Clinical data (described in the data collection section), sputum microbiome, sputum proteomics, and systemic and sputum inflammatory marker measurement will be incorporated for analysis. A sub-study (n=400) will be performed using primary airway epithelial cells. Patients will have brushings of the inferior nasal turbinate with assessment of % ciliation, ciliary beat frequency and pattern by high speed video microscopy before and after culture.

Aim 2 will replicate the phenotyping approach to stable patients with 60 patients during exacerbation. This will identify changes from baseline in microbiota, proteomic and other markers associated with onset of exacerbation and allow classification of clusters of exacerbation.

Aim 3 we will externally validate candidate phenotype/endotypes in registered ethically approved external biobanks and aim to demonstrate that validated markers be linked to potential treatment responses for use in stratified medicine trials.

In total we will recruit approximately 2500 patients for study. These patients will attend one of the participating study centres at least once and undergo sampling along with collecting of clinical data. Patients will be asked to consent for their samples to be linked to data held on an existing pan European bronchiectasis database (the EMBARC registry).

1.5 Nature of outputs and outcomes/results expected:

This study will aim to establish detailed endotypes in bronchiectasis which can guide response to treatment.

2.0 Study background:

Bronchiectasis has been described as one of the most neglected diseases in respiratory medicine. (1,2) There are no licensed treatments, and the burden of disease is high and increasing. In the UK, bronchiectasis affects 485 per 100,000 men and 566 per 100,000 women and the prevalence has increased by approximately 40% in the past decade.(3) Traditional bronchiectasis guideline approaches to treatment are focussed on airway infection (long term oral/inhaled antibiotic treatments), mucus clearance (physiotherapy, devices, mucoactive drugs) and airway inflammation (inhaled corticosteroids, macrolides).(1) Clinical trials have failed to demonstrate clear benefit of inhaled antibiotics across multiple compounds.(4-6) Macrolides reduced the frequency of exacerbations in 3 randomised trials, but up to 40% of patients do not respond to treatment in practice.(7-10) Mucoactive drugs are not widely used and clinical trials of mannitol have failed to meet their primary end-points, DNAse was found to be harmful in bronchiectasis despite benefits in cystic fibrosis, while hypertonic saline has not shown clear benefits over 0.9% saline.(11-14) A Cochrane review concluded that there is insufficient evidence to support the use of inhaled corticosteroids.(15) The failure of therapies to translate from cystic fibrosis to bronchiectasis is thought to be due to the greater inflammatory, microbiological, radiological and aetiological heterogeneity in bronchiectasis. (16)

Achieving success in developing new therapies for this disease requires detailed translational research to define patient phenotypes and endotypes. Personalised, stratified or precision medicine is increasing advocated across a range of conditions to improve targeting of therapies. (17-20).

This study aims to phenotype and endotype bronchiectasis during stable disease and exacerbations, to develop strategies for personalised medicine.

3.0 Study Objectives:

3.1 Primary Objective

To determine molecular endotypes of bronchiectasis which can guide response to treatment.

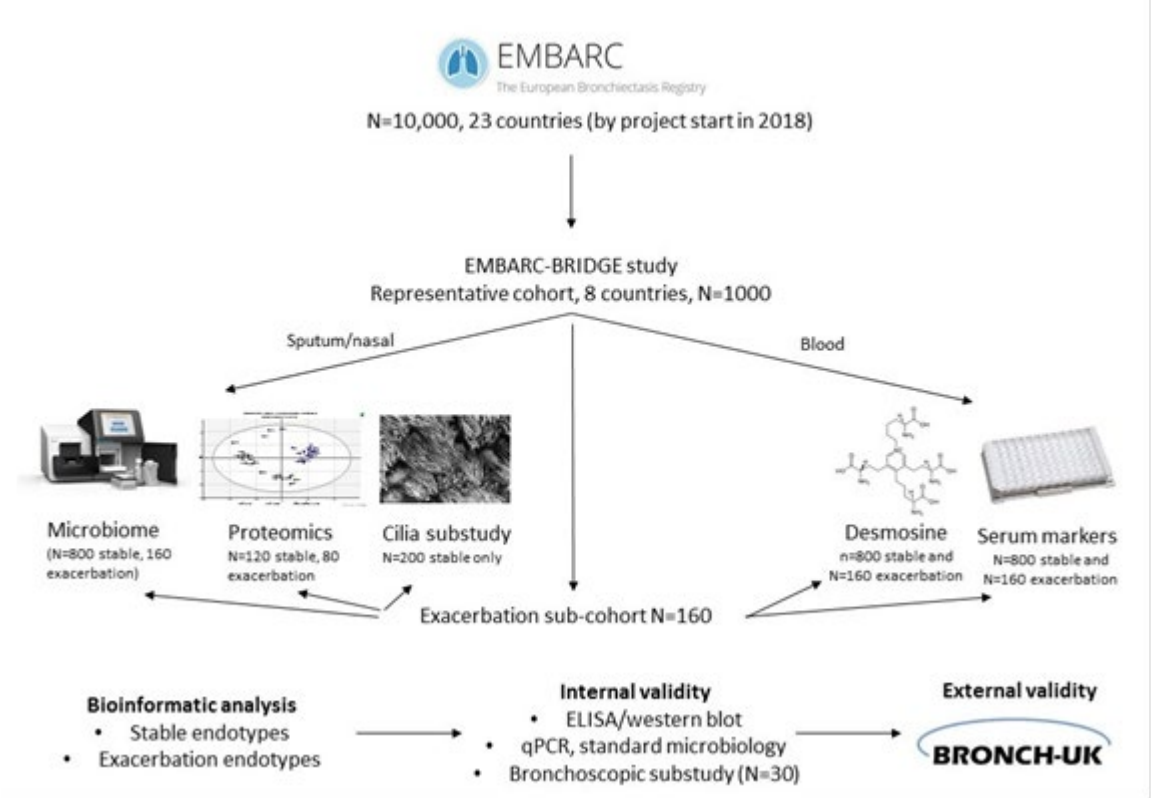
3.2 Secondary Objectives

1. To determine molecular endotypes of stable bronchiectasis
2. To determine the causes and inflammatory profiles of bronchiectasis exacerbations
3. To validate candidate biomarkers of stable and exacerbation endotypes to use in stratified medicine
4. To perform in-vivo or in-vitro proof of concept studies using phenotypic data to identify patient populations likely to benefit in future randomized controlled trials

4.0 Study start date: August 2018

5.0 Study duration: 8 years

6.0 Study outline



Type of visit	Screening and study V1 (n=2500)	Study visit procedures +/- 3 month V2-V4 (N=2500)	Exacerbation Visit (=<72 hours of commencing exacerbation medication)** (Approx. N=300)
Timeline	Single visit Month 0	Visit Months 12, 24 &36	
Informed Consent	X		
Inclusion/Exclusion Criteria Check	X		
Medical History	X	X	
Record Concomitant Medications	X	X	X
Height	X		
Weight	X		
FENO (*only at selected sites with appropriate equipment available to do this*)	X	X	
Post-bronchodilator spirometry	X	X	X
Bronchiectasis quality of life questionnaires (QOL-B, BIM (UK & Spain only), BHQ and CAAT	X	X	X BIM only

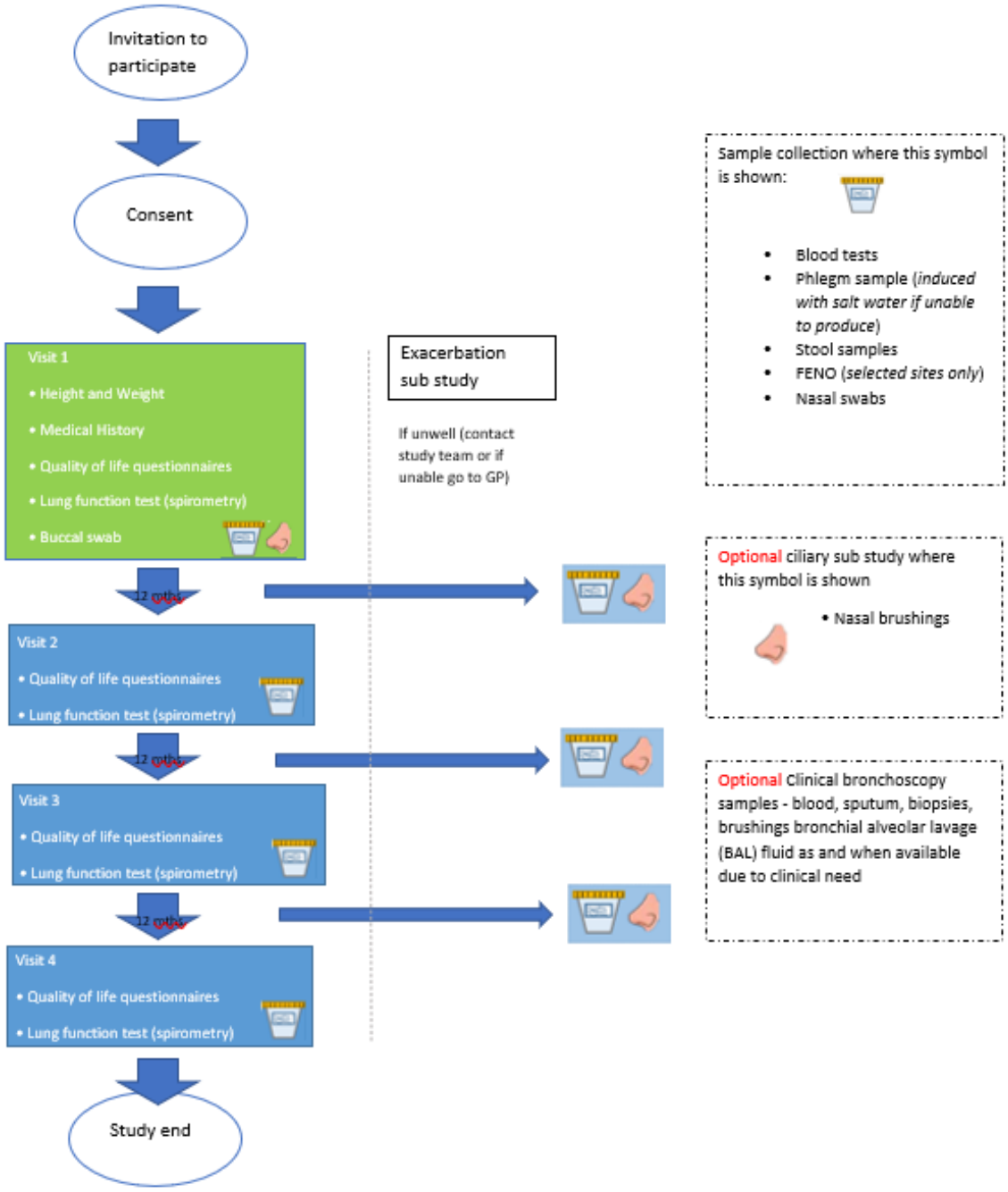
Patient Global Impression Scale – Severity (PGI-S)	X	X	
Patient Global Impression Scale – Change (PGI-C)		X	
Stool samples for storage	X	X	X
Research Blood Samples	X	X	X
Nasopharyngeal Swabs for storage	X	X	X
Buccal swab if needed	X		
Spontaneous sputum samples or induced if required	X	X	X
Saliva samples (optional)	X		X
Adverse Event reporting	X	X	X
Clinical Bronchoscopy samples (optional blood, sputum, biopsies, brushings bronchial alveolar lavage (BAL) fluid***			
Cilia sub-study	V1	V2-V4	Exacerbation
Nasal brushings	X	X	X

**Screening and visit 1 will be combined into a single visit. Exacerbation visits are optional as participants treated by their GP or taking a home supply of antibiotics may choose not to attend for an exacerbation visit.*

*** It will not be considered a breach if the visit window for any type of study visit must be re-arranged for patient/team convenience or clinical significance, for e.g. if an exacerbation visit*

is still deemed relevant to complete by CI/PI after 72 hours because patient is not responding to treatment then that exacerbation visit could still be carried out.
**** As and when available*

7.0 Study flow chart:



8.0 Study Design:

This is a multi-centre study performed through the EMBARC consortium. Data and samples will be collected from sites around the world. Ethical approval of this protocol will be sought at country level.

The UK sites will aim to recruit 600 patients over the course of the study with 2500 recruited world-wide. These numbers are indicative and we reserve the right to recruit more or less patients in the UK and elsewhere according to study need.

Patients will be recruited whilst clinically stable and asked to attend an annual visit at a clinical research facility for the research procedures outlined below. In addition, during an exacerbation individuals will be invited to attend the clinical research facility or to donate surplus samples through their local hospital or GP.

8.1 Main study inclusion criteria

A previous CT scan showing bronchiectasis along with compatible clinical syndrome of cough, sputum production and/or recurrent respiratory tract infections

A primary diagnosis of bronchiectasis made by a respiratory physician

At the screening visit the individual will have been clinically stable for 4 weeks indicated by the lack of any treatment with antibiotics or corticosteroids for a pulmonary exacerbation in the previous 4 weeks

8.2 Main study exclusion criteria

Inability to give informed consent

<18years of age

Patients with active tuberculosis

Treatment with antibiotics or corticosteroids for a pulmonary exacerbation in the previous 4 weeks

Diagnosis of Cystic Fibrosis

Previous heart or lung transplant

Cilia substudy criteria will be the same as the main study and in addition:

8.3 Cilia substudy inclusion criteria

Attending a cilia sub-study recruitment site (for example, Ninewells Hospital and Royal Brompton Hospital)

8.4 Cilia substudy exclusion criteria

Smoker – tobacco or vapes

An acute upper respiratory tract infection within 6 weeks of visit 1

Known blood clotting disorders

Individuals currently taking warfarin or anti-coagulants

8.5 Participant selection and enrolment

Identification of potentially eligible study participants will make use of any or all of the following:

From secondary or tertiary care via contact with patients at specialist respiratory clinics or pulmonary rehabilitation classes. Clinic and class participant lists will be reviewed by the PI (a care team member) or another delegate from the care team and medical records checked to identify suitable patients who will then either be approached and given the Participant Information Sheet (PIS) when they attend clinic or class or will be posted an invite letter and PIS with a reply slip for more information. Contact at clinic or class will be by the PI or delegated person from the care team. Postage of invitation letters with reply slips and PIS will be carried out by the PI or delegate.

From local, national or international databases where patients have given prior consent to be contacted for future research projects e.g. TARDIS, EMBARC, TAYBRIDGE, SHARE, GO-SHARE or related datasets via an invitation letter with reply slip. The local PI will be responsible for recruitment but may delegate to other named individuals within the team. At sites conducting the substudy the PIS will be delivered by the study team (the care team) at visit one to individuals who meet the inclusion criteria.

9.0 Procedures

9.1 Patient procedures

1. Informed consent will include consent for biological sampling, long term storage of biological sampling, use of surplus clinical samples in the future and for data linkage.

2. Following screening patients will give informed consent to participate and will be asked questions regarding their medical history and medication use.

3. Patients will complete the bronchiectasis quality of life questionnaire (Qol-B) and bronchiectasis health questionnaire (BHQ) and at UK sites the bronchiectasis impact measure (BIM).

4. Patients will undergo spirometry and Fractional exhaled nitric oxide (FENO) where the test is available

5. Spontaneous or induced sputum samples will be collected (patients should ideally provide a sample spontaneously at the study visit, however the priority is to ensure completeness of sampling therefore the following hierarchy is appropriate for sputum sampling- Spontaneous sputum samples: if not possible then induced sputum using hypertonic saline according to local protocol; if unsuccessful then patient may bring a spontaneous sputum to site from home on the day or a different day.

6. A blood sample(s) (<50mls) will be collected divided into serum and EDTA anticoagulated blood and Paxgene tubes for RNA studies.

7. A buccal swab will be conducted for alpha-1-antitrypsin levels and genotyping. Note that if the patient has previously been tested for alpha-1 antitrypsin levels and this is documented, there is no requirement to perform this further test.

8. A stool sample and nasopharyngeal swabs will be collected for microbiome, viral testing and endotyping laboratory investigations described in section 9.2

9. For those consenting to the cilia sub-study, nasal brush samples will be collected at baseline and at exacerbation visit for ciliary and epithelial cell investigations described in section 9.2

If individuals have already completed parts of 3-5 as part of the existing ethically approved biobank studies (e.g. BRONCH-UK/TARDIS), or part of their routine clinical care, samples and data may be transferred from the existing biobank. Access to existing samples will be approved by local tissue bank approval processes.

Cilia sub study: At sites in the UK and other sites internationally (where the techniques are available) individuals will be invited to take part in the cilia sub-study. This invitation will be made at the same time as invitation to the main study and will involve additional sampling. Nasal brushing(s) will be taken. This involves removing surface cells from the mucosal lining of the nose with a small cytology brush. Eligible individuals will be invited to take part in the cilia sub study at visit 1 of the main study.

Exacerbation study: Patients will be included in the exacerbation part of the study if they present with an exacerbation during the 3 year study duration which meets the following criteria: At least three of the following: 1) Increased cough 2) Increased

sputum volume or change in sputum consistency 3) Increased sputum purulence 4) Increased breathlessness and/or decrease exercise tolerance 5) Fatigue and/or malaise 6) Haemoptysis, with symptoms lasting for at least 48 hours and requiring treatment with antibiotics. (note that patients may be seen in the first 24 hours of symptoms if appropriate as long as the physician believes that the patient has an exacerbation and that symptoms will last for at least 48 hours).

At this time the individual will have the option to attend the study centre to provide samples or if this is not possible surplus clinical sputum and blood samples will be donated to the study at the patient's convenience during the exacerbation period. If the patient attends their GP, samples can be retrieved through this route or by sending samples from home.

Bronchoscopy study: Individuals in the study undergoing a clinically indicated bronchoscopy at any time during the follow up period will be asked to donate surplus blood, sputum, biopsies, brushings or bronchial alveolar lavage (BAL) fluid.

9.2 Laboratory procedures

Laboratory procedures may include the following:

1. Protein proteomic analysis using liquid chromatography–mass spectrometry
2. qPCR to evaluate bacterial and viral load
3. Assays for inflammatory profiling such as ELISA for cytokine/ chemokine measurement, including neutrophil markers (elastase, resistin, OLF4), alpha 1 anti-trypsin, pH and other candidate markers.
4. Microbiome assessment by 16s rRNA amplicon sequencing on the Illumina MiSeq platform for bacteria and ITS sequencing for Fungi
5. Assessment of gene expression
6. High speed video microscopy to assess and measure ciliary beat frequency, beat pattern and function and electron microscopy (cilia substudy only)
7. Fixation and immunohistological staining for protein expression
5. Cell culture and subsequent sampling of culture supernatant for cell products
6. Challenge of cells with micro-organisms, environmental pollutants and pharmaceutical agents
7. Assessment of eosinophil and neutrophil function
8. Genotyping (including whole genome sequencing)

All methods will be conducted according to Standard Operating Procedures and Protocols. Anonymised (linked) samples may be sent to collaborators with agreements in place. This includes sharing samples outside the European Union. No

identifiable patient details will be provided. Not all of the laboratory procedures will be conducted on all the samples. Procedures conducted at site will depend on local site capabilities and may vary from site to site according to capability.

10.0 Safety assessments

Participants will be asked about adverse events at all visits. We will record adverse events that occur to study participants during a study visit. If any serious adverse events (SAEs) occur they will be reported to the Sponsor based at Ninewells Hospital, Dundee in a timely manner. Refer to section 21.2 for full details on reporting.

The major predictable adverse effects in the study are as follows:

10.1 Induced sputum

The majority of patients will expectorate spontaneous sputum. Some patients may have sputum induction. Bronchospasm is a rare side effect of sputum induction and will be monitored by performing spirometry before or after sputum induction. Patients experiencing symptoms of wheeze, shortness of breath or chest tightness or > 15% reduction in FEV1 from baseline will receive 5mg nebulised salbutamol as a bronchodilator.

10.2 Nasal brushing

This procedure has been used routinely for the diagnosis of the inherited condition primary ciliary dyskinesia for several years. This can cause some temporary discomfort but has been showed to be safe and well-tolerated. Occasionally minor nose bleeds can occur following a nasal biopsy. Any nosebleed will be treated appropriately by applying pressure to the nose whilst seated until bleeding ceases.

11.0 Withdrawal procedures

All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. If they request, all samples and data will be destroyed.

12.0 Data collection and management

12.1 Clinical and demographic data collection

The below are examples of fields already collected by the EMBARC database e.g.- this is not a comprehensive list and other aspects of medical history will be recorded

Age

Ethnicity

Gender
Height
Weight
Smoking history
Medical history
Co-morbidities
Number of exacerbations per year
Radiological distribution of bronchiectasis on last CT scan
Concomitant medications
Cause of bronchiectasis and results of diagnostic tests
Vaccination history
Current physiotherapy techniques
Age of diagnosis
Previous microbiology and lung function results.

Contact telephone number will be collected for contact to arrange and confirm follow-up visits and for reminders about exacerbation visits.

12.2 Data Management System

Data management will be conducted in compliance with the Tayside Medical Science Centre (TASC) standard operating procedure on Data Management. The data management system will be the EMBARC registry system, held by the health informatics centre (HIC) University of Dundee as approved by the Sponsor.

The data management system will be based on the protocol and case report form (CRF) for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The database is managed in line with all applicable principles of medical confidentiality and protection laws. The Data Controller will be the University of Dundee and the Data Custodian will be Health Informatics Centre (HIC).

12.3 Case report form (CRF)

A CRF will be compiled for each participant which will contain subject identification, any correspondence, along with data obtained throughout the study. In addition, details of each visit and any adverse events.

Before this information is shared with any user all identifiable data will be removed. The paper CRFs if used will be stored securely (in a locked room) within the respiratory departments or clinical research centres and will be accessible only by those directly involved within the study. Consent forms will be stored securely and separately from

other study documents. The CRF and consent forms will be stored for a minimum of 10 years and then destroyed.

12.4 Electronic data

Electronic data will be stored as part of the EMBARC project by the Health Informatic Centre (HIC). Individuals registering for this study will also register for the EMBARC study through a single consent form.

Data will be anonymised once all study procedures and follow up are completed.

12.5 Biological samples storage and disposal

All samples will be pseudoanonymised and coded before storage. Samples including blood, culture supernatant and lysed cells will be stored at -80°C. Cells sent for histology will be stored as resin blocks or as slides. Stored samples will be used for any other ethically approved study in the future. Videos and photographs of cells may also be stored. All cellular material will be stored according to the human tissue act under the university license. Ultimately, all cells for which investigation has been completed will be destroyed by incineration.

13.0 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given to the subject. Signed consent will be obtained from the subject at the start of visit 1 by the local investigator. Where a participant requests to speak with a physician from the study 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. Eligible individuals at participating cites will be invited to take part in the cilia sub study at visit 1 of the main study by the local investigator.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. 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.

The informed consent process will be conducted in compliance with TASC SOPs relating to obtaining informed consent from potential participants in clinical research.

14.0 Statistics and data analysis

14.1 Sample size calculation

The sample sizes for each element have had to be chosen subjectively, balancing potential detail against practical limits. As all the sample sizes are greater than 100, they should contain individuals from all subgroups containing more than 10% the population. Study aims one and two classify individuals into groups on the basis of their characteristics, so any realistic power calculations would involve strong assumptions about the distributions and correlations of the measured variables and therefore require data that will be collected during the study. Until that has been collected, the calculations would effectively be guesswork. The investigations for aim three will use as many relevant individuals as are available in the databases and, along with those for aim 4, will be highly dependent on the findings in the earlier stages.

14.2 Proposed analyses

For study aim one, to identify endotypes of bronchiectasis, an unbiased cluster analysis approach will be taken. As the number of practically distinguishable endotypes is unknown, the stability of representations containing different numbers of clusters will be compared, and the importance of the various characteristics to their separation will be investigated.

Study aim 2 will take a similar approach to samples from a smaller number of the patients during exacerbation. As these individuals are a subset of those examined for aim 1, their stable disease endotypes will be considered for inclusion in the cluster analysis. Descriptive statistics will be used to describe the qualities of typical members of each cluster and the differences between clusters.

For aim 3, the patterns identified in the first two parts of the study will be used to classify data from external biobanks and generalized linear models will be used to look for differences in those individuals' responses to treatment and disease trajectories. The classifications will also be applied to the identification of potential participants and samples for the proof of concept studies under aim 4. The analysis of those studies will depend on their particular forms and outcomes but follow generally recognized best practice.

15.0 Transfer of data

Patient data will be transferred between sites via the EMBARC database hosted by HIC.

16.0 Study management and oversight arrangements

16.1 Study management group

The study will be co-ordinated by a Study Management Group (SMG), consisting of the grant holder Chief Investigator (Professor James D. Chalmers), study lead (Professor Amelia Shoemark) external Principal Investigators (PIs), study manager and research nurse or equivalent.

16.2 Study steering committee

A Study Steering Committee will be established to oversee the conduct and progress of the study. The terms of reference of the steering committee are detailed in the study management file. Minutes of the steering committee will be maintained in the study management file.

16.3 Data monitoring committee

An independent data monitoring committee will be established to oversee study progress. The terms of reference of the data monitoring committee are detailed in the study management file. Minutes of the data monitoring committee will be maintained in the study management file.

16.4 Inspection of records

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and research ethics committee review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

16.5 Funding

Funding is provided by Asthma and Lung UK, The European Respiratory Society and by additional sponsors including the European Union Innovative Medicines Initiative and pharmaceutical companies. Investigators will not receive any financial incentive for recruitment or participation in this study over and above their normal conditions of employment.

17.0 Good clinical practice

17.1 Ethical conduct of the study

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). In addition to Sponsorship approval, a favorable ethical opinion will be obtained from an appropriate REC. Authorisation from an appropriate competent

authority(s) and appropriate NHS R&D permissions(s) will be obtained prior to commencement of the study.

18.0 Confidentiality and 19.0 Data Protection

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

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

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate study staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

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

20.0 Insurance and Indemnity

The University of Dundee and Tayside Health Board are co-sponsoring the study.

20.1 Insurance

The University of Dundee holds Clinical Trials indemnity cover which covers the University's legal liability for harm caused to patients/participants.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.
Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

20.2 Indemnity

The sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

21.0 Adverse events

21.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
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

21.2 Recording and reporting adverse events

Participants will be asked about any adverse events related to study procedures at the visit. We will not record all AE's and SAE's that occur to study participants; instead only those events that occur **at the study visit** and which are directly the result of study procedures. This would include adverse events related to venepuncture (*for e.g. bruising, swelling, bleeding from the site, light headedness and rarely, infection at the site that blood has been taken from*) for research purposes. These risks will be clearly

stated in the Patient Information Sheet. All AEs and SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate.

The CI/PI will make a clinical judgment as to whether an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

The CI or delegate will ask about the occurrence of AEs and SAEs and hospitalisations at every visit during the study. SAEs which are both unexpected and related to study participation will be reported to the Sponsor Team and CI in the first instance and then REC as appropriate in accordance with current advice from the Health Research Authority (HRA) regarding safety reporting for Non-CTIMP studies. Non- UK sites will also follow their own countries regulations on safety reporting.

Worsening of the condition under study will not be classed as an AE but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior, where appropriate, will not be considered as an AE.

22.0 Protocol amendments deviations and breaches

The chief investigator will seek approval for any amendments to the protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance office immediately.

23.0 Feedback of results and Incidental findings

In the majority of cases we do not anticipate that results of the tests performed will immediately influence management. Any incidental findings (e.g. previously undiagnosed condition) considered to be clinically significant will be reported to the

participant's GP and/or consultant by the CI or Site PI, with the consent of the participant. The patient's GP will be informed of their participation in this study. Two examples of where relevant clinical information could be found would be new diagnosis of alpha-1 antitrypsin deficiency, as the study will measure alpha-1 antitrypsin and diagnosis of primary ciliary dyskinesia through assessment of cilia function and structure. If these diagnoses are made they will be communicated to the physician at the site who should make appropriate arrangements for management and follow-up of the patient.

24.0 Study Record retention

All study documentation, results and data will be archived in compliance with Sponsor Standard Operating Procedures. All trial documentation, electronic and paper, will be kept for 10 years. Medical records will be maintained in compliance with local NHS policy on retention of medical records. The CI will be responsible for arranging the archiving of the TMF and ensuring that research data is archived in a way that will permit accurate reconstruction of the research. Sites will be responsible for archiving local trial records including the ISF. Sponsor will be responsible for archiving the Sponsor file.

25.0 End of Study

The end of the study is defined as the last patient last visit. The Sponsor or Chief Investigator have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

26.0 Reporting, publications and notification of results

26.1 Authorship policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and a clinical study report will be prepared.

Authorship on publications shall be determined in accordance with ICMJE recommendations.

26.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

26.3 Peer review

This study has been funded by Asthma and Lung UK, the European Respiratory Society and others who have reviewed the grant application and the protocol has been reviewed and approved by the investigators.

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

References

1. Chalmers JD, Aliberti S, Blasi F. State of the art: management of bronchiectasis in adults. Eur Respir J 2015; 45(5):1446-62.

2. Bronchiectasis in: The European Lung White Book, European Respiratory Society 2014.

3. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, Smeeth L, Brown JS. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004-2013: a population based cohort study. Eur Respir J 2016;47(1):186-93.

4. Barker AF, O'Donnell AE, Flume P et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med 2014;2(9): 738-49.

5. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic pseudomonas aeruginosa infection. Am J Respir Crit Care Med 2014; 189(8):975-82.

6. http://investor.aradigm.com/releasedetail.cfm?ReleaseID=1001671, accessed 4th Feburary 2017.

7. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013;309:1251–9.

8. Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013;309:1260–7.

9. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 2012; 380(9842):660-7.

10. Elborn JS, Tunney MM. Macrolides and bronchiectasis: clinical benefit with a resistance price. JAMA 2013;309(12):1295-6.

11. Bilton D, Tino G, Barker AF et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax 2014; 69(12):1073-9.

12. Bilton D, Daviskas E, Anderson SD et al. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest 2013;144(1):215-25.

13. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. Chest 1998;113:1329–34.

14. Nicolson CH, Stirling RG, Borg BM, et al. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012;106(5):661-7.

15. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012; 7:CD002991.

16. Chalmers JD, Loebinger M, Aliberti S. Challenges in the Development of New Therapies for Bronchiectasis. Curr Opinion in Pharmacotherapy. 2015;16(6):833-50.

17. Hetherington KJ, Heaney LG. Drug therapies in severe asthma- the era of stratified medicine. Clin Med (Lond) 2015;15(5):452-6.

18. Ghebre MA, Bafadhel M, Desai D, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 2015;135(1):63-72.

19. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting B-2 agonist efficacy in COPD. Thorax 2016;71(2):118-25.

20. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016;47(2):410-9.