



BronchUK: protocol for an observational cohort study and biobank in bronchiectasis

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ABSTRACT Bronchiectasis has been a largely overlooked disease area in respiratory medicine. This is reflected by a shortage of large-scale studies and lack of approved therapies, in turn leading to a variation of treatment across centres. BronchUK (Bronchiectasis Observational Cohort and Biobank UK) is a multicentre, prospective, observational cohort study working collaboratively with the European Multicentre Bronchiectasis Audit and Research Collaboration project. The inclusion criteria for patients entering the study are a clinical history consistent with bronchiectasis and computed tomography demonstrating bronchiectasis. Main exclusion criteria are 1) patients unable to provide informed consent, 2) bronchiectasis due to known cystic fibrosis or where bronchiectasis is not the main or co-dominant respiratory disease, 3) age <18 years, and 4) prior lung transplantation for bronchiectasis. The study is aligned to standard UK National Health Service (NHS) practice with an aim to recruit a minimum of 1500 patients from across at least nine secondary care centres. Patient data collected at baseline includes demographics, aetiology testing, comorbidities, lung function, radiology, treatments, microbiology and quality of life. Patients are followed up annually for a maximum of 5 years and, where able, blood and/or sputa samples are collected and stored in a central biobank. BronchUK aims to collect robust longitudinal data that can be used for analysis into current NHS practice and patient outcomes, and to become an integral resource to better inform future interventional studies in bronchiectasis.



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BronchUK is a multicentre, observational cohort study and biobank collecting longitudinal patient data to be used for analysis into current NHS practice and patient outcomes, and to better inform the design of future interventional studies <https://bit.ly/3svngZc>

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Introduction

Bronchiectasis is now being recognised for its increasing importance to people affected by the condition, and has been neglected in respiratory medicine [1, 2]. In contrast to conditions such as asthma and COPD, bronchiectasis has previously been viewed as an ‘orphan disease’ [3, 4]. Recent data consistently show an increasing prevalence of the condition across European and US healthcare systems [5–7], emphasising the need for better resourced research in this area.

This need is reflected by a lack of large-scale cohorts and the recruitment of well-characterised patients into intervention studies. There are few, if any, drug therapies specifically licensed for bronchiectasis available across multiple countries [8–10] and current guidelines remain mostly reliant on studies with low-grade evidence [11, 12]. Naturally, this leads to variations in care.

A recent upsurge in interest has revitalised the field and the European roadmap project for bronchiectasis has helpfully delineated the priorities in bronchiectasis [13]. However, major questions remain unanswered that can be facilitated by better epidemiological data, better understanding of the natural history of the disease and risk factors for adverse outcomes such as exacerbations, hospitalisations and mortality [13].

The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) project has helped create a network of bronchiectasis centres across Europe that are recruiting patients into a multinational study [14–16]. In parallel to this, the UK bronchiectasis community recognised a need to understand healthcare outcomes and variation in practice across the UK. The Bronchiectasis Observational Cohort and Biobank UK (BronchUK) is a project arising from a Medical Research Council (MRC)-funded partnership that consists of a consortium and is also the name of the associated database. The UK bronchiectasis consortium is an expanding group based around the recruiting centres plus affiliated scientific experts in other fields (e.g. microbiology and health economics). BronchUK is envisaged as a focal point for the UK bronchiectasis community with a number of workshops led by BronchUK members but open to the wider community. BronchUK complements EMBARC, with significant elements of the projects overlapping, including the database design and platform allowing comparisons across the wider EMBARC dataset.

In addition, BronchUK has a biobank and regulatory approval to link individual patient data to national healthcare data (see table 1, shared and unique elements between EMBARC and BronchUK). Existing and prospective study designs and recruitment will be enhanced by cohorts of well-characterised patients, particularly where patients have given consent to be contacted for future research studies. The UK offers an important test bed for many aspects of bronchiectasis care with free healthcare at the point of access and established bronchiectasis guidelines, published by the British Thoracic Society (BTS) in 2010 and recently updated [1], with subsequent national audits [17, 18]. The potential to utilise UK data systems for healthcare usage and outcomes enables exploratory analyses between the treatment regimens and patient outcomes, which will in turn better inform future intervention studies.

Study objectives

The objectives of the study are: to develop a multicentre bronchiectasis registry incorporating baseline data collection with annual follow-up data for at least 5 years; to facilitate the creation of a biobank in bronchiectasis to underpin future mechanistic studies; to describe the treatment patterns across the UK, phenotypic data, comorbidities and healthcare use; to facilitate multinational cooperation, especially with EMBARC, within academia and with industry to develop new discoveries; to develop key partnerships with experts not currently working in bronchiectasis to optimally use the datasets.

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TABLE 1 EMBARC and BronchUK shared and unique elements

Shared elements	Unique elements to BronchUK
Multicentre	Linked healthcare data to confirm healthcare use (and compare regimens within one healthcare system)
CT-confirmed bronchiectasis	Psychological measurements (anxiety and depression scores)
Severity score	Linked to national mortality data sets
Pathogen status	Potential to link with NHS digital and or other NHS number linked projects (PHOS-COVID)
Treatment/medications	Samples stored in biobank
Quality of life measures	
Mortality and exacerbation rates	

EMBARC: European Multicentre Bronchiectasis Audit and Research Collaboration; BronchUK: Bronchiectasis Observational Cohort and Biobank UK; CT: computed tomography; NHS: National Health Service.

Study design

The registry is a multicentre, prospective, observational cohort study enrolling consecutive adult patients with radiologically confirmed bronchiectasis across the UK. The study is noninterventional and recruiting from secondary care centres (see table 2, full list of participating centres). BronchUK runs in parallel with the EMBARC trial protocol as published and is acknowledged herein, where appropriate repetition is included.

The study collects baseline data and delineates routine practice across participating secondary care centres aligned to prevailing national and international guidelines on aetiological testing and monitoring of bronchiectasis. Patients giving informed consent to participate have baseline data collected and annual review data recorded *via* routine hospital visits for up to 5 years. These include basic demographics; reported comorbidities; results from aetiological testing; pulmonary function tests; recent sputum microbiology; health-related quality of life (HRQoL); symptoms (including MRC dyspnoea); radiological data; treatment and physiotherapy regimens and healthcare usage/exacerbation rates (figure 1).

BronchUK received central ethical approval from the National Research Ethics Service Committee North East – Newcastle and North Tyneside 1, (July 17, 2015, ref. 15/NE/0172) and is led by Newcastle University, UK, with National Health Service (NHS) sponsorship provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust. The study website is located at www.bronch.ac.uk. The registry was developed in alignment with EMBARC with additional features of linking patients' routine study data with national healthcare databases, including the UK Office of National Statistics (ONS) dataset. Furthermore, recruiting centres with access to appropriate facilities can also biobank sputum, serum and plasma.

TABLE 2 Full list of participating NHS centres

Freeman Hospital (Newcastle upon Tyne Hospital NHS FT)
 University College Hospital (University College London Hospitals NHS FT)
 Royal Infirmary of Edinburgh (NHS Lothian)
 The Wellcome Trust-Wolfson NI CRF (Belfast Health and Social Care Trust)
 Royal Papworth Hospital (Royal Papworth Hospital NHS FT)
 University Hospital Llandough (Cardiff and Vale University Health Board)
 Queen Elizabeth Hospital (University Hospitals Birmingham NHS FT)
 Royal Brompton Hospital (Royal Brompton and Harefield NHS FT)
 Southampton General Hospital (University Hospital Southampton NHS FT)
 Altnagelvin Area Hospital (Western Health and Social Care Trust)
 Royal Free Hospital (Royal Free London NHS FT)
 North Tyneside General Hospital (Northumbria Healthcare NHS FT)
 Royal Lancaster Infirmary (University Hospitals of Morecambe Bay NHS FT)
 Aintree University Hospital (Liverpool University Hospitals NHS FT)
 Ninewells Hospital (NHS Tayside)

NHS: National Health Service; BronchUK: Bronchiectasis Observational Cohort and Biobank UK; FT: Foundation Trust.

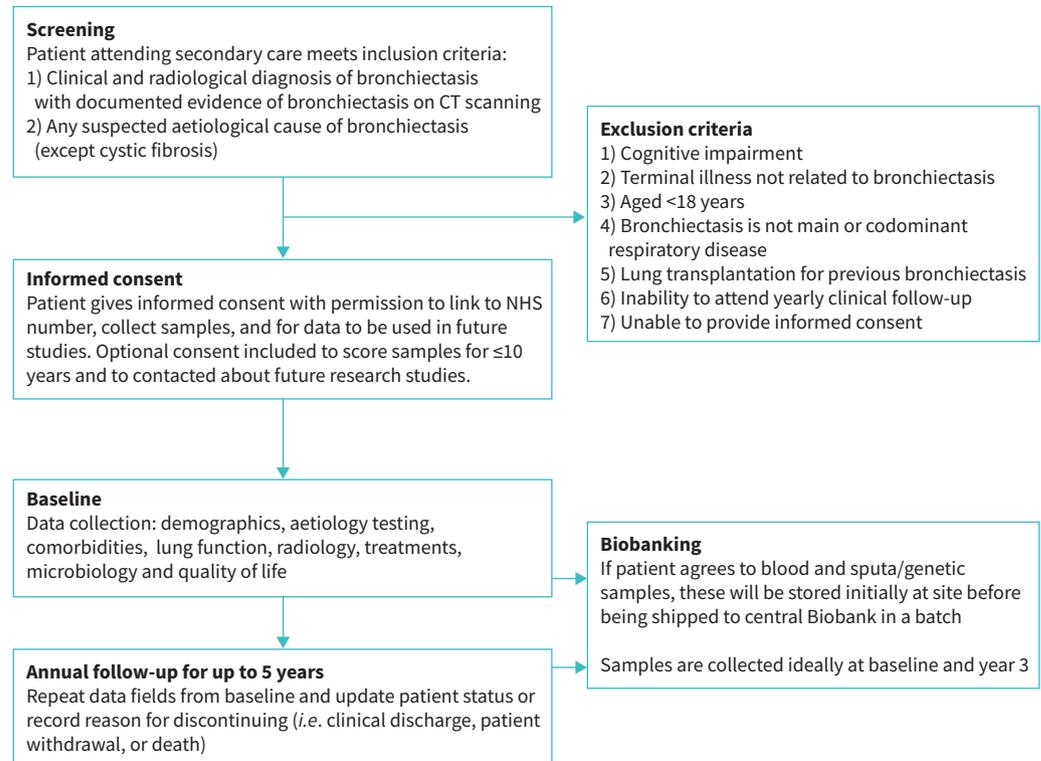


FIGURE 1 Study flow chart. CT: computed tomography.

Participants

Participants are patients with a primary diagnosis of bronchiectasis that meet the following inclusion and exclusion criteria. The inclusion criteria of this study are: adults with a clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections); and historical computed tomography (CT) of chest demonstrating bronchiectasis (bronchial dilatation) affecting one or more lobes.

The exclusion criteria are: patients who are unable or unwilling to provide informed consent; bronchiectasis due to known cystic fibrosis or bronchiectasis is not the main or co-dominant respiratory disease; prior lung transplantation for bronchiectasis; and patients already enrolled into EMBARC.

Identification and recruitment

Patients are identified and recruited from secondary care outpatient clinics in either general respiratory or specialist hospital clinics. It should be noted that participants entering BronchUK cannot be simultaneously entered into EMBARC. This is to avoid inadvertent double counting of the same patient as two individual patients in the larger EMBARC dataset.

Follow-up

Patient data are collected on an annual basis (within a 6-month variance) aligned to routine clinical attendance for up to 5 years, unless a patient is clinically discharged or withdraws from the study.

HRQoL

The registry uses both the 'Quality of Life – Bronchiectasis' questionnaire version 3.1 [19] and the St George's Respiratory Questionnaire (SGRQ) [20]. An automatic calculator tool is incorporated into the registry platform to aid calculation. The former reflects the use of this in EMBARC as it is the only disease-specific HRQoL tool that has been specifically developed and validated for bronchiectasis. We have included the SGRQ as this has prior validation in bronchiectasis and allows comparison to other datasets. We also included the Hospital Anxiety and Depression Scales to define the extent of psychological comorbidity in bronchiectasis.

Aetiology

The aetiology of bronchiectasis is determined by the physician caring for the patient. However, extensive data are collected on the aetiological testing performed. Based on the testing recommended by consensus guidelines, the underlying basis for an aetiological diagnosis is collected and can be validated [21].

Exacerbations

We followed the EMBARC proposal to use a pragmatic definition of an exacerbation, allowing self-managed exacerbations to be included [14]. Severe exacerbations are defined as per BTS criteria as an exacerbation requiring hospital admission (or hospital-at-home management [1]). Hospital attendances such as emergency room visits that do not result in hospital admission are also recorded.

Sputum colour

Sputum colour is evaluated using a validated photographic sputum colour chart that rates colour from 1 (mucoid) to 4 (highly purulent) [22].

Lung function

Lung function is recorded as noted in the EMBARC protocol with height, weight and post-bronchodilator spirometry values [23] consistent with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines as per EMBARC [14].

Severity of disease

The variables required to calculate the Bronchiectasis Severity Index (BSI) are recorded [24], such as history of hospitalisations, MRC dyspnoea score and radiological extent of disease. Like EMBARC, the database platform automatically calculates BSI scores [14, 24].

Smoking status

Current and past smoking status was determined, including pack-years smoked.

Comorbidity

We record other respiratory (e.g. asthma, COPD) and nonrespiratory comorbidity.

Microbiology

Microbiology data arising from any sample (sputum, bronchoalveolar lavage, induced sputum) collected in either stable state or at exacerbation is recorded. To align data with EMBARC, we adopted the definition of colonisation as two positive samples at least 3 months apart when clinically stable. We also collect any routinely available antibiotic susceptibility test results. Again, in alignment with EMBARC, reflecting the clinical importance of *Pseudomonas aeruginosa* in driving exacerbations and mortality, the database will collect specific data on *P. aeruginosa*, including any historical isolation of *P. aeruginosa*. Furthermore, wherever recorded clinically, we also enter mucoid *versus* nonmucoid status for *Pseudomonas* data. There is a section for entry of anti-*Pseudomonas* therapy, including nebulised antibiotics and any eradication treatments used.

Radiology

Reflecting the simple nature of the Reiff score [25] and the adoption of this into the EMBARC registry, we are asking recruiting centres to use this system. Historical CT scans are recorded at baseline and any scan undertaken during the study for clinical reasons are entered in the subsequent annual review form. There is the ability to look at longitudinal changes in CT but only where scans were undertaken for clinical reasons as per routine hospital care. We have not sought funding for over-reading of CT scans, in part, as it is highly complex and expensive to coordinate across multiple centres.

Treatments

Details are recorded on treatment, including all oral and inhaled therapies and maintenance antibiotics (systemic or pulmonary targeted, mucoactive drugs and anti-inflammatories). Comprehensive data on physiotherapy practise are also recorded, along with vaccination status. Treatment options are regularly updated as new therapies complete randomised trials and become available during the study.

Quality control

The database has been adapted from the EMBARC platform allowing a well-established platform with integral quality control to be applied. As previously, the database incorporates automated logic checks to alert users when data entered are outside expected range and to prevent incorrect values being entered. Each case entered into the registry is manually verified by a member of the central study team and data

queries, including any missing values, are resolved with the study site. We have followed the source data verification and random audit at study sites employed in EMBARC to ensure quality. Furthermore, we have included on-site monitoring and assessment of data entry in a subset of patients where necessary. Source data verification and random audit is also conducted across study sites.

Governance and unique identifiers

Reflecting the study's aim to characterise disease burden and healthcare use, we gained overarching national regulatory approval and individual patient permission during consent to link patient data to a unique identifier. This identifier allows patients to be cross-referenced with UK healthcare data (digital.nhs.uk) and the ONS (www.ons.gov.uk) giving us both healthcare use and mortality data. This ability to identify patients results in a data-handling protocol limiting all data to a 'Safe Haven'. We have worked with the Health Informatics Centre (HIC) based at the Farr institute, University of Dundee, to provide a process that prevents identifiable data to be exported from Safe Haven.

Biobank sampling

Samples being biobanked depend on the capability of each individual centre. We are biobanking whole blood suitable for DNA extraction and genotyping studies, as well as serum and plasma suitable for biomarker studies. Sputum is stored for future microbiome analysis and in selected centres sputum sol is also prepared suitable for inflammatory marker analyses. These samples should allow endo-typing of bronchiectasis and correlation with genomic data from both the host and microbiome in future studies. The biobanking follows a standardised operating procedure (SOP), though not all sites are able to provide all samples in all patients. The quality control for the samples is based on audits of the SOP worksheets. Patients can still be recruited into the study even if they are unable to provide samples.

Sample size

We chose a pragmatic sample size of 1500 patients, allowing for rare disease aetiologies to be captured. Our aim was to have at least nine centres recruiting to allow for a geographic spread across the UK. We have broadened this to include up to 15 centres with further centres welcomed.

Governance, oversight and data sharing

The study is conducted in accordance with the principles of Good Clinical Practice. We have obtained approvals from the national Health Research Authority and each partner site requires separate institutional approval.

The registry is held securely in the University of Dundee HIC parallel to the EMBARC registry. Our data are shared with EMBARC to allow a bigger European dataset.

Access to the data is first considered *via* an approvals process and access committee. The data are retained within the Safe Haven model (www.scot-ship-toolkit.org.uk/information-page/ship-safe-havens) and can be accessed either through a closed virtual desktop that allows secure access and data analysis but prevents copying or downloading of data, or data can be extracted and processed into summary format by the study team and then provided to the requesting researcher with no identifiers. Both models ensure complete data security. Active investigators and other stakeholders have unrestricted access to their own NHS site data. As per EMBARC, the database and governance processes surrounding data management and access are fully compliant with the UK Data Protection Act 1998 and the Data Protection Directive 95/46/EC of the European Parliament and of the Council (1995).

Access to the biobank also requires approvals from the biobank access committee of BronchUK. Priority is given to those with formed projects and appropriate ethical approval and funding in place to conduct the study.

The BronchUK study group follows the International Committee of Medical Journal Editors recommendations regarding authorship. The results of the study are disseminated in the form of annual reports, conference abstracts and peer-reviewed publications.

Discussion

Bronchiectasis research is helping to tackle major gaps in our understanding of the disease and moving us towards completion of the roadmap tasks [13]. Reflecting the heterogeneity within bronchiectasis, the larger European registry is well placed to define the importance of certain rare aetiologies and provide a good view of variation across countries.

These large registries are needed as rare diseases or aetiologies are unlikely to be well represented in single centre studies. Prior multicentre studies have helped show the importance of bronchiectasis and

rheumatoid arthritis overlap (BROS) as having possible adverse prognostic effects [26]. One notable aspect of this study was the variation in rates of BROS between centres. This may depict referral patterns, local healthcare systems or genuine differences in the rates of BROS between countries. The aim of BronchUK is therefore to study variation within a country where access to healthcare is expected to be similar and where we can track disease outcomes using national datasets of healthcare use [27].

Strengths of the project include using a platform compatible with EMBARC datasets and the rigorous quality control mechanisms already successfully applied within EMBARC. Consistency of data collection methods and alignment of databases will allow comparison across international registries such as EMBARC, the Indian Bronchiectasis Registry, the Australian Bronchiectasis Registry [28] and KMBARC registry [29]. These data enable a more global comparison of disease characteristics and management and this approach has already helpfully highlighted important differences between European and Indian patients [30].

A further strength is the biobanking of samples for future biomarker and/or genetic analysis. This allows mechanistic studies to be conducted.

Certain limitations need to be acknowledged. The study is recruiting from a number of centres across the UK with a large sample size. However, despite this, it is possible we will not capture the full experiences of patients across the UK. Importantly, patients that are being recruited into EMBARC from UK sites cannot be simultaneously recruited into BronchUK. Keeping the projects separate at recruitment allows centres that cannot biobank contribute to EMBARC, and centres that can biobank, contribute to BronchUK. This avoids double counting of the same patient when BronchUK datasets are shared/imported into the larger EMBARC dataset. The ability to pool EMBARC-UK data and BronchUK data will, however, give us a powerful tool to capture not only a broader national view of bronchiectasis care in the UK but also how variation across a single healthcare system might inform better care.

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Microbiology and Infectious Diseases Aspergillosis Guidelines group, and the British Society for Medical Mycology Standards of Care committee. R. McNally reports that he is a coinvestigator on the MRC grant for the current study.

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