BRistol Evaluation of novel Airways diagnostics, Therapies & Healthcare outcomEs: BREATHE

Short title: BREATHE

Ethics Ref:

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SUMMARY

Airways disease describes a group of conditions primarily consisting of asthma and chronic obstructive pulmonary disease (COPD). 5.4 million people suffer from asthma in the UK and COPD admissions account for over 1 million hospital bed days and 30,000 deaths. They are also among the most costly chronic diseases, with the annual costs of COPD £1.9 billion and asthma £3 billion[1,2]. Airways disease disproportionately effects lower socioeconomic groups and this group of patients represent an extremely vulnerable and underrepresented group in British healthcare with a significant burden of morbidity and mortality[1,2,3].

The North Bristol NHS Trust provides a NHSE specialist commissioned Complex Airways Service which manages referrals from throughout the region. This provides an exciting opportunity to improve our understanding of the presentation and clinical outcomes of a detailed clinical phenotyped cohort with asthma and COPD. This study aims to build strong links with other centres and establish meaningful cross-disciplinary collaborations.

The BREATHE study is a longitudinal cohort study, using routinely collected data, that will assess treatable and non-treatable traits of patients with confirmed or suspected airways disease both during exacerbation and at stable state. Participants will be recruited directly from the Complex Airways Clinic. They will be assessed routinely by a multi-disciplinary team, basic diagnostics will be performed and a management plan decided. The BREATHE study will then record data from the initial clinic appointment, at 6, 12 and 24 months after recruitment. This 2-year data collection method will ensure key data points and outcomes are captured. It may be necessary for patients to be included in more than one treatment pathway during their care. Patient's may also be discharged and re-referred by primary care. Each pathway will record data for a maximum of 24 months. During an exacerbation we may see the patient on day 0, 7 and 14 via our Airways urgent clinic as part of their routine clinical care. We will assess the prevalence of asthma 'mimics' including inducible laryngeal obstruction which is a considerable burden in terms of non-asthma morbidity and drain on healthcare.

BREATHE does not intend to conduct any additional sampling or data collection that will not be part of a patient's clinical care. However, this is a rapidly developing area in respiratory medicine, especially with the emergence of new biologics. The adaptive nature of this study will allow for changes (with ethical approval) to the protocol with the emergence of novel diagnostics and therapies so that our objectives can be met whilst the landscape of airways medicine changes.

OVERVIEW

Study Title	BRistol Evaluation of novel Airways diagnostics, Therapies & Healthcare outcomEs: BREATHE study
Internal ref. no. / short title	BREATHE
Study Design	Prospective Longitudinal Observational Cohort Study
Study Participants	Patients with known or suspected airways disease that have been referred to the Complex Airways Service
Planned Sample Size	250 patients per year
Planned Study Period	5 years
Objectives	
Primary	To describe clinical and biological characteristics of patients with suspected or known airways disease.
Secondary	1. Establish airways disease phenotypes and impact on disease outcomes 2. Assess how the multidimensional clinical assessment impacts disease outcomes 3. Assess response to treatment offered as part of the Complex Airways Service 4. Establish prevalence of asthma mimics in this population, including inducible laryngeal obstruction.

ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
BPD	Breathing Pattern Disorder
COPD	Chronic Obstructive Pulmonary Disease
CF	Consent Form
CI	Chief Investigator
CLE/CLP	Continuous Laryngoscopy with Exercise/Provocation
CRF	Case Report Form
CT	Computed tomography
CXR	Chest radiograph
DEXA	Dual-energy X-ray Absorptiometry
FEV_1	Forced expiratory volume in 1 second
FeNO	Fraction exhaled nitric oxide
FVC	Forced vital capacity
GCP	Good Clinical Practice
HRA	Health Research Authority
ICU	Intensive Care Unit
ILO	Inducible Laryngeal Obstruction
NBT	North Bristol NHS Trust
NHS	National Health Service
PI	Principal Investigator
PIS	Patient Information Sheet
PROMS	Patient Reported Outcome Measures
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SALT	Speech and Language Team
TMF	Trial Master File

BACKGROUND AND RATIONALE

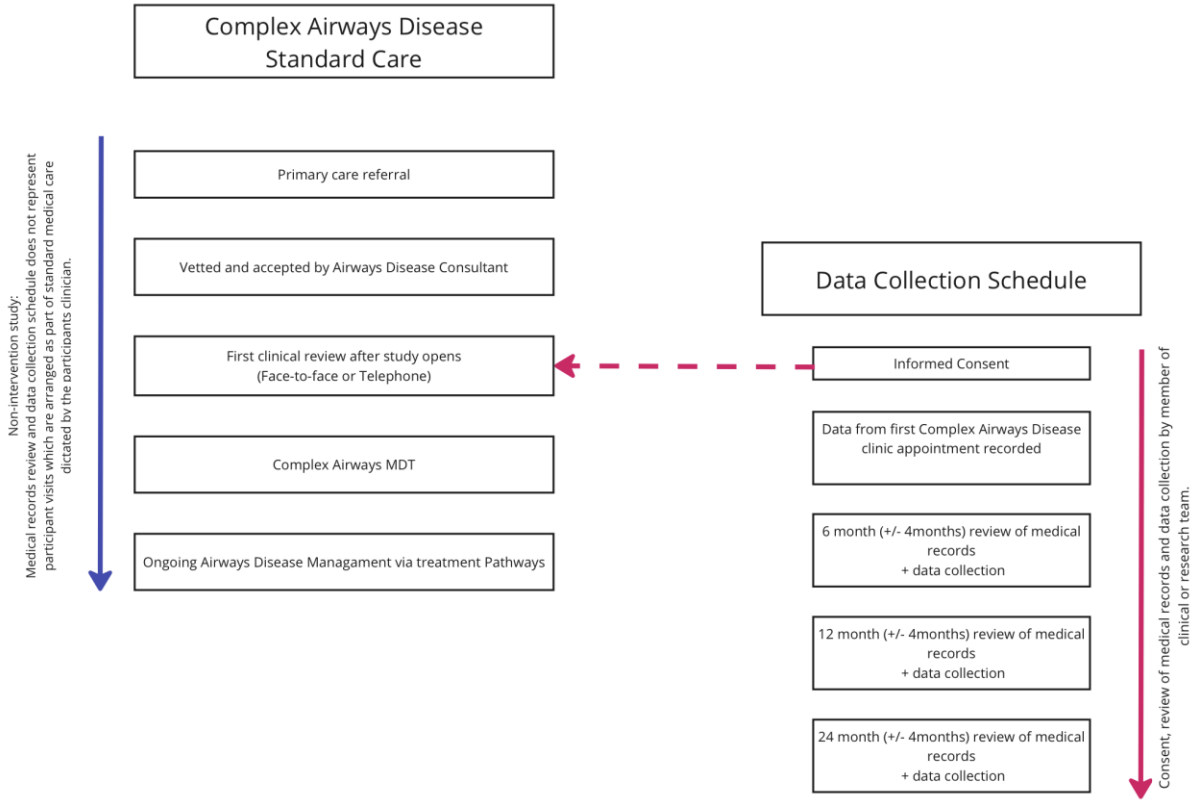
Lung disease in the UK costs a staggering £11 billion a year, with £9.9 billion falling directly on the NHS or patients in private costs. Furthermore, over £1.2 billion falls on the wider economy through workdays lost. As such, lung disease is the 4th most costly disease area in the UK, after mental health conditions, musculoskeletal diseases and heart disease. Furthermore, reducing the impact of respiratory disease and associated health inequalities is a UK Government priority[1,2,3,4].

Airways disease is an umbrella term for chronic obstructive pulmonary disease and asthma. They are both complex diseases which are difficult to define, diagnose and treat. Nonetheless, they are conditions characterised by cough, wheeze and breathlessness which occur in a clinically stable state and worsen during acute deterioration, or exacerbations. Acute exacerbations of airways disease are associated with significant risk of death, 5% of COPD patients will not survive an acute exacerbation (30,000 deaths per year), the third highest mortality rate in Europe. COPD is common, effecting up to 3 million people in the UK, accounting for 55% of all chronic respiratory diseases[3,5,6,7]. Almost half of COPD patients are undiagnosed and at risk of disease progression whilst exposures and exacerbations go unmanaged[6,7]. Asthma effects 12%, or 5.4 million people in the UK and has an annual price tag of £3 billion[2,8]. Patients who suffer frequent recurrences of an exacerbation of COPD and asthma have more numerous primary care interactions, increased emergency room visitation, increased hospitalisations, and increased admissions to the Intensive Care Unit (ICU)[5,6,7]. Bristol is amongst the highest, 5% nationally, in terms of acute admission to hospital with an exacerbation of COPD and it is well understood that whilst airways disease affects people from all walks of life, it disproportionately affects lower socioeconomic groups.

The airways diseases have been neglected in comparison to other non-communicable diseases. Poor financial and intellectual investment coupled with the heterogeneity of both conditions is such that we are still debating definition of disease, severity and what constitutes an exacerbation. Whilst these seemingly simple concepts remain elusive we are unable to push forward with preventative approaches both in the development of these conditions but also in the management of acute deterioration which is so detrimental to morbidity and mortality.

The **BR**istol **E**valuation of novel **A**irways diagnostics, **T**herapies & **H**ealthcare outcom**E**s: BREATHE study is designed to improve the health and outcomes of our patients with airways disease by gaining a better understanding of the underlying pathology and the effects of treatments. By characterising and phenotyping each of our patients we can add to the mechanistic understanding of underlying disease processes which will in turn allow us to tailor our potential treatment options and better manage their disease[8]. The North Bristol NHS Trust Complex Airways Service leads the way in novel diagnostics and systematic multidimensional assessment of patients presenting with severe asthma and COPD.

STUDY FLOW CHART



See DATA COLLECTION section for more detailed description of standard care

OBJECTIVES AND OUTCOME MEASURES

Primary Objective:

To describe clinical and biological characteristics of patients with suspected or known airways disease.

Secondary Objectives:

1. Establish airways disease phenotypes and impact on disease outcomes
2. Assess how the multidimensional clinical assessment impacts disease outcomes
3. Assess response to treatment offered as part of the Complex Airways Service
4. Establish prevalence of asthma mimics in this population, including inducible laryngeal obstruction.

Below is a list of potential research questions based on current diagnostics and therapeutics. These are the areas that will further airways management based on the data that is available as part of current clinical care. The Complex airways service manages patients with asthma, COPD and bronchiectasis. Some research questions will share common themes, and others will be disease specific:

1. Clinical Outcomes
   1.1 Do 70% of patients on maintenance oral corticosteroid who are initiated on monoclonal antibody therapy see a reduction in their steroid use?
   1.2 Is frequency of airways exacerbation associated with cardiovascular co-morbidity
   1.3 Is the prevalence of Th2 high disease in the southwest comparable to the national average?
   1.4 Is a Th2 high phenotype associated with greater exacerbation in bronchiectasis patients?
   1.5 What is the prevalence of Th2 high, biologics non responder phenotype?
   1.6 What is the prevalence, risk factors and outcomes of inducible laryngeal obstruction in disease population?
   1.7 What is the prevalence, risk factors and outcomes of breathing pattern disorder in disease population?
   1.8 What is the impact of co-morbidity on disease outcome in this study population?
   1.9 Do biologics improve small airways function (airways oscillometry)?
   1.10 What is the impact of pharmacological and non-pharmacological therapies, lung function, co-morbidities and mental health and wellbeing?
   1.11 Does gender impact exacerbation frequency?

2. Patient-reported outcomes
   2.1 What proportion of patients with COPD have an abnormal MOCA?

3. Biomarkers of disease
   4.1 What biomarkers are associated with patients who fail to respond to monoclonal antibody therapy?
   4.2 What proportion of those diagnosed with ABPA have classic features on CT scan?
   4.3 What is the role of sputum eosinophils in predicting outcomes in COPD?
   4.4 What proportion of super-responders to dupilumab have Th2 low disease?

STUDY DESIGN

BREATHE is a single centre, prospective longitudinal cohort study of patients who are referred to the Complex Airways Clinic at North Bristol NHS Trust (NBT). It is a platform which will include different sub-studies when they are developed in the future (with amendments reviewed by the sponsor and HRA at the time). The BREATHE-ILO is the first sub-study for which we will enrol participants alongside the BREATHE platform study. BREATHE will record routinely collected clinical data at each stage of the multidisciplinary assessment, diagnosis and management of each patient from initial assessment, until they are discharged by the service, or the study ends. The study will not include any additional investigations, questionnaires or patient visits which would not have been included as part of each patient's routine clinical management. We anticipate that the landscape of airways disease management will change over the next 5 years. As such we will incorporate an adaptive study design[9,10]. As novel diagnostics and therapeutics emerge, we anticipate that changes will be made to standard care which would necessitate changes to the data that we collect. If substantial changes are made, we will assess them for inclusion into the study and request further ethical approval if

necessary. We intend for the BREATHE cohort to be a source of potential subjects for future studies. For studies which involve a clinical trial of an investigational product or diagnostic method we will adopt a 'Trials within cohorts' design (TwiC)[11,12]. The method identifies participants for a trial from an existing cohort who are suitable for an upcoming interventional study. Participants are randomised to an intervention arm and further consent is obtained. Those not randomised to the intervention arm will continue standard care in line with the BREATHE study and act as the control group but without additional consent[11,12]. We will describe the two stage consent TwiC process at the point of consent into the BREATHE cohort with a choice to opt out if the participant wishes. Participants can still consent to participate in the BREATHE study without consenting to be contacted about future studies.

BREATHE-ILO sub-study

Outcomes (Report of outcomes at 2 years):

1. *Understanding the incidence of CLE/P confirmed ILO in patients referred to the Complex Airways Service.*
2. *Understanding the incidence of BPD in patients referred for CLE/P.*
3. *An analysis of the predictors of ILO or BPD in patients referred to the Complex Airways Service.*
4. *An analysis of the predictors of response to interventions for ILO and BPD.*
5. *An analysis of whether the diagnosis and treatment of ILO and BPD improve quality of life for the patient and reduce treatment burden.*

Inclusion Criteria

1. *Participant is willing and able to give informed consent for participation in the study*
2. *Known or suspected asthma mimics or inducible laryngeal obstruction*

Exclusion Criteria

1. *Participants who lack capacity to consent for themselves.*
2. *Aged below 16 years*

Recruitment

Recruitment for the BREATHE-ILO sub study will be identical to the recruitment processes of the BREATHE platform study (see section below). If a clinician suspects an underlying diagnosis of ILO or asthma mimics based on their history or from previously recorded investigations then they will be asked to consider consent to the BREATHE-ILO sub study. Participants can be enrolled onto both studies simultaneously.

PARTICIPANT IDENTIFICATION

Study Participants

Any patient over 16 years seen in the Complex Airways Clinic at the North Bristol NHS Trust

Inclusion Criteria

1. Participant is willing and able to give informed consent for participation in the study

2. Known or suspected airways disease

Exclusion Criteria

1. Participants who lack capacity to consent for themselves.
2. Aged below 16 years.

RECRUITMENT

Every patient with suspected airways disease who attends the complex airways clinic will be eligible to participate in this study as per the inclusion and exclusion criteria. Patients seen in this clinic are vetted by a Consultant Respiratory Physician who works in the complex airways service. This study does not involve recruitment from any other source.

Screening

Every patient with an appointment to attend the complex airways clinic with a known or suspected diagnosis of airways disease will be approached to participate in the study by the clinical care team who have access to personal information. Each participant will have time to read the PIS and ask questions before being asked to provide informed consent. No other information is required at screening.

Informed Consent

The participant must have provided written or verbal consent using the latest approved version of the Informed Consent Form before any data is recorded on the REDCap database for study purposes. The BREATHE study will use e-consent forms via the REDCap database. The consent data will be removed from REDCap for long-term storage as a pdf file as soon as clinically possible. The study manager will ensure this is done regularly in line with University of Bristol guidance on REDCap e-consent. A paper version of the e-consent form will also be available in the event that the e-consent form is unavailable. Standard NHS translation services are available to us in this clinical setting. If there is sustained need then we will translate the PIS and consent form at this stage. E-consent forms will be emailed to the participant immediately and can be printed off at a participants request. The e-consent PDF will be uploaded onto the hospitals Electronic Document & Records Management (EDMS) system or printed off as a paper copy for the participants medical notes.

Written and verbal versions of the Participant Information Sheet and Informed Consent Form will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant and the implications and constraints of the protocol. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. Participants can withdraw from the study in person but they will also be provided information on how to contact the clinical or research team by email, post or telephone to inform us that they would like to withdraw.

1. Face-to-face consent

If the patient is due to attend hospital for a face-to-face appointment, then the summary PIS will be sent in the post with their clinic letter. This will detail a summary of what the study will entail ahead

of their clinic visit so the patient will be aware of the study and know what to expect. The full PIS will be given to the patient during their appointment. The participant will be allowed as much time as they need to consider the information, and the opportunity to question the Investigator, their GP, or other independent parties to decide whether they will participate in the study. Written informed consent will then be sought by means of participant dated signature and dated signature of the person who presented and received the informed consent.

2. Remote Consent

The NBT Complex Airways Service is a regional service. As such patients may live out of area and will be offered a telephone consultation, not face-to-face, as part of their usual clinical care. In this situation we will post or email the full PIS to the patient ahead of their appointment. The participant will be given as much time as they need to consider the information, and the opportunity to question the investigator. We will seek consent from the patient either by posting a consent form to the patient for signing, or as witnessed verbal consent via telephone or virtual media (e.g video-conference). For witnessed verbal consent, the participant must be seen and/or heard to express their agreement with each element of the consent form by two members of the research team. The research team members must then both sign the consent form in the appropriate section. A copy of the completed consent form will be sent to the participant.

The person who received the consent must be suitably qualified, GCP trained and on the delegation log. A copy of the signed Informed Consent Form will be given or sent via post or email to the participant and a copy will be inserted into the patient's medical records. All study documentation will be kept secure in an access restricted environment. This will include paper consent forms, the Trial Master File (TMF) and the Investigator Site File (ISF). This area will only be accessible by BREATHE study staff and authorised representatives from the Sponsor and regulatory authorities for study-related monitoring, audits and inspection.

Participants can consider the information provided written or verbal consent after their initial assessment at the complex airways clinic. We will then retrospectively collect their baseline information and continue the study alongside routine clinical care thereafter.

Participants will be asked whether they would be willing to be approached regarding future studies run by the Academic Respiratory Unit, including commercial studies. Requests will be based on the information we gather as part of the BREATHE study. Participants can decline without this having an impact on their ability to enrol in BREATHE.

Subsequent Visits

Subsequent visits and investigations will be determined as per routine clinical care. Baseline data will be taken at the initial clinic appointment, at 6 (+/- 4months), 12(+/- 4months) and 24(+/- 4months) months after recruitment. These timepoints do not represent patient visits as they will be dictated by the clinician in charge of the participants airways care in line with standard care. They are the timepoints at which the participants medical records are scrutinised and data pertaining to their Airways disease entered into REDcap. Patient's may also be discharged and re-referred by primary care and participants will continue in the study in a new or different pathway. Each pathway will record data for a maximum of 24 months (see study flow chart). If a participant is under the care of the

Complex Airways Team for longer than the 2 year data collection schedule then we will store the outcome from annual MDT decisions until they are discharged from the service or the study ends.

Discontinuation/withdrawal of participants from study

Each participant has the right to withdraw from the study at any time. Data can also be withdrawn at the participant's request at any time up until the point it is analysed.

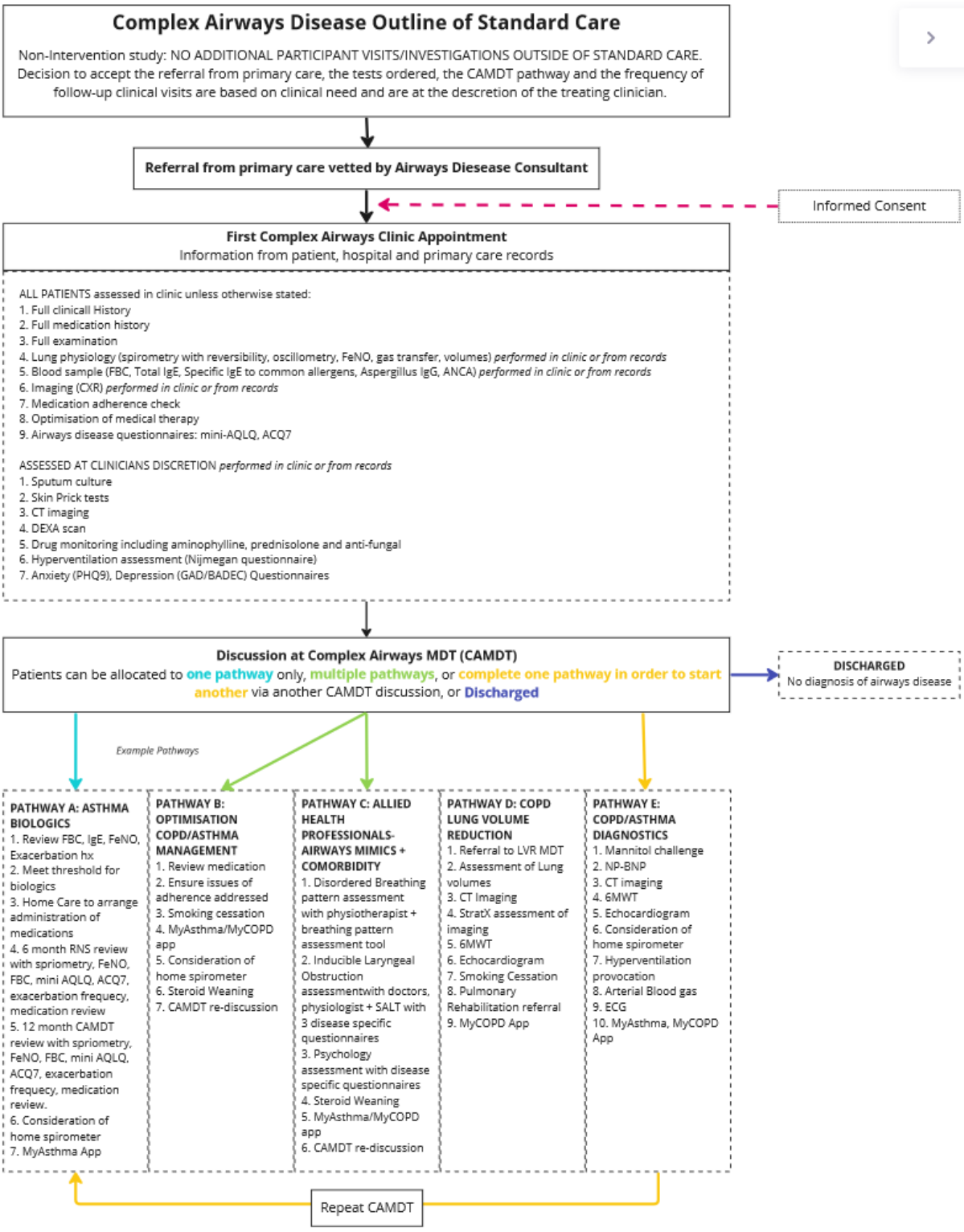
Definition of End of Study

The BREATHE study is a planned 10 year cohort study. It is currently funded for 5 years. As a cohort study it will have continuous outcomes and as such we fully expect to secure funding for a further 5 years. At the end of 2 years we will have reported on the BREATHE-ILO sub-study outcomes.

As per our current funding the last patient will be recruited at 3 years after the study start date. After which, data will be collected on remaining patients up to 24 months (5years). The end of study is the date that we have the final data lock.

DATA COLLECTION

The data sets outlined below include diagnostic and monitoring tests for all airways diseases and asthma-mimics. Each participant will have different information collected based on their diagnostic and treatment pathway.



First Appointment – Attendance at Complex Airways Clinic

At consent, participants will give permission for members of the approved research and clinical team to access their medical records. Researchers may use results found in the medical records or collected

at the first appointment. Researchers may also contact patients' primary care team for further information (such as medical and medication histories). This information will be conveyed to the research team over the phone, sent via secure NHS email systems or by using Connecting Care.

1. Clinical Information
    - Demographics including weight and height
    - Index of Multiple Deprivation (IMD)
    - History and examination by a Respiratory Physician (specialty grade and above) including medication history, exacerbation history, co-morbidity, triggers, admission to hospital and intensive care (ICU), history of ventilation, smoking history, social history
    - Sputum culture
    - Previous skin prick tests
2. Radiology
    - Chest x-ray (CXR)
    - Computed Tomography (CT) chest
    - Dual-energy X-ray Absorptiometry (DEXA)
3. Lung Function
    - Spirometry
    - Bronchodilator reversibility
    - Oscillometry
    - Fraction exhaled nitric oxide (FeNO)
    - Lung volumes, gas transfer
4. Blood Tests
    - Full blood count
    - Total IgE
    - Specific IgEs including Cat, Dog, House dust mite, Timothy Grass, Mixed moulds, Aspergillus
    - IgG Aspergillus
    - ANCA
    - Drug monitoring including theophylline, prednisolone and anti-fungal
5. Questionnaires
    - Mini-AQLQ
    - ACQ7
    - GAD
    - Nijmegan
    - Cognition (MOCA)
    - anxiety (PHQ9), depression (HADS)
    - CAT
    - Wellbeing WEMWBS
6. Adherence check and Optimisation of medications

Complex Airways Multi-Disciplinary Team Meeting (CAMDT)

Each participant will be discussed at an MDT following their First Appointment as part of their routine clinical care. They will have their airways phenotype documented. Their outcome will be documented as one of the following interventions which will be in keeping with the study flow chart:

CAMDT Intervention		**Rediscussion at CAMDT**	
		6m	12m
[A] Biologics pathway		✓	✓
[B] Optimisation Pathway: Medications		✓	✓
[C] Optimisation Pathway: Allied Health Professsional			
	1. Physiotherapy: Chest clearance clinic		✓
	2. Physiotherapy: Disordered Breathing Clinic		✓
	3. SALT: Nasendoscopy + ILO Assessment	✓	
	4. Psychology		✓
	5. Specialist Pharmacology: Full compliance check	✓	
[D] LVR Pathway			✓
[E] Diagnostics Pathway			
	1. Physiology	✓	
	2. Imaging	✓	
	3. Cardiac Assessment		
	4. Bloods	✓	
[F] Not in keeping with airways diagnosis- discharge to primary care			

Follow-up Streams

Re-discussion at CAMDT is proposed as a guide and it remains at the discretion of the lead clinician. Following diagnostics or specialist clinic referral, some patients may be re-discussed earlier in the interests of patient care. Follow-up in clinic is at the discretion of the clinician. Participants may be assigned to more than one treatment pathway as detailed below:

A. Biologics Pathway
   - Initiated on treatment within 4 weeks of discussion at CAMDT
   - Biologics follow-up: 6 and 12 month follow-up as per departmental protocol with either an Airways clinician or RNS
   - Lung function, FeNO, mini-AQLQ, ACQ7, clinical history and FBC.

B. Optimisation Pathway: Medications
   - Optimisation of inhaled therapy prior to commencing biologics
   - Treatment for those not eligible for biologics including Th2 low disease, bronchiectasis, COPD

C. Optimisation Pathway: AHP
   - Referral to a specialist clinic and follow-up at the discretion of the specialist
   - ILO; Newcastle Laryngeal Hypersensitivity Questionnaire, Vocal Cord Dysfunction Questionnaire
   - BPD; Nijmegen questionnaire, Breathing Pattern Assessment Tool

D. LVR Pathway
    - This will require discussion at a specific LVR MDT with input from thoracic surgeons and satellite hospitals

E. Diagnostics Pathway: It is at the discretion of the treating clinician when diagnostic tests will be reviewed and acted on. At a minimum, diagnostics will be re-discussed (if required) at a 6 month 'Follow-up CAMDT'
    - Physiology diagnostics will include: bronchodilator reversibility, provocation testing, FeNO, Lung volumes and gas transfer, 6MWT and oscillometry
    - Imaging will include CXR, CT, DEXA, StratX assessment
    - Cardiac Assessment will include ECG and echo
    - Blood testing will include Full blood count, Total IgE, Specific IgEs including Cat, Dog, House dust mite, Timothy Grass, Mixed moulds, Aspergillus, IgG Aspergillus, ANCA and Drug monitoring

Home Spirometry + MyAsthma/MyCOPD

Some participants will benefit from using a home spirometer. For example, those with a high oral steroid use, those who are failing a biologic therapy or those who are optimising their medications. We will issue them with a home spirometer and teach them how to use it. The study participants will perform home spirometry as specified by their lead clinician. MyCOPD and MyAsthma are self-management smart phone applications which have already been rolled out to willing asthma and COPD patients under the complex airways team as part of standard care. All participants are free to decline the home spirometer and smart phone applications with their reason documented if possible.

RISK ASSESSMENT

Investigations are only being performed as per routine clinical care. Therefore, no additional safety concerns are anticipated as all these activities are standard of care. The North Bristol NHS Trust Home Spirometry patient information leaflet and patient information video provides the patient with information regarding situations in which they should not perform spirometry.

STATISTICS

Sample Size

We estimate 250 participants each year over a 5 year study period. This is an exploratory study and does not have a power calculation to detect a specific outcome. The number of participants is based on the number of new patients referred to the current Complex Airways Service at North Bristol NHS Trust and the estimated number of patients willing to participate in the study.

Analysis of Outcome Measures

This is an adaptive study design and as such the nature of the statistical analysis will vary depending on the research questions posed.

DATA MANAGEMENT

Data Collection and Record Keeping

Patient Identification

Patients recruited into the study will be assigned a unique study number.

Source data

Consent forms will be stored electronically within the North Bristol NHS Trust REDCap environment. Other paper documentation (questionnaires) will be retained, scanned, and stored electronically as per usual clinical practice. As there is no data collection outside of routine data collection for clinical practice all data will already exist as source data, therefore data will be entered directly into an eCRF using REDCap hosted by NBT. All data entered onto REDCap will be entered under the participants unique study ID~~, date of birth~~ and identifiable hospital number (MRN). Date of birth will be stored separately in the database to these identifiers as part of standard care. Only those members of the research or clinical team directly involved in the participants standard clinical care or the BREATHE study would have access to the database. The database would be subject to the security of NHS password protected servers. The database would only be accessible from an NHS computer at North Bristol NHS Trust (single centre study). An electronic cross-referencing list shall be stored on NHS password protected computers that shall link MRN numbers with their unique study number. Only anonymised data utilising the unique study number will be used for analysis. All study documentation will be kept secure in an access restricted environment. This will include paper consent forms, the Trial Master File (TMF) and the Investigator Site File (ISF). This area will only be accessible by BREATHE study staff and authorised representatives from the Sponsor and regulatory authorities for study-related monitoring, audits and inspection.

Data Quality and Security

All data will be stored in line with Good Clinical Practice (GCP) requirements and the General Data Protection Regulation (GDPR).

REDCap is password protected with only approved users having access and is regularly backed up. User access can be restricted to different levels by assigning users with limited permissions based on their role (i.e., data entry only). Interaction with the software automatically creates an access log data trail, ensuring that the access of data can be audited to ensure data protection (e.g., by data point, function or individual user).

REDCap includes data validation checks which are inbuilt into the database build and a data query management system to allow management of data quality throughout the study. The BREATHE

database will be validated as part of the Database Activation process and final data quality checks will be incorporated as part of the Database Lock process.

Archiving of the REDCap database and paper documents pertaining to the BREATHE study will be as per NBT standard operating procedure. As it is a non-CTIMP with NBT sponsor, we will archive for 5 years. After which all documentation will be destroyed.

ETHICAL AND REGULATORY CONSIDERATIONS

Consent will only be sought after the patient has received a full explanation of what is involved in the study. The right of the patient to refuse to participate in the study without giving any reason must be respected.

Guidelines for Good Clinical Practice

All investigators will ensure that this study is conducted in accordance with relevant regulations, local policies and in accordance with GCP

Approvals

The protocol, informed consent form, participant information sheet and any other patient facing documentation will be submitted to an appropriate Research Ethics Committee (REC), HRA and host institution(s) for written approval.

The investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Participant Confidentiality

Staff involved in the study will ensure that all participants' confidentiality is always maintained. The participants will be identified by a unique number and hospital number (MRN) on the eCRF and all electronic records. Data that can identify the patient will be stored on North Bristol NHS Trust servers securely and on the REDCap database. All data removed from the trusted research environment (REDCap) for analysis will be fully anonymised. In the case of further follow-up being required, the study investigators will pass on the relevant details to the most appropriate clinician. The study will comply with GDPR and other relevant local requirements alongside the principles of GCP.

Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

FUNDING

The study has been funded by Southmead Hospital Charity and some research infrastructure funding provided by the NIHR Biomedical Research Council. Further funding from industry is being applied for.

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