Clinical Trial Protocol

Full Title:	A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis
Short Title/Acronym:	Dual Bronchodilators in Bronchiectasis Study (DIBS)
Protocol Version:	V6.0, 15th July 2022
Trial Identifiers	IRAS Number: 275595
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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The undersigned agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

The undersigned confirm that the findings of the trial will be made publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Representative of the Research Sponsor

Name: Rebecca Errington/Chris Price
Position: Deputy Regulatory Compliance Manager
Signature: Date:

Chief Investigator

Name: Professor Anthony De Soyza
Position: Professor of Pulmonary Medicine
Signature: Date:

Statistician

Name: Professor James Wason
Position: Senior Statistician
Signature: Date:

Newcastle Clinical Trials Unit (NCTU)

Name: Professor Helen Hancock/Professor Dawn Teare
Position: Director/Deputy Director, Newcastle Clinical Trials Unit
Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: **Dual Bronchodilators in Bronchiectasis Study (DIBS)**

Site Name:

Principal Investigator

I have carefully read and understood protocol version 6.0 dated 15th July 2022. I agree to conduct the trial in compliance with the protocol, Good Clinical Practice and all required regulatory requirements.

Name:

Position:

Signature: Date:

KEY TRIAL CONTACTS

Chief Investigator	Professor Anthony De-Soyza Professor of Pulmonary Medicine Population Health Sciences Institute Faculty of Medical Sciences Newcastle University Room L2060 Framlington Place Newcastle upon Tyne NE2 4HH Telephone: +44 (0) 191 2227043 Email: anthony.de-soyza@newcastle.ac.uk
Sponsor	The Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle Joint Research Office Level 1, Regent Point Regent Farm Road Gosforth Newcastle upon Tyne NE3 3HD *Sponsor Contact: Rebecca Errington / Chris Price* Telephone: +44 (0) 191 2824454/2824452 Email: tnu-tr.sponsormanagement@nhs.net
Trial Manager(s)	Mr Richard Joyce / Dr Victoria Hildreth Newcastle Clinical Trials Unit Newcastle University 1-4 Claremont Terrace Newcastle Upon Tyne NE2 4AE Email: dibs@newcastle.ac.uk

Senior Trial Manager

Dr Miranda Morton

Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle Upon Tyne
NE2 4AE
Email: dibs@newcastle.ac.uk

Database/Data Manager(s)

Ms Laura Simms

Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle Upon Tyne
NE2 4AE
Email: laura.simms1@newcastle.ac.uk

Trial Statistician(s)

Dr Nina Wilson

Population Health Sciences Institute
Faculty of Medical Sciences
Newcastle University
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4ZX
Email: nina.wilson@newcastle.ac.uk

Senior Trial Statistician

Professor James Wason

Population Health Sciences Institute
Faculty of Medical Sciences
Newcastle University
Baddiley-Clark Building

Richardson Road
Newcastle upon Tyne
NE2 4ZX
Email: james.wason@newcastle.ac.uk

Health Economist Ms Tara Homer

Population Health Sciences Institute
Faculty of Medical Sciences
Newcastle University
Baddiley Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4AX
Email: tara.homer@newcastle.ac.uk

Senior Health Economist Dr Laura Ternent

Population Health Sciences Institute
Faculty of Medical Sciences
Newcastle University
Baddiley Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4AX
Email: laura.ternent@newcastle.ac.uk

Pharmacy Contact Ms Maria Allen
Clinical Trials Operations Manager

The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN
Email: nuth.PharmacyRandD@nhs.net

Funder(s)	NIHR Health Technology Assessment Programme Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS Tel: +44 (0) 238 059 5586
Protocol Contributors	Professor Anthony De-Soyza, Dr Alaa Abouhajar, Ms Maria Allen, Professor Graham Devereux, Dr Charles Haworth, Professor John Hurst, Dr Rachel Lakey, Ms Rebecca Maier, Dr Alison Steel, Dr Laura Ternent, Mr Adam Walker, Professor James Wason, Dr Nina Wilson, Dr Miranda Morton, Dr Svetlana Cherlin

Co-Investigators/Co-Applicants

Professor James Wason, Professor of Biostatistics, Lead Statistician, Population Health Sciences Institute, Ridley Building 1, University, Newcastle upon Tyne NE2 4AA , james.wason@newcastle.ac.uk

Dr Nina Wilson, Trial Statistician, Senior Research Associate, Population Health Sciences Institute, Ridley Building 1, University, Newcastle upon Tyne NE2 4AA, nina.wilson@newcastle.ac.uk

Dr Laura Ternent, Senior Lecturer, Health Economics, Population Health Sciences Institute, Baddiley Clark Building, Newcastle University, Newcastle upon Tyne, NE2 4BN, laura.ternent@ncl.ac.uk

Professor James Chalmers, British Lung Foundation, Chair of Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, DD1 9SY jchalmers@dundee.ac.uk

Professor Judy Bradley, Director of Clinical Research Facility, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, University Road, Belfast, BT7 1NN, Northern Ireland, United Kingdom, Judy.Bradley@qub.ac.uk

Dr Charles Haworth, Director, Cambridge Centre for Lung Infection, Royal Papworth Hospital NHS Foundation Trust, Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0AY, charles.haworth@nhs.net

Professor John Hurst, UCL Respiratory: Centre for Inflammation and Tissue Repair, Rayne Building, London, WC1E 6JF, j.hurst@ucl.ac.uk

Professor Graham Devereux, Professor Respiratory Medicine, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, Graham.Devereux@lstmed.ac.uk

Mr Alan Timothy, Expert Patient, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Respiratory Medicine

Professor Adam Hill, Consultant Physician and Honorary Professor, Department of Respiratory Medicine, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, adam.hill@ed.ac.uk

Mrs Fiona Copeland, Patient representative PCD Society, C/O Newcastle University CTU PPI group

Collaborators

Mr Gareth Davies, Research Lead Respiratory Trials Unit Freeman Hospital, Newcastle upon Tyne NE77DN

TRIAL SUMMARY

Trial Title	Dual Bronchodilators in Bronchiectasis Study
Acronym	DIBS
Clinical Phase	Phase III
Summary of Trial Design	A pragmatic multi-centre, placebo-controlled three-arm double blind randomised controlled trial, incorporating an internal pilot and 12 month follow-up testing two hypotheses: I. Dual bronchodilators (LABA/LAMA) either as stand alone therapy or in combination with ICS are superior to placebo at reducing mean exacerbation rates over 12 months II. Dual bronchodilators (LABA/LAMA) are non-inferior to triple therapy (ICS/LABA/LAMA) at reducing mean exacerbation rates over 12 months
Summary of Participant Population	Adult patients (aged ≥18 years) with a CT scan confirmed primary diagnosis of bronchiectasis and a history of 2 or more exacerbations in any 12 month period in the preceding 2 years. Patients must provide written informed consent, have evidence of airflow limitation (FEV1/FVC ratio less than 0.7) or daily sputum production, and have either (1) a smoking history of less than 20 pack years or (2) where smoking history is more than 20 pack years patients must have FEV1% predicted >79%. Patients where bronchiectasis is not the main respiratory disease or where there are clear indications for inhaled corticosteroid (ICS) treatment (e.g. comorbid asthma) are excluded.
Planned Sample Size	Total = 600 participants (randomised 2:2:1 dual therapy/triple therapy/placebo) Internal pilot: 98-125 (equating to 1.25-1.6 participants per site per month) recruited at approximately 15 trial sites Main phase: 475-502 participants recruited across 25 trial sites

Treatment Duration	12 months	
Planned Trial Period	Trial set-up = 6 months (prior to grant start) Internal pilot = 12 months (approximately 15 sites) Recruitment to main trial = 14 months (pilot sites + additional sites up to approximately 25 sites) Treatment duration = 12 months Follow-up = 12 months per participant Data lock, analysis and reporting = 10 months Total trial period = 6 months set-up + 48 months	
	Objectives	**Outcome Measures**
Primary	To compare the effects of inhaled dual bronchodilators either as a stand-alone therapy (LABA/LAMA) or in combination with ICS (ICS/LABA/LAMA; triple therapy) therapy to placebo on the number of protocol defined bronchiectasis exacerbations (per participant)	Number of protocol defined bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports/ participant completed weekly exacerbation diary.
Primary Economic	To compare cost-effectiveness measured in terms of incremental cost-per-QALY gained over the 12 month treatment period.	Incremental cost-per QALY at 12 months. Costs based on the cost of the interventions, use of health services via a Health Care Utilisation Questionnaire administered at baseline, 1, 6 and 12 months post randomisation and adverse events. Transport and time for participants to utilise health care appointments will be assessed via the Time and Travel Questionnaire

		administered at 12 months post randomisation.
Secondary	To compare the effects of dual bronchodilators (LABA/LAMA) and triple (ICS/LABA/LAMA) therapy and placebo on:	
	• Hospital admissions with a primary diagnosis of exacerbation of bronchiectasis	Number of hospital admissions for bronchiectasis exacerbations during 12 month treatment period as measured using participant reports and completed weekly exacerbation diary and verified where possible by hospital discharge summary/HES data. Hospitalisation due to bronchiectasis exacerbation data collected up to 24 months after visit 1: screening/baseline, will be used to extend modelling beyond 12 months as a sensitivity analysis.
	• Time to first exacerbation of bronchiectasis	Time to first exacerbation of bronchiectasis as measured using participant reports /completed weekly exacerbation diary.
	• Number of emergency hospital admissions	Number of emergency hospital admissions (all cause) as ascertained at 1, 6 and 12 months visits and where needed from primary care records.
	• Adverse events/drug reactions and cessation of treatment	Number of adverse events/drug reactions and cessation of treatment as reported by

		participant to research team and at 1, 6 and 12 months visits.
	• Disease related health status using the St Georges Respiratory questionnaire (SGRQ) and Quality of Life Bronchiectasis (QOL-B)	SGRQ and QOL-B at baseline, 1, 6 and 12 months visits
	• Health related quality of life using the EQ-5D-5L	EQ-5D-5L at baseline, 1, 6 and 12 months visits
	• Breathlessness using Baseline and Transition Dyspnoea Indices (BDI and TDI)	BDI at baseline TDI at 1, 6 and 12 months visits
	• Lung function using spirometry	Post bronchodilator lung function (LABA within 8 hours, short acting beta2 agonist within 2 hours) as measured by spirometry performed to ATS/ERS standards at baseline, 1, 6 and 12 month visits: • forced expiratory volume in 1 second (FEV1) • forced vital capacity (FVC)
	• All-cause, respiratory and cardiac mortality	As ascertained from medical records or ONS records of trial participants (collected up to 24 months after visit 1: screening/baseline)
	• Incremental cost per exacerbation avoided	Costs based on cost of the interventions (micro-costed), use of health services collected via a Health Care Utilisation

		Questionnaire administered at Baseline, 1, 6 and 12 months post randomisation and adverse events collected via case report forms.
	• Costs to the NHS and patients and lifetime cost-effectiveness based on extrapolation modelling	The main source of data to populate the model will come from the trial and will be supplemented by HES and ONS data (collected up to 24 months after visit 1: screening/baseline) and by relevant literature and expert opinion and extrapolated over a patient lifetime.
	• Rates of radiologically confirmed pneumonia, compared to participant's normal baseline	Number of pneumonia events and total number of participants suffering pneumonia. This will be measured by asking the participants during follow up visits.
Exploratory	• To investigate the relationship between key outcomes (exacerbations and quality of life as measured by SGRQ and QOL-B) with baseline eosinophil (single level recorded at baseline), median eosinophil level (median of last 3 available recording when not on oral steroids) and baseline BSI	Eosinophil measurement at baseline and the median of the last 3 measurements available. SGRQ and QOL-B as completed by participants at 1, 6 and 12 month follow-up visits. BSI measured at baseline. The number of protocol defined bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports/participant completed weekly exacerbation diary.

	• Subgroup analyses of suspected aetiology comparing idiopathic and post infectious to all other aetiologies for the key outcomes of exacerbations and quality of life (SGRQ and QOL-B)	Disease history collected at baseline. The number of protocol defined bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports/ participant completed weekly exacerbation diary. SGRQ and QOL-B as completed by participants at 1, 6 and 12 month follow-up visits.
Investigational Medicinal Product(s)	The inhalers used in the trial are identical to the commercially available products of dual inhaler Anoro Ellipta and triple inhaler Trelegy Ellipta and for the purpose of the trial they will be referred to as Dual therapy or Triple therapy. 1) Dual therapy (LAMA/LABA): Anoro Ellipta dry powder inhaler OR 2) Triple therapy (ICS/LAMA/LABA): Trelegy Ellipta dry powder inhaler OR 3) Identical matched placebo dry powder inhaler	
Formulation, Dose & Route of Administration	Dual therapy: • Anoro Ellipta dry powder inhaler • 55 micrograms umeclidinium (LAMA) and 22 micrograms vilanterol (LABA) • One inhaled dose once daily OR Triple therapy:	

	• Trelegy Ellipta dry powder inhaler 92 micrograms fluticasone furoate, 55 micrograms umeclidinium and 22 micrograms vilanterol • One inhaled dose once daily OR Matched placebo: • Matched placebo dry inhaler • One inhaled dose once daily
Sites	Approximately 25 UK NHS secondary (includes approximately 15 pilot sites and approximately 10 sites in the main phase). Primary care Patient Identification Centres (PICs).

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
A&E	Accident and Emergency
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR	Adverse Reaction
ATS	American Thoracic Society
BDI	Baseline Dyspnoea Index
BE	Bronchiectasis
BSI	Bronchiectasis Severity Index
BTS	British Thoracic Society
CAPA	Corrective and Preventative Actions
CEACs	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computed tomography
CTIMP	Clinical Trial of an Investigational Medicinal Product
CYP3A4	Cytochrome P450 3A4
DIBS	Dual Bronchodilators in Bronchiectasis Study
DMC	Data Monitoring Committee

DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
ERS	European Respiratory Society
FBC	Full Blood Count
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLI	Global Lung Function Initiative
GP	General Practice
GSK	GlaxoSmithKline plc
HCUQ	Health Care Utilisation Questionnaire
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICS	Inhaled corticosteroid
IDMEC	Independent Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention-to-treat

IV	Intra-venous
LABA	Long acting beta agonist
LAMA	Long-acting muscarinic antagonist
MHRA	Medicines and Healthcare products Regulatory Agency
MRC Dyspnoea Score	Medical Research Council Dyspnoea Score
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	NHS Research Scotland
ONS	Office of National Statistics
PI	Principal Investigator
PIC	Participant Identification Centre
PP	Per-Protocol
PPI	Patient and Public Involvement
PPU	Pharmacy Production Unit
QA	Quality Assurance
QALY	Quality-adjusted life-year
QOL-B	Quality of Life Bronchiectasis
QP	Qualified Person
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SABA	Short-acting inhaled beta-agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SGRQ	St Georges Respiratory questionnaire

SOP	Standard Operating Procedure
SAP	Statistical Analysis Plan
sIMPD	simplified Investigational Medicinal Product Dossier
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDI	Transition Dyspnoea Index
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TWICS	Theophylline with Inhaled CorticoSteroids
UCL	University College London
UK	United Kingdom
USM	Urgent Safety Measure
Y/N	Yes/No

1. BACKGROUND

Bronchiectasis is a long-term lung condition, unrelated to smoking, characterised by chronic sputum (phlegm) production and repeated chest infections[1]. There are over 300,000 patients in the UK with this condition[2] with the majority suffering from chronic lung infections and persistently culture positive sputum[3, 4]. There is a growing consensus that bronchiectasis research and treatment has been relatively neglected despite the rising prevalence of the condition. Bronchiectasis has significant impacts on quality of life, causing over 4000 hospital admissions per year and shortens lifespans [5-7]. A prominent feature of bronchiectasis is deterioration in symptoms or exacerbations defined by increased cough, sputum discolouration, excess sputum production, breathlessness and/or malaise. Recurrent exacerbations are both predictive of worsening lung disease, future exacerbations and hospitalisations and an increased risk of death [6, 8, 9]. One in four patients with severe bronchiectasis, as defined by the Bronchiectasis Severity Index (BSI) [10], dies within 4 years [5, 6, 9] giving this disease a poorer prognosis than some cancers. Both UK (British Thoracic Society; BTS) and international guidelines note the critical lack of high quality studies in the disease area [3, 11]. To date no treatments have been specifically approved for bronchiectasis, consequently treatment is mostly empiric, being extrapolated from other lung conditions such as asthma and chronic obstructive pulmonary disease (COPD) and there is significant variation in care [11]. The aims of treatment in bronchiectasis are preventing worsening damage to the airways, improving mucus clearance, relieving airflow limitation and reducing infective exacerbations [3, 12]. Standard care is chest physiotherapy (chest clearance exercises) [1, 3, 4, 13] and antibiotics for acute infections [1, 3, 12].

Reducing exacerbations is a key goal in bronchiectasis as these worsen health status, disrupt normal work and lifestyle, impair health related quality of life and drive both worsening lung disease and mortality[3, 5, 14, 15]. Those with two exacerbations in the previous 12 months are highly likely to develop two more exacerbations in the following year and those with three prior exacerbations have an incident rate ratio of nearly 6 per year [5]. Current maintenance treatments in bronchiectasis are therefore used with the aim of reducing infective exacerbations [15], though there is very limited evidence of efficacy. Those used most widely are bronchodilators and inhaled corticosteroids (60%) and long term antibiotics (20-40%) [1, 16]. Long term antibiotics are delivered either orally or nebulised directly to the lung [1, 3, 12]. There is good evidence for long term oral antibiotics, particularly oral macrolides in preventing exacerbations [17-20] and these are recommended in available guidelines [1, 3]. However long term systemic antibiotic use is associated with up to 50% antimicrobial resistance rates of upper airway bacteria [21]. Finding treatments that avoid the antimicrobial resistance risks associated with antibiotics for life are attractive to patients. Nebulised

antibiotics are only used in in those with repeated infective exacerbations and current studies and the UK audit data show that at most about 20% of adults with bronchiectasis receive nebulised antibiotics [16]. Clearly a therapy that reduces exacerbations, that is low cost, avoids the microbial stewardship consequences of long term macrolide antibiotics or the treatment burden of nebulised therapy and is applicable to a broad range of patients is highly attractive. There are however no such licenced therapies in bronchiectasis where current practice involves the "off-label" use of inhaled drugs developed and proven in asthma and smoking related COPD.

2. RATIONALE

The role of long acting bronchodilators and Inhaled corticosteroids (ICS) in bronchiectasis has been reviewed within both national guidelines (BTS 2010) [1], the 2017/18 revised BTS guidelines [22], Cochrane reviews [11] and the European Respiratory Society (ERS) guidelines [3]. These all highlight the dearth of large scale, adequately powered high quality studies of inhaled therapies in bronchiectasis. Current guidelines highlight the clear need for robust studies to be undertaken. A Cochrane review noted that in total, all 7 studies of ICS for bronchiectasis included fewer than 400 participants, and most studied patients for less than 6 months [11, 23]. In addition to very small sample sizes the outcomes studied were often neither standardised nor relevant to the NHS. The very low quality evidence led the Cochrane reviewers to only include two studies in their meta-analysis. Hence the current widespread use of ICS in bronchiectasis is based on very limited data. ICSs are potent anti-inflammatories which are used in the hope of reducing airway inflammation [24]. Recent meta-analyses have however shown that ICS when combined with long acting bronchodilators can significantly reduce annual infective exacerbations rates but also increase the risk of pneumonia [25-27]. As there is likely a much higher infection risk in bronchiectasis reflecting the higher bacterial burden in the bronchiectasis airways there is the very real risk that indiscriminate ICS use in bronchiectasis may be detrimental. Hence there is no specific evidence of ICS effectiveness in bronchiectasis but a potential for harm, such as pneumonia [25-27].

Other inhaled therapies frequently used in bronchiectasis include long acting bronchodilators such as long acting beta agonists (LABA) or long acting muscarinic antagonists (LAMA). Similar to the case for ICS, Cochrane reviews of long acting bronchodilators in bronchiectasis have also highlighted the stark absence of high quality trials defining their role in managing bronchiectasis. One systemic review found no studies in 2001 (updated in 2010) [28] and a review in 2014 [29] noted that there were no studies assessing exacerbation rates. The few single centre studies have confirmed that ICS/LABA were

well tolerated and improve cough but have not been designed to assess exacerbation reduction[30, 31]. International guidelines call for better studies in bronchiectasis [3].

Recent trials in COPD show that newer combination dual bronchodilators using a LABA combined with a LAMA contained in a single inhaler are superior to existing therapies such as salmeterol (a LABA developed 20 years ago) and tiotropium (a LAMA) in separate inhalers [32]. More recent studies have shown LABA/LAMA combinations are as good as or better than ICS/LABA combinations at reducing exacerbations when studied in selected COPD populations [25], suggesting that ICS regimens might not be needed in all patients with COPD. However, ICS regimes clearly help in more severe COPD patients – a recent landmark study using the agents proposed herein showed a 25% reduction in exacerbations with ICS containing triple therapy (ICS/LAMA/LABA) vs LAMA/LABA dual bronchodilator therapy [33]. Using the inhaled drugs proposed herein in a moderate-severe COPD population has shown clear benefits: Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol (ICS/LABA) or umeclidinium–vilanterol (LAMA/LABA). Triple therapy in COPD also resulted in a lower rate of hospitalisation due to than LAMA/LABA [33].

Newer bronchodilators and inhaled steroids have therefore emerged in COPD [25] that may prove effective in bronchiectasis and are already lower cost than widely prescribed ICS/LABA combinations. The mechanism by which newer bronchodilators such a LAMA and LABA exert potentially beneficial effects in COPD are likely multifactorial. These have been recently reviewed and reach beyond reducing bronchoconstriction with effects on airway cilia, mucus production, airway nerve desensitisation and reducing gas trapping [34]. These effects mean newer bronchodilators may target mechanisms relevant to bronchiectasis.

3. RISK ASSESSMENT

The dual therapy inhaler (containing umeclidinium bromide/vilanterol) is currently indicated as a maintenance bronchodilator to relieve the symptoms of COPD in adults. The triple therapy inhaler (containing fluticasone furoate/umeclidinium bromide/vilanterol) is currently indicated as a maintenance treatment in adults with moderate to severe COPD who are not adequately treated by a combination of ICS and LABA or a combination of LABA and LAMA. Both inhalers are currently widely used off-label in adults with bronchiectasis at the doses indicated for COPD. For the purposes of this protocol, the dual therapy inhaler and triple therapy inhaler will be used in patients with moderate to

severe bronchiectasis with a history of 2 or more exacerbations within a 12 month period during the preceding two years which have required antibiotics and/or steroid treatment.

This trial is categorised as:

- Type B = somewhat higher than the risk of standard clinical care

There are three potential treatments that a participant can be randomised to, one of which is placebo. 20% of participants in the trial will receive placebo.

The common side effects for the dual therapy are as listed in the Summary of Product Characteristics (SmPC) for Anoro Ellipta and are based on the available evidence from use in adults with COPD.

The common side effects for the triple therapy are as listed in the SmPC for Trelegy Ellipta and are based on the available evidence from use in adults with COPD.

For participants randomised to placebo there may be an increased risk of bronchospasm. For those randomised to receive triple therapy there may be an increased risk of pneumonia.

Adverse event (AE) recording and reporting will be undertaken at clinic follow ups visits and telephone follow ups. Bronchiectasis exacerbations will be collected via the participant exacerbation diary. There is a risk of an increased number of exacerbations in participants randomised to placebo.

Adverse event reporting and discontinuation of trial treatment as a result of adverse events will be monitored throughout the trial.

4. TRIAL OBJECTIVES AND OUTCOME MEASURES

	OBJECTIVE	OUTCOME MEASURE
Primary	To compare the effects of inhaled dual bronchodilators (LABA/LAMA) either as a stand-alone therapy or in combination with ICS (ICS/LABA/LAMA) therapy on the number of protocol defined bronchiectasis exacerbations (per participant) requiring treatment with	Number of bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports and completed weekly exacerbation diary.

	antibiotics during the 12 month treatment period as compared to placebo.	
Primary Economic	To compare cost-effectiveness measured in terms of incremental cost-per-QALY gained over the 12 month treatment period	Incremental cost-per QALY at 12 months. Costs based on the cost of the interventions, use of health services via a Health Care Utilisation Questionnaire administered at baseline, 1, 6 and 12 months post randomisation and adverse events. QALYs measured via the EQ5D-5L at baseline, 1, 6 and 12 months post randomisation. Transport and time for participants to utilise health care appointments will be assessed via the Time and Travel Questionnaire administered at 12 months post randomisation.
Secondary	To compare the effects of dual bronchodilators (LABA/LAMA), triple (ICS/LABA/LAMA) therapy and placebo on:	
	• Hospital admissions with a primary diagnosis of exacerbation of bronchiectasis	Number of hospital admissions for bronchiectasis exacerbations during 12 month treatment period as measured using participant reports and completed weekly exacerbation diary and verified by hospital discharge summary/HES data. Hospitalisation due to bronchiectasis exacerbation data collected up to 24 months after visit 1: screening/baseline, will be used to extend modelling beyond 12 months as a sensitivity analysis.

	• Time to first exacerbation of bronchiectasis	Time to first exacerbation of bronchiectasis as measured using participant reports and completed weekly exacerbation diary.
	• The number of emergency hospital admissions	Number of emergency hospital admissions (all cause) as ascertained at 1, 6 and 12 months visits and from primary care records.
	• Serious Adverse events/drug reactions and cessation of treatment	Number of serious adverse events as a result of drug reactions or reactions to cessation of treatment as reported by participant to research team or at 1, 6 and 12 months visits.
	• Health status using the St Georges Respiratory questionnaire (SGRQ) and Quality of Life Bronchiectasis (QOL-B)	SGRQ and QOL-B at baseline, 1, 6 and 12 months visits
	• Health related quality of life using the EQ-5D-5L	EQ-5D-5L at baseline, 1, 6 and 12 months visits
	• Breathlessness using Baseline and Transition Dyspnoea Indices (BDI and TDI)	BDI at baseline, TDI at 1, 6 and 12 months visits
	• Lung function using spirometry	Post bronchodilator lung function (LABA within 8 hours, short acting beta2 agonist within 2 hours) as measured by spirometry performed to ATS/ERS standards at baseline, 1, 6 and 12 month visits: • forced expiratory volume in 1 second (FEV1) • forced vital capacity (FVC)

	• All-cause, respiratory and cardiac mortality	As ascertained from ONS records of trial participants (collected up to 24 months after visit 1: screening/baseline)
	• Incremental cost per exacerbation avoided	Costs based on cost of the interventions (micro-costed), use of health services collected via a Health Care Utilisation Questionnaire administered at baseline, 1, 6 and 12 months post randomisation and adverse events collected via case report forms.
	• Costs to the NHS and patients and lifetime cost-effectiveness based on extrapolation modelling	The main source of data to populate the model will come from the trial and will be supplemented by HES/ONS data (collected up to 24 months after visit 1: screening/baseline) relevant literature and expert opinion and extrapolated over a patient lifetime.
	• Rates of radiologically confirmed pneumonia, compared to participant's normal baseline	Number of pneumonia events and total number of participants suffering pneumonia. This will be measured by asking the participants during follow up visits.
Exploratory	• To investigate the relationship between key outcomes (exacerbations and quality of life as measured by SGRQ and QOL-B) with baseline eosinophil (single level recorded at baseline), median eosinophil level (median of last 3	Eosinophil measurement at baseline and the median of the last 3 measurements available. SGRQ and QOL-B as completed by participants at 1, 6 and 12 month follow-up visits. BSI measured at baseline.

	available recording when not on oral steroids) and baseline BSI	The number of protocol defined bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports/participant completed weekly exacerbation diary.
	• Subgroup analyses of suspected aetiology comparing idiopathic and post infectious to all other aetiologies for the key outcomes of exacerbations and quality of life (SGRQ and QOL-B)	Disease history collected at baseline. The number of protocol defined bronchiectasis exacerbations requiring treatment with antibiotics during 12 month treatment period as measured using participant reports/ participant completed weekly exacerbation diary. SGRQ and QOL-B as completed by participants at 1, 6 and 12 month follow-up visits.

5 TRIAL DESIGN AND OVERVIEW

This is a pragmatic multi-centre, placebo-controlled, three-arm, double blind, randomised controlled trial, incorporating a 12 month internal pilot and 12 month follow up testing two hypotheses. This trial will enable evaluation of patient-focused, clinical and health economic outcomes in patients with bronchiectasis, over a 12 month treatment period.

5.1 Internal pilot

The internal pilot phase of recruitment will involve approximately 15 sites, aiming to recruit 98-125 trial participants (equating to an average recruitment of 1.25 – 1.6 participants per site per month) over a 12 month period. It will include the monitoring of recruitment and retention at each site, investigation of processes at each site and identify good practice that can be shared. At the end of the pilot phase a review of findings in accordance with the stop and guidance criteria will be undertaken by TMG and Trial Steering Committee (TSC); a discussion with the funder will also occur.

Sites will be opened as soon as possible, in a staggered way; with a planned minimum collective period of 78 recruitment months. It is expected that 98-125 patients (equating to 1.25 – 1.6 participants per

site per month) should be recruited during the 12 month internal pilot. This period of 12 months is from the first site being activated.

The progression criteria to proceed from the internal pilot to the main trial are as follows:

- Average recruitment ≥ 1.6 participants/month/site activated – continue to main trial and open additional sites (up to 25 sites total)
- Average recruitment ≥ 1.25 participants/month/site activated – continue to main trial and open additional sites (up to 25 sites total) plus provide an improvement plan after identifying barriers to recruitment through discussion with sites, TMG, TSC and IDMEC as required
- Average recruitment < 1.25 participants/month/site activated – seek further guidance from funder

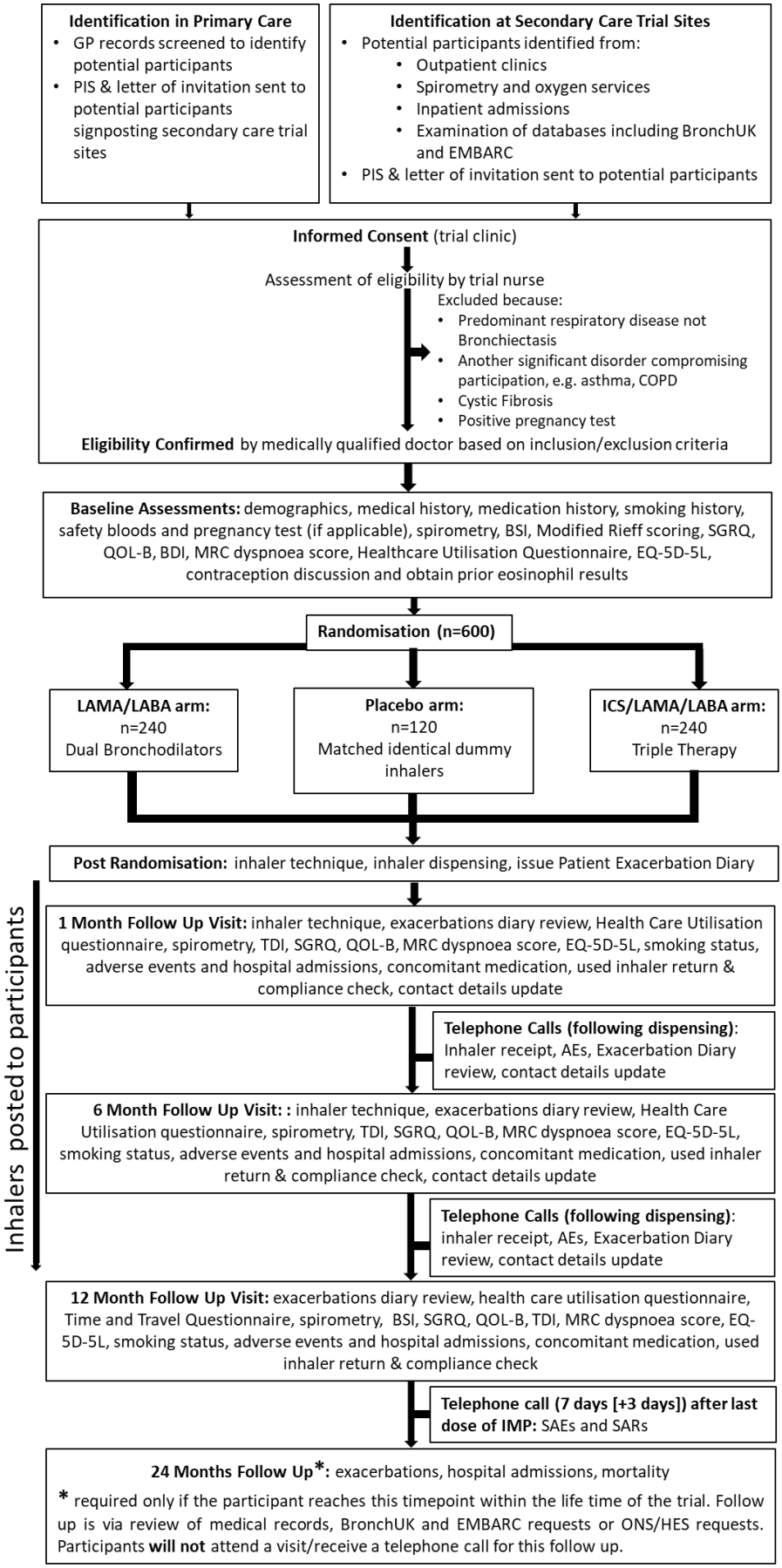
5.2 **Main trial**

Following the extended pilot phase, additional sites, up to a total of approximately 25 sites, will be opened in a phased manner, aiming to recruit an average of 1-2 participants per month per site to collectively reach the target sample size of 600. Sites which open earlier will be encouraged to recruit more participants.

Patients will be identified and approached in both secondary and primary care. All participants will be randomly allocated in a 2:2:1 ratio with the smallest group representing the placebo group. Researchers, site staff and participants will not know to which group an individual has been allocated. The Investigational Medicinal Product (IMP) will be taken once daily over a 12 month period (365 days), with follow up visits taking place a 1, 6 and 12 months after the start of the trial IMP. The trial will have a 6 month set-up period and will then last 48 months including site set-up, recruitment, follow–up and analysis/reporting.

The number of participant reported hospital admissions will be validated for a random sample of 10% of participants by examination of primary and secondary care records post trial. Concordance between participant recorded and primary/secondary care records will be computed using percentage agreement with >80% being deemed acceptable. Mortality will be ascertained by flagging the Office of National Statistics (ONS) records of trial participants.

Figure 1 – Trial flowchart



6 TRIAL SETTING

This is a multi-centre trial, conducted at approximately 25 UK NHS secondary care sites with experience in conducting bronchiectasis studies. Basic bronchiectasis care has already been established at these sites in accordance with national guidelines.

Participants will be identified in both primary and secondary care settings by clinical research teams, with recruitment and delivery of the trial taking place at secondary care sites.

Trial Visits

Trial visits will be conducted in an outpatient setting with no expected in-patient activities. Appointments and assessments, where practicable, may take place remotely if in line with local NHS site policies and procedures i.e. due to COVID-19 restrictions being in place.

If a participant has an exacerbation and is admitted to hospital, data from the admission will be reviewed at the next trial visit e.g. to confirm or refute presence of pneumonia.

7 ELIGIBILITY CRITERIA

Eligibility must be assessed by a medically qualified doctor and this assessment documented in the participant's medical records. Only personnel formally delegated by the Principal Investigator to assess eligibility may perform this task.

7.1 Inclusion Criteria

Patients are eligible for the trial if all of the following apply:

1) Adult patients with CT scan confirmed bronchiectasis and bronchiectasis is the predominant primary respiratory disease in the view of the investigator (CT images / CT reports must be available to complete radiological scoring for BSI)
2) History of 2 or more exacerbations in any 12 month period in the preceding 2 years requiring antibiotics and/or steroids
3) Evidence of airflow limitation with an FEV1/FVC ratio less than 0.7 and/or daily mucus expectoration
4) Have either:
   (i) less than 20 pack year history of smoking
   OR

(ii) greater than 20 pack year history of smoking with an FEV1 >79% predicted (to exclude COPD)

5) For patients taking ICS, LAMA or LABA treatment prior to recruitment, willing to have these treatments changed or stopped
6) Stable bronchiectasis with no exacerbations for 4 weeks prior to baseline
7) Stable dose of oral steroid for 4 weeks prior to baseline (only applicable for patients taking oral steroid as part of standard care)

7.2 Exclusion Criteria

Patients are excluded from the trial if any of the following apply:

1) Cystic fibrosis related bronchiectasis
2) Where bronchiectasis is not the main disease or there are contraindications to ICS withdrawal
3) Predominant COPD or asthma *
4) Indication to remain on ICS (e.g. asthma, COPD, allergic bronchopulmonary aspergillosis, inflammatory bowel disease) or known intolerance to any of the trial drugs or their ingredients
5) Patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
6) Inability to perform spirometry or quality of life questionnaires
7) Patients who are:
    a) pregnant
    b) breast feeding
    c) of childbearing potential with a positive urine pregnancy test prior to starting trial IMP
    d) male or female of childbearing potential unwilling to use contraception throughout the trial (postmenopausal women must be amenorrhoeic for at least 12 months to be considered of non-childbearing potential).
8) Anyone with cognitive impairment who may not be able to consent
9) Those who do not speak English or cannot comply with trial procedures
10) Any potential participant who the investigator believes will not be able to complete the trial visits and procedures

11) A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator contraindicates trial participation
12) Use of acute antibiotics or systemic steroids within 4 weeks of baseline (except for antibiotics and/or stable doses of prednisone ≤ 5mg used to treat non-respiratory conditions)
13) Malignancy diagnosed within 5 years of the first trial medication administration where the investigator feels the trial may be affected by recurrence or progression of the malignancy (e.g. patients with stable breast cancer, current prostate cancer or "expected curative" cancer surgery may not be excluded at the investigators discretion)
14) Administration of an investigational agent within 30 days of first dose of trial medication

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. Protocol waivers are not permitted.

*Patients who have a historical diagnosis of asthma and/or COPD but where the investigator has sufficient evidence to refute these diagnoses can still be included. This is to be documented in the source documentation (i.e. patient medical records) and the CRF.

8 TRIAL PROCEDURES

8.1 Recruitment

8.1.1 Patient Identification

Potential trial participants will be identified via two routes.

Patient Identification in Secondary Care

Patients will be recruited from secondary care sites; the patient population is known to have a high baseline morbidity based on national audit data. Sites have been pre-selected through knowledge of previous large observational cohort studies and intervention studies in bronchiectasis. Potential participants will be identified in secondary care by clinicians, research nurses and Clinical Research Network (CRN) nurses (or the NRS Primary Care Network for Scottish sites and the Health and Social Care (HSC) Trusts for the Northern Irish sites) from

patients attending respiratory outpatient clinics, spirometry and oxygen services. Participants will also be identified from inpatient admissions and by examination of databases of patients with bronchiectasis held by the trial sites (including the BronchUK and EMBARC registries). Clinic records will be examined to confirm the diagnosis of bronchiectasis and records of patient reports of exacerbation and their treatment, key pieces of information routinely recorded by physicians in chest clinics will be reviewed for potential eligibility. Potential participants will be sent a letter of invitation (from their caring physician) and a participant information sheet along with details of how to inform the trial team of their interest in participating (including a paid reply envelope). Wherever possible potential participants will be invited to participate 1-2 weeks prior to a planned routine clinical visit. Patients may also be approached in clinic by their routine clinical care team as they present for routine appointments. Routine appointments may be carried out as face to face visits, by telephone or any other format in line with the sites policies and procedures for outpatient appointments.

Patient Identification in Primary Care

To increase the patient population covered by the trial, primary care practices will be set up as Participant Identification Centres (PICs) to signpost potentially eligible patients to recruitment sites in secondary care. Identification of potential participants will be conducted by practice staff or local NIHR CRN funded research nurses (or equivalents). GP records will be screened to identify potential participants with a diagnosis of bronchiectasis who have had two or more exacerbations in any 12 month period in the preceding 2 years requiring antibiotics and/or steroids . Exacerbations will be identified by a record of the prescription of courses of antibiotics and GP records examined to check that these had been prescribed for exacerbations of bronchiectasis. PICs will only signpost potentially eligible patients after providing patients with a patient information sheet and will not take consent or carry out any trial procedures. At the Scottish sites the NRS Primary Care Network will mirror the role undertaken by the English CRN by identifying potential participants in primary care. In Northern Ireland the HSC Trusts coordinate the identification of participants in PIC sites.

8.2 Consent

8.2.1 Secondary Care

Potential participants expressing an interest in participating in the trial will be invited to attend an appointment for their first trial visit. The Participant Information Sheet and Informed

Consent Form will be checked with the potential participants and they will have the opportunity to discuss the trial in more detail, including the implications of the protocol, known side effects and any risks involved in taking part, with a member of the research team.

It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for their cessation of trial medication. The patients will be encouraged to remain within the trial after cessation of IMP where possible.

8.2.2 Primary Care

Consent will be obtained from patients who have been referred from primary care as they attend a clinic appointment in secondary care setting prior to a full eligibility check.

8.2.3 Consent Process

All potential participants will be allowed time to consider the trial information, and will have the opportunity to discuss any questions, including risks and benefits, with the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will be received by means of the patient initialling to confirm agreement of each consent statement followed by a dated signature with the person who is receiving the informed consent also signing and dating the ICF. The person who received the consent must be medically qualified and experienced, and have been authorised to do so by the Principal Investigator on the delegation log.

The original signed consent form must be retained in the Investigator Site File (ISF) by site staff, with a copy provided to the participant and a copy filed in the participant's medical records.

Details of the participant's consent will be documented on a NCTU consent notification pro forma, a copy of the completed proforma will be sent securely (i.e. nhs.net to nhs.net or encrypted email) to the nctu.dibs.conf@nhs.net email address within **5 working days** of the date of consent.

No participant identifiable data will be recorded on the NCTU consent and eligibility pro forma. The purpose of this pro forma is to allow for the mandatory monitoring of the consent and eligibility process in accordance with ICH (E6) GCP principles. Participants will specifically consent to their GP being informed of their participation in the trial. Consent to continue with

trial participation will be checked verbally at each trial visit and documented in the participant's medical records.

Consent will be sought for long term follow up of participants. Long term follow up will be carried out to obtain data relating to participants at 24 months (24 months after visit 1: screening/baseline and 12 months after the participant's scheduled last dose of IMP), for participants whom reach this time point within the lifetime of the trial. Participants will not be contacted as part of the 24 month follow up, instead data will be collected from one of the following sources:

- Participant medical records
- BronchUK and/or EMBARC, where the participant has consented to follow-up with these registries
- Routinely collected data including HES and ONS data (not applicable for Scottish sites)

Due to data from these sources being requested in batches, 24 month follow-up data may be requested up to two years after a participant's involvement in the trial has ended (i.e. participant's last dose of IMP), however, the data collected will be data relating to the 24 month point (24 months after visit 1: screening/baseline and 12 months after the participant's last scheduled dose of IMP).

8.3 Contraception

To be eligible for the trial potential participants of childbearing potential (male and female) must be willing to use contraception throughout the trial, from the date of consent until 7 days after the last dose of IMP. Postmenopausal women must be amenorrhoeic for at least 12 months to be considered of non-childbearing potential.

Sexual abstinence is only acceptable as true abstinence when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Acceptable contraceptives for participants of childbearing potential are:

Male participants	Female participants
• Condom • Sexual abstinence	• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:

	○ oral ○ intravaginal ○ transdermal • progesterone-only hormonal contraceptive associated with inhibition of ovulation: ○ oral ○ injectable ○ implantable • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tube occlusion • vasectomised partner • sexual abstinence

Applicable contraceptive methods should be recorded in either medication history (if started prior to date of consent) or as a concomitant medication (if started after the date of consent).

8.4 Screening/Baseline Visit

Potential participants will be invited for a baseline visit where informed consent will be obtained. A full screening and eligibility check will be carried out in a dedicated session held in the clinic facility (or equivalent). Each potential participant will be assigned a screening number to identify them, which at the point of randomisation will become their participant ID for the trial. All patients considered for the trial, including those who fail screening, must be entered onto a screening log and recorded on the trial screening database.

Following consent and prior to entry into the trial, potential participants will be screened to assess full eligibility ensuring compliance with the trial inclusion and exclusion criteria (section 7). Eligibility must be assessed by a medically qualified doctor formally delegated to the task by the Principal Investigator. If hospital or primary care records are not complete/ available in order to confirm eligibility and suitability to randomise, trial specific procedures will be halted after initial consent and medical records requested. A statement of eligibility must be documented in the participant's medical records by the person performing the assessment. A trial Eligibility Checklist form must also be completed and filed in the participant's medical records. A copy of the Eligibility Checklist will be sent securely (i.e. nhs.net to nhs.net or

encrypted email) to the nctu.dibs.conf@nhs.net email address within **5 working days** of the date of completion. No participant identifiable data will be recorded on the Eligibility Checklist. The purpose of this process is to allow for the monitoring of eligibility in accordance with ICH (E6) GCP principles. An Eligibility Checklist should be completed for all patients screened for the trial, including screen failures, eligibility must also be recorded in the trial database for all patients screened.

8.5 Washout of baseline inhaled therapy

There is no planned washout of baseline inhaled therapy. Patients should continue their existing inhaled therapy until randomisation. At the point of randomisation inhaled therapy (ICS, LAMA and LABA), with the exception of short-acting inhaled beta-agonist (SABA), will be stopped and the trial inhaler commenced.

8.6 Payment

Trial participants will be re-imbursed travel expenses up to £25 per patient per visit. Each site will receive payment of £25 per patient per visit and will manage the internal travel budgets as required within the site budget, attributing travel costs to those with longer distances, balanced against other participants with shorter journeys.

8.7 Randomisation

Following screening assessments, eligible participants will be randomised by a delegated and trained member of the research team at each site using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Eligible participants will be randomised in a 2:2:1 ratio to receive one of the three trial treatments; dual therapy (LAMA/LABA), triple therapy (ICS/LAMA/LABA), or placebo. Randomisation will be stratified by two variables; the Bronchiectasis Severity Index (BSI) score that factors in Pseudomonas status, prior exacerbations/ hospitalisations and age (BSI score of 0-8 or 9+) and by baseline ICS drug therapy (ICS user or non-ICS user at baseline).

Randomisation system web address: https://www.sealedenvelope.com/access/ The system is available 24 hours a day, 7 days a week

In the event that the online randomisation system is not accessible, the site team should contact the NCTU Database Management Team in normal working hours (9am – 5pm Monday to Friday, excluding bank holidays and Newcastle University closures):

E-mail: nctu.database.support@newcastle.ac.uk

NCTU can liaise with Sealed Envelope support to investigate the cause.

8.8 Blinding

This is a double-blind trial. Participants and site staff including the PI, pharmacy and clinical team will not know the treatment allocation assigned to each participant. All members of the Trial Management Group will be blinded to the treatment allocation apart from the trial statistician(s) and database manager(s). Participants will be randomised to receive dual therapy, or triple therapy, or placebo. The three trial IMPs/inhalers will be manufactured, packaged and labelled in an identical manner in terms of appearance to maintain the blind. Newcastle Specials PPU will be unblinded due to the labelling of the product. To ensure blinding of all involved for the duration of the trial, a participant's GP will be informed of their participation in the trial and instructed to manage the participant for exacerbations as per normal clinical practice, assuming that the participant is taking an inhaled corticosteroid and the prescribing of interacting drugs should be avoided. The NCTU Blinding Log will be kept in the TMF and will provide a comprehensive list of all blinded and unblinded DIBS staff. It is not anticipated that emergency unblinding will be required within this trial; patients are already widely on dual or triple therapy. Treating clinicians who wish to alter the drug regimen can discuss IMP discontinuation with the trial team/CI including the need for unblinding.

8.9 Emergency Unblinding

Emergency unblinding should only occur for valid medical or safety reasons where it is necessary for the treating clinician to know which treatment the participant has been receiving. It is deemed highly unlikely that unblinding will be required within this trial as the medications are in widespread use and there are a number of alternative agents that could be used if the clinician wishes to prescribe dual/ triple therapy. Emergency unblinding should be carried out by the PI or another medically qualified trial member designated this task on the delegation log by accessing the 24 hour web-based randomisation system.

In the unlikely event that the randomisation system is unavailable participants will be medically managed at the investigators discretion. If the randomisation system is unavailable within

working hours (Monday to Friday, 9am to 5pm) the NCTU database team can be contacted for assistance, details are given in section 8.7.

The site should follow their local procedures for unblinding in emergency situations. If possible and time allows advice can be sought from the PI but this is not absolutely necessary in order to unblind. If the PI has not been able to be involved they must be told as soon as possible that a participant has been unblinded. The PI should not need to be told what arm the participant had been allocated to in the trial as this will unblind them. In the event of a potential suspected unexpected serious adverse reaction (SUSAR), any unblinding will be undertaken in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs).

The Chief Investigator and Trial Manager will be kept informed of all instances of unblinding but should remain blind to the treatment allocation wherever possible. A record of the process followed to unblind a participant should be maintained at site and filed in the site file.

8.10 Trial assessments

8.10.1 Schedule of Events

Assessments	Visit 1 Screening/ Baseline Day 0	Visit 2 1 Month Follow Up 1 month (-1/+ 2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 2, 3, 4, 5, 6/7 (as applicable)	Visit 3 6 Month Follow Up 6 months (-1/+2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 6/7 (as applicable), 8, 9, 10, 11, 12 and 13	Visit 4 12 Month Follow Up 12 months (+2 weeks)	Telephone call to participant 7 days after last dose of IMP (+ 3 days)	24 Month Follow up **
Written informed consent[a]	X							
Demographics	X							
Contact details (participant telephone number and address)	X	X	X	X	X			
Medical history	X							
Medication history	X							
Smoking history	X	X		X		X		
Spirometry including % predicted (FEV1 & FVC)	X	X		X		X		
Bronchiectasis Severity Index calculation	X					X		
Modified Rieff scoring of prior CT scan	X							
St George's Respiratory Questionnaire (SGRQ)	X	X		X		X		
Quality of Life – Bronchiectasis (QOL-B)	X	X		X		X		
Breathlessness – Baseline and Transition Dyspnoea Indices (BDI and TDI)	X	X		X		X		
MRC Dyspnoea Score	X	X		X		X		
Healthcare Utilisation Questionnaire	X	X		X		X		

Assessments	Visit 1 Screening/ Baseline Day 0	Visit 2 1 Month Follow Up 1 month (-1/+ 2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 2, 3, 4, 5, 6/7 (as applicable)	Visit 3 6 Month Follow Up 6 months (-1/+2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 6/7 (as applicable), 8, 9, 10, 11, 12 and 13	Visit 4 12 Month Follow Up 12 months (+2 weeks)	Telephone call to participant 7 days after last dose of IMP (+ 3 days)	24 Month Follow up **
Time and Travel Questionnaire						X		
Quality of life EQ-5D-5L	X	X		X		X		
Baseline blood test (FBC with differential)*	X							
Pregnancy test (urine, females of childbearing potential)	X							
Contraception discussion	X							
GP results request/ prior eosinophil levels extracted from medical records/ primary care datasets	X							
Eligibility confirmation[b]	X							
Randomisation	X							
Stop pre-randomisation inhalers with the exception of SABA and commence trial inhalers	X							
Trial inhaler delivered to participant on site at face to face visit	X							
Trial inhaler delivered to participant by post (2-4 days prior to each telephone call)			X	X	X			
Confirmation of trial inhaler receipt			X	X	X			
Inhaler technique	X	X		X				
Concomitant medication		X		X		X		
Issue Patient Exacerbation Diary	X							
Participant exacerbation diary review (or reminder to use at telephone calls)		X	X	X	X	X		

Assessments	Visit 1 Screening/ Baseline Day 0	Visit 2 1 Month Follow Up 1 month (-1/+ 2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 2, 3, 4, 5, 6/7 (as applicable)	Visit 3 6 Month Follow Up 6 months (-1/+2 weeks)	Telephone call to participant 3 days (+/- 1 day) following dispensing 6/7 (as applicable), 8, 9, 10, 11, 12 and 13	Visit 4 12 Month Follow Up 12 months (+2 weeks)	Telephone call to participant 7 days after last dose of IMP (+ 3 days)	24 Month Follow up **
Compliance check and documentation (count of returned trial inhalers and dose counts)		X		X		X		
Number of hospital admissions for bronchiectasis exacerbation		X		X		X		X
Number of emergency hospital admissions		X		X		X		X
Adverse event reporting		X	X	X	X	X	X[c]	
Review of primary care records						X		
Mortality Data								X

* To include haemoglobin, white blood count, platelet count, red blood cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils.

** 24 month follow up is completed 24 months after visit 1: screening/baseline and is required only for participants who reach this time point within the life time of the trial. The 24 month follow up does not require contact with the participant, instead data is collected as detailed in section 8.10.23.

[a] A copy of the completed consent proforma will be sent securely (i.e. nhs.net to nhs.net or encrypted email) to the nctu.dibs.conf@nhs.net email address within **5 working days** of the date of consent for all patients consented.

[b] A copy of the Eligibility Checklist will be sent securely (i.e. nhs.net to nhs.net or encrypted email) to the nctu.dibs.conf@nhs.net email address within **5 working days** of the date of completion for all patients completing screening. No participant identifiable data will be recorded on the Eligibility Checklist.

[c] Only AEs meeting the serious criteria (i.e. SAEs and SARs) are required to be reported at the telephone call 7 days (+3 days) after the participant's last dose of IMP.

8.10.2 **Demographic data and medical history**

Demographic data and medical history will be collected at visit 1: screening/baseline visit.

Data to be collected are:

- Gender
- Date of birth & current age
- Ethnicity
- Details of history of disease
- FEV1, FEV1% predicted
- Bronchiectasis Severity Score (www.bronchiectasisseverity.com)
- Current medical conditions (recorded to month/year of onset where possible)
- Surgical interventions (previous and planned)
- Any non-drug therapy
- Completed pulmonary rehab in last 12 months/ever/ never
- Physiotherapy training in past y/n
- Current physio regimen
- Pneumococcal, Influenza and COVID-19 vaccination status

8.10.3 **Medication history**

Medication history for all respiratory, non-respiratory and nutritional supplements will be collected at visit 1: screening/baseline visit. The data to be collected for each medication are:

- Medication name
- Dose
- Start/stop date (if started more that 1 year ago recorded to month/year of onset where possible)
- Indication

8.10.4 **Smoking history**

The smoking history is part of the exclusionary history. To be pragmatic and avoid recruiting patients with significant COPD we will exclude patients with greater than 20 pack years unless there is absence of spirometric criteria consistent with COPD, i.e., patients with greater than 20 pack years with an FEV1> 79% predicted are eligible so long as they also met other inclusion criteria such as having an obstructive ratio FEV1/FVC <70% and/or daily musus expectoration.

Smoking history will be collected at each trial visit (visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit). The data to be collected are:

- Details of smoking history (including pack years)
- Current smoking status

Smoking pack years should be calculated using the method detailed on the smoking packyears website: https://www.smokingpackyears.com/.

8.10.5 **Lung Function measurement - spirometry**

The BTS guidelines for the management of bronchiectasis (BE) state that spirometry and lung function should be measured in all patients with BE and that these measurements should be made at least annually. Measurements of lung function can give an indication of the degree of airflow obstruction and disease severity; it is hypothesised that the use of inhaled agents may ease the degree of obstruction and this will be evidenced through the lung function results at each time point.

At each trial visit (visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow up visit and visit 4: 12 month follow up visit) spirometry will be completed to determine FEV1 and FVC (predicted values will be as per GLI reference equations [25]). The FEV1/FVC ratio will be derived and FEV1 % predicted will be calculated (using GLI reference equations). Spirometry should be performed according to national/international standards [41]. For those patients using bronchodilators normally as standard care, spirometry performed at visit 1: screening/baseline should ideally be performed within 8 hours of the patients last dose of LABA or within 2 hours of the patients last dose of SABA (where applicable). Spirometry is not required immediately after the first dose of IMP as part of the protocol and is to be avoided unless clinically indicated. At subsequent visits (visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit) spirometry will be performed within 8 hours of the participant's last dose of IMP. At each spirometry assessment the time of the patients last inhaler/bronchodilator/IMP use will be recorded.

Spirometry measurements do not need to be performed at Visit 1 (screening/baseline visit) if they have been performed in the preceding 30 days.

Lung function measurement and calibration of the spirometer will be performed according to the standardised methods described by the American Thoracic Society (ATS)/European Respiratory Society. It is suggested that, in each site, the model of the used spirometer does not change during the trial.

Lung function measurements should be performed at approximately the same time of the day during clinic visits (obviously dependent on IMP administration) with subjects either standing or sitting (for each subject, this should be consistent throughout the trial) with the nose clipped after at least 10 minutes rest. Calibration of the spirometer must be performed preferably by the same Investigator at each visit prior to spirometry measurements and the reports must be kept with the source trial documents.

For FEV1 and FVC the highest value from 3 technically satisfactory attempts should be considered (irrespective of the curve they come from), and entered into the trial database.

8.10.6 **CT Scoring using modified Reiff score**

Knowledge of the radiological severity of bronchiectasis is important to allow appropriate stratification for the by BSI be carried out. It is important that the scoring of CT scans is carried out using the most recent CT scan available. New scans are not required as part of the trial, however, if a CT scan is unavailable (resulting in the patient being ineligible) and it is clinically indicated that a CT scan would be useful due to a high exacerbation rate, patients can be re-screened after this has taken place.

Radiological severity of bronchiectasis can be assessed using a modified Reiff score, which assesses the number of lobes involved (with the lingula considered to be a separate lobe) and the degree of dilatation (tubular = 1, varicose = 2, and cystic = 3). The maximum score is 18 and minimum score is 1. This score has been used previously in studies of bronchiectasis [10]. This trial requires a minimal data set on CT scan scoring; investigators are asked to answer yes or no to the following question:

“Does the CT scan show more than 3 lobes are affected by bronchiectasis or is there evidence of cystic bronchiectasis”. This should be undertaken prior to randomisation as it forms part of the BSI scoring system.

8.10.7 **Quality of life measurements**

The quality of life measurements should be the first procedure undertaken after consent and prior to any lung function tests or venepuncture. The patient should be instructed to answer each question in turn and that prompts by or queries to the trial team are to be avoided. The patient should answer each question and the trial team should check the questionnaires before the end of the visit. A member of the trial team should be available to provide additional support to patients who find the contents of the questionnaires, for example sensitive questions, distressing or upsetting. While patients should be encouraged to complete questionnaires fully, they are not obliged to answer any question that will cause distress or upset. If required, for example if trial visits are restricted due to a COVID-19, it should be endeavoured to complete questionnaires remotely by a method within the validated use for the questionnaire.

8.10.7.1 Quality of Life Bronchiectasis (QoL-B)

The QoL-B is a self completed specific tool for measuring the quality of life in bronchiectasis and has been shown to correlate with disease severity. It assesses symptoms, functioning and health-related quality of life specific to patients with Bronchiectasis through eight different items including, respiratory symptoms, physical, role, emotional and social functioning, vitality, health perceptions and treatment burden. This questionnaire is reliable and valid [35, 36].

Research staff will advise participants how to complete the QoL-B and about the contents of the questionnaire. Participants will self-complete the QoL-B at each trial visit; visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit.

8.10.7.2 St George's Respiratory Questionnaire (SGRQ)

SGRQ was designed to measure health impairment in people with COPD and asthma [35]. It has been validated for use in the BE population [38]. It is a two-part questionnaire; part 1 addresses the frequency of their respiratory symptoms, assessing the patients' perception of their respiratory problems in the past. Part 2 assesses the patients' current state in relation to their respiratory problems.

Research staff will advise participants how to complete the SGRQ and about the contents of the questionnaire. Participants will self-complete the SGRQ at each trial visit; visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit.

8.10.7.3 5-level EuroQol 5D index (EQ-5D-5L)

EQ-5D-5L is a validated questionnaire that is applicable to a wide range of health conditions; it provides a simple descriptive profile and a single index value for health status that can be used in both morbid and healthy populations. It consists of two parts; part 1 is descriptive and consists of a visual analogue scale which records the respondent's self-rated health on a 20 cm vertical with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. Part 2 is profile based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression considered at 5 increasingly worsening levels. Published, validated tariff values can then be easily attached to the returned profiles to use as health state valuations in determining Quality Adjusted Life Years (QALY) gains [39, 40].

Research staff will advise participants how to complete the EQ-5D-5L and about the contents of the questionnaire. Participants will self-complete the EQ-5D-5L at each trial visit; visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit.

8.10.8 **Bronchiectasis Severity Index (BSI) Score**

The BSI will be calculated using the online calculator http://www.bronchiectasisseverity.com/15-2/ or equivalent at visit 1: screening/baseline visit and visit 4: 12 month follow-up visit.

The parameters required for the calculation of BSI are: age, BMI, %FEV1 predicated, information about whether the patient has been hospitalised with a severe exacerbation in the past 2 years, the number of exacerbations experienced in the previous year, MRC Dyspnoea Score, details of sputum pseudomonas/other organism colonisation and radiological severity. The CT scan / report most recent to randomisation will be used for baseline and for follow up scoring at 12 months where no further imaging data are available.

8.10.9 **MRC Dyspnoea Score**

The MRC Dyspnoea score assesses the effect of breathlessness on daily activities. The MRC Dyspnoea Score consists of five scores:

1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4. Stops due to breathlessness after walking 100 meters
5. House bound due to breathlessness, or breathless on dressing or undressing

The MRC Dyspnoea Score will be measured by a member of the trial team in discussion with the participant at each trial visit; visit 1: screening/baseline, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit.

8.10.10 **Baseline and Transition Dyspnoea Indices (BDI and TDI)**

Breathlessness will be assessed by using the BDI at visit 1 (screening/baseline visit), and TDI at subsequent visits (visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow-up visit).

BDI and TDI are interviewer-administered, therefore a member of the trial team will complete the questionnaires in conjunction with the participant.

8.10.11 Healthcare Utilisation Questionnaire

The Healthcare Utilisation Questionnaire is a participant completed questionnaire assessing their use of healthcare services during their trial participation. It will be completed at each trial visit; visit 1: screening/baseline visit, visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 month follow up visit.

8.10.12 Time and Travel Questionnaire

The Time and Travel Questionnaire is a participant completed questionnaire assessing the transport and time used to utilise healthcare appointments. It is completed at the visit 4: 12 month follow up.

8.10.13 Baseline bloods

Blood samples will be collected at visit 1: screening baseline visit. The blood samples should be collected according to local Trust guidelines and sent to the local hospital laboratory for analysis of the following:

- Full blood count (FBC) with differential, to include haemoglobin, white blood count, platelet count, red blood cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils

The results should be recorded in the participants medical records, with documented investigator review, and on the CRF. The results are not expected to be ready before randomisation but should be entered as soon as possible thereafter. Sites are expected to link with local laboratories to ensure that eosinophil counts can be expressed as number of cells per microliter of blood. Patients do not need recalled if this data is incomplete, for example insufficently filled blood tube(s) or a laboratory processing issue.

8.10.14 Urine sample for pregnancy testing

For female participants of childbearing potential only, a urine sample will be taken at visit 1: screening/baseline visit and a pregnancy test carried out by the local hospital.

8.10.15 Contraception discussion

At visit 1 (screening/baseline visit) it should be confirmed that patients with child bearing potential (male and female) are willing to use contraception (as detailed in section 8.3) throughout the trial from the date of consent until 7 days after the last dose of IMP. This discussion and confirmation of contraception methods must be documented in the patient's medical records.

Any relevant contraceptive (i.e. contraceptive pill or implant) must be recorded in the CRF as medication history (if started prior to the date of consent) or concomitant medication (if started after the date of consent).

8.10.16 Prior eosinophil counts

Prior eosinophil results for the most recent three available recordings should be extracted from the patient's medical records, by requesting results from GP records or primary care datasets if required.

8.10.17 Participant Exacerbation Diary

The participant exacerbation diary will be issued at the baseline visit. Participants will be advised by the trial team of the importance of them completing the exacerbation diary weekly for the duration of their participation in the trial as this document is essential for the primary outcome of the trial.

The diary should be reviewed by a member of the trial team at each of the follow-up visits (visit 2: 1 month follow-up, visit 3: 6 month follow-up and visit 4: 12 month follow-up).

It is not mandatory that there is radiographic evaluation to define if there is a pneumonic element to the exacerbation.

Any exacerbation events will be recorded as

1) Patient defined (patient self-diagnosed and managed without healthcare advice/ assessment)
2) Healthcare professional involved exacerbation (where an exacerbation has involved a HCP in diagnosing and treating the exacerbation
3) Hospitalised

8.10.18 Concomitant medication

Concomitant medication should be reviewed and recorded at visits 2 (1 month follow-up visit), 3 (6 month follow-up visit) and 4 (12 month follow-up visit). The data to be collected for each medication are:

- Medication name
- Dose
- Start/stop date
- Indication

Pneumococcal, influenza and COVID-19 vaccinations which take place after the date of consent will also be captured as concomitant medications.

8.10.19 Inhaler technique

The correct inhaler technique is critical to the success of the trial. Instruction on inhaler technique will be provided to participants by a member of the trial team at visit 1 (the screening/baseline visit). Inhaler technique will be checked by a member of the trial team, and if necessary further training provided, at all follow-up visits (visit 2: 1 month follow-up visit, visit 3: 6 month follow-up visit and visit 4: 12 months follow-up visit).

8.10.20 Inhaler Dispensing and confirmation of receipt

Each participant will require a total of 13 inhalers for the 12 month (365 days total) treatment period.

The first inhaler will be dispensed to the participant by site pharmacy at visit 1: screening/baseline visit (this is dispensing number 1).

Subsequent inhaler dispensing (dispensings 2 through to 13) to the participant by site pharmacy will be posted/couriered directly to the participant's home approximately monthly (note: each inhaler is used for 30 days, however the shelf-life of the inhaler is only 6 weeks once it has been removed from the foil packaging by the site pharmacy for dispensing to the participant). Inhaler dispensing should be timed to ensure ongoing daily supply of medication.

The research nurse, or another member of the trial team, will telephone the participant a week following each inhaler dispensing/shipment to check that the participant has received the new trial inhaler by post. They will also enquire about any planned holidays/travel that may affect the timing of the subsequent inhaler shipping or any changes of address.

8.10.21 Compliance

Participants will be required to bring all trial inhalers, includes used inhalers, to all trial visits with the final return being at visit 4: 12 month follow-up visit. A member of the trial team will conduct and document compliance checks in the participants medical records, including the number of returned inhalers and inhaler dose counts. Any discrepancies from the expected returns and doses administered must be discussed with participants and details documented in the participants medical records.

8.10.22 Hospital admissions

Participants will be asked details of hospital admissions at visits 2 (1 month follow-up visit), 3 (6 month follow up visit) and 4 (12 month follow-up visit), details of hospital admissions must be recorded in the participants medical records.

The number of hospital admissions with a bronchiectasis exacerbation will be ascertained through review of the participant completed Exacerbation Diary.

The total number of emergency hospital admissions, irrespective of cause, will be ascertained.

The participants primary care records will be reviewed by a member of the trial team at 12 months for confirmation of the number of hospital admissions with a bronchiectasis exacerbation and the number of emergency hospital admissions (all cause).

8.10.23 24 Month follow-up

Long term follow up will be carried out at 24 months after visit 1: screening/baseline, for participants who reach this time point within the lifetime of the trial. Participants will not be contacted as part of the 24 month follow up, instead data will be collected from one of the following sources:

- Participant medical records
- BronchUK and/or EMBARC, where the participant has consented to follow-up with these registries
- Routinely collected data including HES and ONS data

The data collected at the time point are:

- Mortality data
- Number of emergency hospital admissions
- Number of emergency hospital admissions with bronchiectasis exacerbations

Review of participant medical records will be performed by site research staff. Data from BronchUK and EMBARC information requests will be sent directly to sites and inputted into the trial database. Other information requests (i.e. HES, ONS) will be performed centrally, where this is performed the NHS numbers for participants will be requested by the NCTU. Participant NHS numbers, alongside the associated participant trial ID, will be sent by secure email (i.e. nhs.net to nhs.net or encrypted email) to nctu.dibs.conf@nhs.net. NHS numbers will be stored securely by the NCTU in accordance with Newcastle University Information Governance for Health Research. Data for this follow up could be collected for up to one year following the 24 month visit timepoint due to HES/ONS data being collected in batches.

8.11 Protocol definition of an exacerbation of bronchiectasis

The protocol definition of an exacerbation is a continued worsening of one or more of the following symptoms, alongside antibiotic treatment for the exacerbation:

- increased cough

- sputum discolouration
- excess sputum production
- breathlessness
- fatigue

The start date of an exacerbation will be defined as the start date of antibiotic treatment and the end date of an exacerbation as the end date of antibiotic treatment, these dates will be recorded in the participant completed Exacerbation Diary and transcribed to the CRF.

During analysis the exacerbations occurring within 14 days of a previous exacerbation will be classified as one single exacerbation. Should an antibiotic treatment end date not be recorded in the CRF for any reason the Trial Statistician will classify the end date of the exacerbation as 14 days after the start date of antibiotic treatment for the exacerbation.

8.12 Discontinuation of Participants from Trial Treatment

Participants have the right to discontinue their allocated trial medication at any time. The participant is not required to provide a reason, however they will be encouraged to do so to ensure that information relevant to the trial design, medication tolerability and efficacy is collected where possible. A Discontinuation of Trial Treatment Form needs to be completed and any reason provided should be documented in both the CRF and the participant's medical records.

In addition, the investigator/treating clinician may discontinue a participant's allocated trial medication if deemed necessary for any reason, including pregnancy, intolerable side effects and inefficacy. The investigator will be encouraged to discuss these cases with the CI prior to the participant stopping trial medication and must complete the Investigator Led Discontinuation of Trial Treatment Form and document the reasons in the medical records and on the CRF.

The occurrence of an adverse event is not a reason to withdraw a participant from the trial. However, if the participant needs to be withdrawn due to an adverse event related to trial IMP (adverse reaction or serious adverse reaction - see section 10), the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. Adverse events that are not related to the trial IMP will be followed up to the point of trial completion.

Participants will not be withdrawn from the trial if treatment contamination occurs (such as they have used a non-trial inhaler) or trial treatment is discontinued. In these instances they will

remain in the trial and complete follow-up, and any reasons for contamination will be recorded and reported as part of the trial.

Participants and investigators will be encouraged to continue the allocated trial treatment where possible, as long as this does not put the participant at risk.

All participants choosing to discontinue trial medication should be encouraged to continue with trial follow-up. The investigator/treating clinician will discuss with the participant which remaining trial visits are required and acceptable. It is strongly preferred that the 12 month follow-up visit is completed. If this is not possible, then the participant should be asked to return their exacerbation diary to site by post (primary outcome).

Following cessation of trial IMP, the participant's treatment regimen will be decided by the investigator/treating clinician as per routine care.

8.13 Withdrawal from Trial

Participants who withdraw from the trial once they have been randomised will not be replaced.

A Withdrawal Form needs to be completed for any participant who withdraws from the trial and the reason for withdrawal recorded in the CRF and participant's medical records.

8.13.1 Participant Requested Withdrawal

When a participant states they want to withdraw from the trial, sites should try to ascertain the reason for withdrawal and document this reason within the CRF and participant's medical records.

Discontinuation of allocated trial medication is not a withdrawal from the trial if the participant is willing to continue with trial follow-up visits. If a participant does not want to attend any further trial visits but is willing to complete questionnaires by phone/post and return their exacerbation diary by post then they should continue in the trial.

Where a participant withdraws consent or their participation in the trial is discontinued, the data collected up to the point of withdrawal will be retained and included in the analysis. Where a participant withdraws consent, a Participant Withdrawal Form should be completed where the participant can consent to the continued use of routinely collected data until the end of the study follow up period, or confirm that they do not allow the continued use of routinely collected data.

8.13.2 Investigator Led Withdrawal

The investigator may withdraw a participant from the trial at any time if they deem it necessary for the following reasons:

- Continuing to attend trial visits and undergoing trial assessments would place unreasonable demands on the physical or psychological health of the participant. However, if it would be reasonable to continue to measure questionnaire outcomes by phone/post the participant would not be withdrawn from the trial. If participant and investigator agree, any assessments occurring as part of routine care would also be recorded in the eCRF.
- The participant loses capacity for a prolonged period
- An adverse event, which results in inability to continue to comply with trial procedures

8.14 End of Trial

The end of trial will be defined as the last patient last visit (LPLV), which will be when the last trial participant completes the 12 month follow up.

9 TRIAL MEDICATION

9.1 Name and Description of IMP

The participants in this trial will be randomised in a 2:2:1 ratio to receive either dual therapy dry powder inhaler, triple therapy dry powder inhaler or matched placebo dry powder inhaler.

THERAPY	**CONTENTS OF EACH DOSE DELIVERED**	**NAME OF EQUIVALENT COMMERCIALLY AVAILABLE PRODUCT**
Dual therapy (LAMA/LABA)	55 micrograms umeclidinium 22 micrograms vilanterol	Anoro Ellipta dry powder inhaler
Triple therapy (ICS/LAMA/LABA)	92 micrograms fluticasone furoate 55 micrograms umeclidinium 22 micrograms vilanterol	Trelegy Ellipta dry powder inhaler
Placebo	placebo	Matched placebo dry powder inhaler

The commercially available products, which contain identical active medication to the active product IMPs used in this trial, are licensed for use in the EU in adults with asthma or COPD. As this trial is evaluating the IMPs for use in adults with bronchiectasis, a new respiratory indication, the potential risks associated with the use of these IMPs in this trial would be categorised as:

Type B: somewhat higher than standard clinical care

A simplified Investigational Medicinal Product Dossier (sIMPD) will be used for Anoro Ellipta, Trelegy Ellipta and matched placebo due to the packaging and labelling requirements.

9.1.1 Drug Storage and Supply

All the inhalers to be used in this trial will be supplied by GlaxoSmithKline (GSK) as unlabelled product to Newcastle Specials PPU. Newcastle Specials PPU will label, QP release, store and distribute the IMPs for use in this trial. The products have a shelf life of two years with the inhaler presented in a sealed foil tray with desiccant and in an outer box (see image below). On opening of the foil tray, in use shelf life of inhalers is reduced to 6 weeks. All IMPs must be stored segregated from other medicinal products below 30°C. Stock will be supplied to individual trial sites as required, maximising available shelf life of trial stock as packs remain unopened.

9.1.2 Preparation and Labelling of IMP

Newcastle Specials PPU will label, in accordance with Annex 13 requirements, the foil tray with secondary packaging labels and the outer box with tertiary packaging labels. It will not be possible for Newcastle Specials to label the primary packaging (inhaler) due to the reduction in shelf life once the foil packaging is opened.

The secondary packaging label will be an extended label with peel off sections to allow for sites to label the primary packaging (inhaler) at the point of dispensing. This activity will be performed

prior to supply to a participant and under the supervision of a pharmacist in line with Regulation 37 of The Medicines for Human Use (Clinical Trial) Regulations. Contained within the secondary packaging label will be the following:

- Peel off label for the addition to the front of the inhaler
- Peel off label for addition to the rear of the inhaler
- Peel off label for addition to the accountability log.

Sites will be provided with a pharmacy manual which details the labelling process and completion of documentation relating to the dispensing of these IMP. Training requirements for staff involved in this process will be detailed in the pharmacy manual.

Each IMP product will contain a unique kit number which will be allocated by the randomisation system on a per participant per dispensing basis by the site research team. At the point of dispensing, the foil package must be opened in order to apply the primary packaging labelling on the inhaler. This will reduce the product expiry to 6 weeks from the date of opening which must be detailed by staff dispensing the IMP in the space provided on the product label. The site team will be given the unique kit number of the IMP, they will remain blinded to the IMP allocation for the kit number.

It is expected that site will post IMP to participants for all visits except baseline which will be given to the participant at site. If a scheduled visit where a participant is attending site in person coincides with a dispensing event, IMP can be given to the participant at site in these circumstances. Details regarding the secure posting of IMP are covered in the pharmacy manual. If local procedures do not allow IMP to be posted to participants, sites will need to develop a local delivery solution to allow transport to the patient. This process must be reviewed and approved by Sponsor prior to implementation. Trial staff at each site will be asked to phone the participant to ensure receipt of IMP or, if the participant prefers, they can contact the local trial site to confirm receipt.

The quantity of product within each inhaler allows for 30 doses and participants are expected to use all doses within the inhaler before starting a new inhaler. A total of 13 inhalers will be required by each participant for the 12 month (365 days total) treatment period. It is therefore essential to have good communication within the team at each trial site in order to ensure that supplies to participants are posted within an appropriate time frame to guarantee that the participant does not run out of IMP supply between visits. Participants will be counselled to return used inhalers

at face to face visits for compliance checks and to bring the "in use" inhaler for each face to face visit for inhaler technique assessments if needed. Inhaler technique should be performed as per local Trust standards.

9.2 Dosage Schedule

Participants will take one dose (one inhalation) of the IMP they have been randomised to once a day for the 12 month (365 days total) treatment period. The dose should be administered at the same time of day each day. The contents of each inhalation provides a delivered dose as detailed in section 9.1 for each IMP. No dose modifications are allowed.

Participants will be trained in the correct technique for use with their IMP inhaler at their baseline visit. Due to the importance of inhaler technique to the outcome of the trial, inhaler technique will also be checked at the subsequent 1 month and 6 month follow up visits. Inhaler technique should be performed as per local Trust standards.

9.3 Known Drug Reactions and Interactions

There are a number of known pre-existing medical conditions where triple inhaled therapy should be used with caution. These include severe uncontrolled thyrotoxicosis, severe glaucoma or urinary obstruction. Beta-agonists may worsen hypokalaemia when used alongside other drugs which are known to reduce potassium levels. These drugs should be carefully considered when patients are taking strong CYP3A4 inhibitors (e.g. ketoconazole, ribinavir, cobicistat-containing products). It will be at the discretion of the investigators if patients with such pre-existing conditions can be randomised into the trial. Patients with medically diagnosed lactose intolerance which is known to be severe must be excluded. Patients who suffer with mild to moderate gastrointestinal side effects whilst on lactose containing diets can be included in the trial as the ingested dose of lactose is likely to be very small. In contrast inclusion of patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption to the trial should be avoided. Due to the pragmatic design of the trial most medical conditions will not be exclusionary unless they prevent trial end points being measured e.g. large aortic aneurysm that precludes spirometry testing.

9.4 Concomitant Medications

No concomitant medications are prohibited. A complete listing of all concomitant medication, including applicable contraceptive medications, pneumococcal and influenza vaccinations

received during the data collection period should be recorded in the CRF and the participant medical records.

9.5 Assessment of Compliance

Participant treatment compliance will be assessed from return of used inhalers at 1, 6 and 12 month clinic visits. Pharmacy will assess and document returns on the pharmacy accountability log, a copy of the log will be provided to site staff for uploading to the trial database, which will be verified during site monitoring visits against the pharmacy accountability log. During the monthly phone calls staff will remind patients to take their inhaler and ask the patient to report the number on the inhalers dose counter. In the event that it is identified the inhaler is being used less than 80% of doses (less than 24 doses used/ more than 6 doses remaining from an inhaler) patients will be prompted to take it daily and offered retraining.

10 PHARMACOVIGILANCE

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions

Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

10.2 Recording and Reporting AEs and SAEs

All AEs occurring from randomisation to end of trial participation must be recorded on the AE CRF page as well as in the participant's medical records.

All SAEs occurring from randomisation (visit 1: screening/baseline visit) up to 7 days (+3 days) after the participant's last dose of IMP, or up to 7 days (+3 days) after participants end of trial

visit for those participants that have withdrawn from treatment but continued in the trial must be reported to NCTU on an SAE form and also recorded on the AE CRF page, flagged as serious.

All SARs occurring from randomisation (visit 1: screening/baseline visit) up to 7 days (+3 days) after the participant's last dose of IMP must be reported to NCTU on an SAE form and also recorded on the AE eCRF page. Following this defined active monitoring period for SARs, investigators are still required to report any SARs/SUSARs they become aware of whilst the trial is ongoing.

All SAEs/SARs must be reported to NCTU on an SAE Form via secure email (i.e. nhs.net to nhs.net email or encrypted email) to nctu.dibs.sae@nhs.net within 24 hours of site staff becoming aware of the event. A copy will be sent to all relevant individuals (CI, NCTU trial management, Sponsor and NCTU QA) to ensure they are aware of the event occurrence.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24 hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. All initial SAE reporting must be reported on an initial SAE form and all subsequent information should be provided on the follow-up SAE form. The initial SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved Reference Safety Information if a causal relationship is suspected

Any change of condition or other follow-up information should be submitted to NCTU via secure email nctu.dibs.sae@nhs.net as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs where the Investigator considers there to be no reasonable possibility of a causal relationship to the IMP and where unblinding is not required for medical or safety reasons, will be submitted to GSK retrospectively by the Sponsor within 90 days of the draft final report being sent to NIHR funder. Any SAE which arises during the trial, where the Investigator considers there to be a reasonable possibility of a causal relationship with the IMP and where unblinding of the participant is required for safety or medical reasons will be forwarded to GSK by Sponsor or a representative. Sponsor will provide a copy of the initial SAE report within five (5) business days of becoming aware of the reportable information. Associated follow-up information will be submitted to GSK via a line listing on a 3 monthly basis until the point of resolution. However, if the follow-up information relates to a change in classification of the event, this information will be provided to GSK by Sponsor on the SAE follow-up form within five (5) working days of Sponsor becoming aware of the information.

The commercial products Trelegy Ellipta (triple therapy) and Anoro Ellipta (dual therapy) are currently under intensive surveillance by the MHRA as Black Triangle medicines. This is to confirm the benefit/risk profile that was established during clinical development and ensure that any previously unrecognised side effects are identified quickly. An awareness of all known adverse reactions is required, however there are no pharmacovigilance reporting requirements in addition to those described for the trial above.

10.3 Reference Safety Information

The approved Reference Safety Information (RSI) are:

- for the dual therapy is section 4.8 of the SmPC for Anoro Ellipta (dated 7th April 2021)
- for the triple therapy section 4.8 of the SmPC for Trelegy Ellipta (dated 30th April 2021)

Details of the known side effects of the drugs are found within the SmPCs.

10.4 Protocol Specific Reporting Exclusions

Adverse events (AEs) judged by the Investigator responsible for patient care, as consistent with the usual clinical pattern for patients with bronchiectasis, do not meet the definition of a reportable AE. For patients with bronchiectasis, their clinical course commonly involves:

- Cough
- Increased sputum volume and/or consistency
- Change in sputum colour
- Wheeze

- Breathlessness
- Fatigue
- Haemoptysis (coughing of blood)

All other AEs which occur, including known side effects of the IMPs, should be assessed, recorded and reported in compliance with applicable procedures outlined in section 10.2 of the protocol.

The following hospital admissions are specifically excluded from reporting as an SAE:

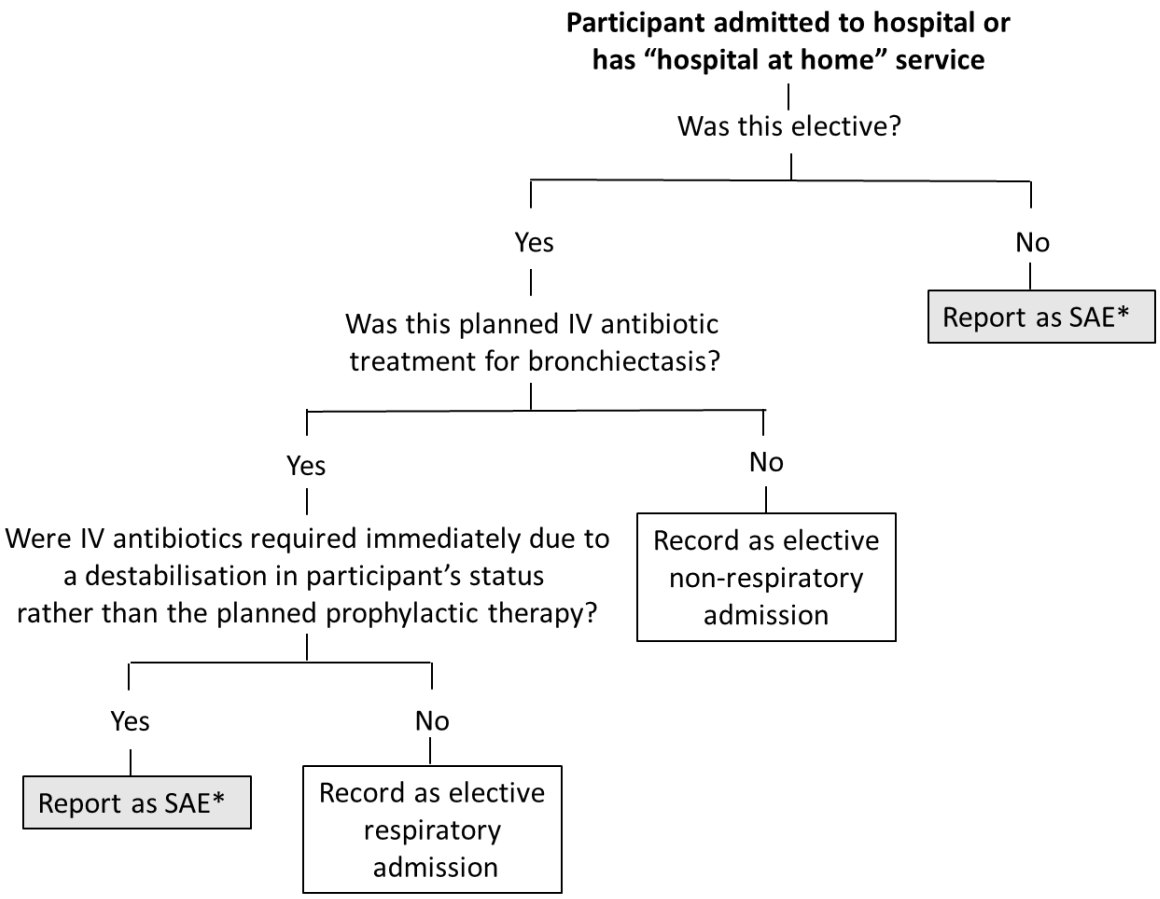
- Planned hospital admission for scheduled IV antibiotics (either as an inpatient or "hospital at home") used as prophylactic therapy for bronchiectasis exacerbations
- Elective or scheduled hospital admission for treatment of a pre-existing condition that did not worsen during the trial

Any other hospital admission that is not elective will need reporting as an SAE (see protocol section 10.2). This includes:

- Hospital admission for a bronchiectasis exacerbation even though this is an expected event within this trial
- Treatment of a bronchiectasis exacerbation with a "hospital at home" approach where a participant receives IV antibiotics as their status has destabilised
- Hospital admission for pneumonia / Bronchiectasis admission where pneumonia is noted to be the cause of the exacerbation

For the purposes of this trial, radiographic evaluation is not mandated for clinicians managing exacerbations unless they feel it is clinically indicated. However if an X-ray has been undertaken as part of clinical practice e.g. during hospitalisation for an exacerbation, data will be collected in the trial database on the presence/absence of consolidation.

The diagram below summarises when SAE reporting is required for participants in this trial admitted to hospital or having "hospital at home" service:



* For respiratory events report presence or absence of X-ray to confirm pneumonia

10.5 Recording and Reporting SUSARs

All SUSARs occurring from first administration of IMP (visit 1: screening/baseline visit) up to 7 days after the last dose of IMP, or that investigators become aware of whilst the trial is ongoing, must be reported to the MHRA and REC. NCTU will inform the trial Sponsor of all SUSARs within 24 hours of becoming aware of the event to ensure timely reporting to the MHRA and REC can be conducted. The Sponsor will perform this reporting. Unblinding must be undertaken in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs). The trial management team and CI must remain blinded, all unblinded information will be processed by the NCTU QA department and stored in a restricted access folder.

Unblinded SUSAR reports and associated follow-up information will be reported to GSK once the Sponsor's regulatory reporting requirements for SUSARs to the MHRA and REC have been met. Unblinded SUSAR reports will be submitted to CMG.Clinical-Contacts@gsk.com by the sponsor or a representative. The reporting of unblinded SUSARs to GSK will be carried out by the Sponsor

QA team, to ensure that the Sponsor and NCTU Trial Management Teams remain blinded throughout the trial. GSK must ensure that all correspondence relating to unblinded SUSAR reports are sent via the Sponsor QA team to avoid unblinding of Sponsor or trial management staff.

The assessment of expectedness will be performed by the CI against the approved Reference Safety Information (RSI) for the trial as detailed in section 10.3.

Fatal and life-threatening SUSARS must be reported to the MHRA and REC no later than 7 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported to the MHRA and REC no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a SUSAR they must contact the trial manager immediately, who will immediately inform the CI and Sponsor. The reporting timeframe to the MHRA and REC starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Participant ID number and date of birth
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided on the trial SAE reporting form. The trial management team and CI should remain blinded, all unblinded information will be processed by the NCTU QA team. The site is expected to fully cooperate with NCTU in order that a full and detailed report can be submitted by Sponsor to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs occurring in the trial by NCTU/CI. This documentation and confirmation of receipt must be filed in the investigator site file.

10.6 Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) for all SAEs and SARs.
- Confirming when changes to RSI are required as part of the annual review process
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).
- Providing GSK with a report of the trial detailing the methodology, results and analysis within 60 days of submission of the final report to the NIHR HTA programme.

Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).

- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the MHRA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occur (may be delegated to NCTU).
- Reviewing RSI at least annually, submission of substantial amendments to MHRA where changes to RSI are required and notifying PIs of any required updates (may be delegated to NCTU).
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC (may be delegated to NCTU)
- Review of safety data collected to date to identify any trends
- Providing GSK with copies of initial SAE reports (suitably de-identified prior to transfer) for events where the investigator considers there to be a reasonable possibility of a causal association with GSK IMP and where there is a requirement to unblind the participant for safety or medical reasons. Providing GSK with any associated follow-up data.
- Providing GSK with unblinded SUSAR reports and associated follow-up information once Sponsor's regulatory reporting requirements for SUSARs to the MHRA and REC have been met.

- Providing GSK with pregnancy information for trial participants who become pregnant while participating in the trial following exposure to the IMP, where there is a requirement to unblind for safety or medical reasons. Pregnancy outcome information will also be provided.
- Informing GSK of any findings they become aware of that may alter the safety profile of the GSK IMP
- Sharing any final submitted DSUR with GSK
- Providing GSK with a suitably de-identified data set within 60 days after the final report has been submitted to the NIHR HTA programme

10.7 Notification of Deaths

All deaths will be reported as SAEs irrespective of the cause of death and reported to Sponsor.

10.8 Pregnancy Reporting

In the event of a trial participant or the partner of a trial participant becoming pregnant on the trial, the site must notify the Trial Manager or trial management team within 24 hours of becoming aware of the pregnancy of the pregnancy and complete a pregnancy reporting form. If

a female participant becomes pregnant while participating in the trial, trial IMP will be discontinued immediately.

Site must approach the trial participant or the partner of a trial participant to obtain consent to follow the pregnancy to completion. For the female partner of a male trial participant, a DIBS Partner Pregnancy Information Sheet will be provided.

In the event that a congenital anomaly or birth defect does occur, this must be reported as a SAE.

Sponsor must report pregnancy information to GSK for all trial participants who become pregnant while participating in the trial following exposure to the IMP, where there is a requirement to unblind the participant for safety or medical reasons during the trial. The NCTU Pregnancy Reporting Form will be sent to GSK within five (5) working days of Sponsor being made aware of the unblinding. The participant will be followed up to determine the outcome of the pregnancy (including any premature termination of the pregnancy). This information will be forwarded to GSK within (5) five working days of receipt by Sponsor of the updated NCTU Pregnancy Reporting Form.

10.9 **Overdose**

Where an occurrence of over dosing is discovered, this should be notified to the PI immediately and any appropriate care or guidance given to the patient.

An overdose, whether intentional or accidental must also be reported immediately to the Trial Manager or trial management team (email: dibs@newcastle.ac.uk). Whilst it is not in itself an adverse event or serious adverse event any untoward medical occurrence as a result of an overdose, or any condition that leads to an overdose being taken is considered an AE or SAE and should be reported as per section 10.2. Details of the event must be recorded in the case report form for the trial and the participant's medical records.

Participants will be trained on how to take trial medication and reminded of the dose and frequency at each telephone follow-up. The amount of trial medication taken will be checked at each telephone follow-up call in order to ensure that the correct dose is being taken.

10.10 **Reporting Urgent Safety Measures**

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the participants of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified

immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures. The MHRA may alert the trial team to a new safety signal identified for any of the trial IMPs. In the event of this occurring, the IMP may need to be discontinued with immediate effect and a temporary halt submitted to the competent authorities. The sponsor is required to put the trial on hold with immediate effect.

10.11 Development Safety Update Reports

Data relating to SAEs will also be provided to the Medicines and Healthcare products Regulatory Agency (MHRA) in the annual Development Safety Update Report (DSUR). The DSUR will also be sent to the REC.

11 STATISTICAL CONSIDERATIONS

11.1 Analysis Population

We will consider the intention-to-treat (ITT) and per-protocol (PP) analysis populations. As is recommended, for the non-inferiority comparison, the PP analysis will be the primary analysis, with the ITT the primary analysis for the superiority comparison. However, both comparisons will be performed in both analysis populations and reported.

11.2 Statistical Analyses

11.2.1 Analysis of the Primary Outcome Measure

The primary outcome - number of bronchiectasis exacerbations per participant requiring antibiotics in the 12 months after randomisation - will be compared between randomised groups using negative binomial regression (as an alternative to the usual Poisson approach) adjusted for stratification factors. This model will be used to form confidence intervals (CIs) to test the superiority and non-inferiority hypotheses. The two-sided 95% CI for difference in mean number of exacerbations per year between LAMA/LABA, ICS/LAMA/LABA and placebo will be found: the placebo vs LAMA/LABA hypothesis will be rejected if the upper limit is lower than 0. We will estimate the difference between LAMA/LABA and ICS/LAMA/LABA arms on the relative scale using the incidence rate ratio, and test whether the upper boundary of the two-sided 90% CI is lower than 1.2.We will consider the time at

risk to be the time not spent in exacerbation (so that whilst a patient is in an exacerbation they are not included as at risk for another).

A secondary analysis will define the at-risk time as the entire length of follow-up for the patient. Estimates will then be adjusted for sites, the stratification factors and other baseline covariates that are known to be strongly related to outcome (e.g. age, smoking, bronchiectasis hospitalisations in year prior to trial – these will be pre-specified in the Statistical Analysis Plan (SAP)). Despite the participants being followed up for 12 months, some will withdraw early and, given their chronic illness, some will inevitably die [5, 6, 42].

To further assess the impact of death (found to be around 5% of the randomised participants in the first 12 months after randomisation from the TWICS study in a similarly morbid population) [43] on our potential treatment effect, we will undertake a sensitivity analysis by excluding those participants who have died. If there is any indication of a differential effect on deaths by treatment, we may consider models that allow the censoring to be informative. For participants that are lost to follow up at some time during the 12-month follow-up, their information will be included in the statistical models up to the point that they are lost to follow up. If loss to follow-up is higher than 10% we will explore applying sensitivity analyses to investigate the impact of loss to follow-up.

We will also explore time to first exacerbation using a Cox regression, and a recurrent events analysis to allow for subsequent exacerbations. In addition, we will utilise mortality and hospitalisations due to bronchiectasis exacerbation data collected up until 24 months to extend the modelling beyond 12 months as a sensitivity analysis. These models will be specified in the SAP.

For the primary superiority hypothesis, statistical analyses will be according to the intention to treat principle with a per protocol analysis performed as a sensitivity analysis. The protocol analysis will exclude participants who were not compliant (at less than 75%) with their trial medication or who had a major protocol violation (to be pre-specified in the Statistical Analysis Plan (SAP)). All analyses will be governed by this comprehensive SAP which will be agreed by the Trial Steering Committee (TSC) and reviewed by the IDMEC prior to any analyses being undertaken. Unless pre-specified, a 5% two-sided significance level will be used to denote statistical significance throughout. The Trial Management Group statisticians may be unblinded in order to prepare data for the initial IDMEC meeting after the pilot phase.

11.2.2 Analysis of Secondary Outcome Measures

The secondary outcomes - total number of bronchiectasis exacerbations requiring hospital admission, total number of emergency hospital admissions (all causes) will each be analysed in the same way as for the primary outcome described above. Disease related health status (measured using the SGRQ, FEV1 and FVC) are each measured at baseline, 6 and 12 months follow-up. A mixed effects model will be used to compare each outcome by randomisation group unadjusted and adjusted for site, stratification factors, patient characteristics and/or baseline clinical variables. Random effects for patient will be included.

11.2.3 Exploratory and Subgroup Analyses

Exploratory analyses will investigate the relationship between key outcomes (exacerbations and quality of life as measured by SGRQ and QOL-B) with baseline eosinophils (single level recorded at baseline), median eosinophil level (median of last 3 available recordings when not on oral steroids) and baseline BSI. Eosinophils and BSI will be analysed as continuous and dichotomised variables. Eosinophils will be categorised as low - normal (0-150/mm^3) and normal - high (>150/mm^3). Baseline BSI will be categorised a 0-8 compared to 9+.

Subgroup analyses of suspected aetiology comparing idiopathic and post infectious to all other aetiologies for the key outcomes of exacerbations and quality of life (SGRQ and QOL-B) will also be carried out.

11.3 Sample Size Calculations

The original sample size calculation was based on the number of exacerbations amongst a similar population in prior national audits (16, 39). The average number of exacerbations was 2.3 per year. Restricting trial entry to those who had >=3, the original inclusion criteria, (assuming a Poisson distribution) gives an average of around 3.8. We therefore assumed, given Hawthorne effect and regression to the mean that the placebo arm would have a lower mean exacerbation rate than this, and assumed a mean of 2.4 over 1 year. The sample size was chosen so that the trial was well powered to detect a clinically meaningful fall in mean exacerbation rates for bronchiectasis exacerbations to 1.9 year in LAMA/LABA and ICS/LAMA/LABA arms (approximately 20% reduction). This effect size is realistic when compared with the 20-30% reduction seen in COPD trials with dual bronchodilators/ triple therapy and is accepted as clinically meaningful. Although likely studying a different sub population in bronchiectasis, a recent inhaled antibiotic trial in bronchiectasis reduced exacerbations by 39% [38].

For 90% power (two-sided 5% significance level) to conclude that LAMA/LABA is more effective than placebo with the above parameters, we have calculated (assuming large-sample approximation of the Poisson distribution) a sample size of 600 participants is needed, randomised 240:240:120 between LAMA/LABA, ICS/LAMA/LABA and placebo. This allows for a 5% loss to follow-up. This represents a conservative retention rate compared to over 95% observed in the NIHR HTA TWICS study with similar pragmatic design and limited patient burden. This calculation assumes a difference between placebo and LABA/LAMA of 0.5 exacerbations per year (21% relative reduction).

If superiority of LAMA/LABA vs placebo is concluded, we will then test non-inferiority of LAMA/LABA against ICS/LAMA/LABA. The sample size will give 90% power (one-sided 5% type I error) with a 0.38 non-inferiority margin (reflecting 20% of the assumed LAMA/LABA rate).

Since we assumed a normal approximation to the Poisson, we confirmed the power with 100000 simulated replicates. The simulated power of the superiority and non-inferiority hypotheses are actually slightly higher than from the large-sample approximation formulae (91% and 90.3% respectively). We have also considered over dispersion by simulating from a negative binomial distribution (with a negative binomial regression used to analyse the simulated replicates). Over dispersion does cause the power to drop, but our sample size remains robust: for example, if over dispersion causes a 30% increase in the variance, the power to declare superiority is still 85%. We expect that power will be gained from including partial information from participants who are lost to follow-up as described below.

In the early stages of the trial it was found that exacerbation rates in pre-baseline periods were lower than they had been historically, mostly due to the effect of COVID restrictions. The inclusion criteria were therefore updated in protocol V5.0 (see Section 7). A recalculation of the power of the trial was conducted assuming that there would be lower exacerbation rates in the follow-up period. We assumed that the placebo exacerbation rate would be an average of 1.9 per year. We recalculated the power for two scenarios: 1) assuming that the same absolute difference (0.5) between LAMA/LABA vs placebo and the same non-inferiority margin (0.38) as previously; 2) the same relative difference (21%) between LAMA/LABA vs placebo and relative non-inferiority margin (20%) as before. The following table shows the power of the trial to conclude non-inferiority and superiority:

Scenario	**Mean exacerbation rate**		**Power***

	Placebo	**ICS/LAMA/LABA (Intervention)**	**LAMA/LABA (Active control)**	**NI Margin (relative to active control)**	**Non-inferiority**	**Superiority**
Presented in original grant application	2.4	1.9	1.9	0.38 (20%)	90.3%	89.8%
Updated inclusion criteria (same absolute differences)	1.9	1.4	1.4	0.38 (26.7%)	96.3%	95.8%
Updated inclusion criteria (same relative differences)	1.9	1.5	1.5	0.3 (20%)	83.4%	83.4%

*Note this is assuming analytical formulae, with simulations giving consistent but slightly higher powers

12 HEALTH ECONOMICS

12.1 **Analysis**

The economic analysis will consist of two parts: a within-trial analysis estimating the cost-effectiveness of dual therapy (LABA/LAMA) versus triple therapy (ICS/LABA/LAMA) versus placebo for the treatment of patients with bronchiectasis at 12 months; and a model based analysis extrapolating the within-trial results to estimate the cost-effectiveness of those treatment options over the patients' life course.

The perspective of the analysis will be the NHS and the participants and their families. Intervention costs will primarily be the costs of medications and inhaler devices used in the intervention therapies and these will be based on manufacturers' list price. Additionally, adverse events and treatments required will be recorded on the eCRF. Bronchiectasis has a significant impact on participants' quality of life with exacerbations leading to costly usage of healthcare resources, such as emergency admissions and A&E visits. A purposely designed Health Care Utilisation Questionnaire (HCUQ) will be used to collect detailed information on participants' use of healthcare resources (primary and secondary) as well as their out of pocket expenses during the trial's follow-up period, and will be collected at baseline and then 1, 6 and 12 months post randomisation. The design of the HCUQ will centre on minimising patient burden while maintaining the accuracy of data given that the healthcare use during follow-up among participants with bronchiectasis may potentially be the key difference in costs between the interventions. A broader, societal perspective will also be taken by including participant costs such as costs to access care and time off work and usual activities. This will be measured by the Time and Travel Questionnaire completed at the 12 month follow up visit. Overall costs will be estimated by combining the information provided by the Time and Travel Questionnaire and the Health Care Utilisation questionnaires.

Participants' health-related quality of life will be measured using EQ-5D-5L. The EQ-5D-5L will be administered at baseline and then, 1, 6 and 12 months post randomisation. Responses to the EQ-5D-5L will be converted into utility scores using a national tariff relevant at the time the trial reports. The area under the curve method will be applied to calculate QALYs from the utility scores over the trial follow-up period.

Mean cost and QALYs, incremental mean costs and QALYs and incremental cost per QALY gained at the end of the trial follow-up will be calculated for each randomised group. This data will be presented as point estimates, cost and QALY plots, cost-effectiveness and cost-effectiveness acceptability curves (CEACs). Due to the time horizon of the trial being 1 year, discounting will not be undertaken. Uncertainty in parameter estimates will be addressed using a bootstrapping technique to provide confidence intervals around estimates of mean incremental costs and incremental effectiveness. Cost and effectiveness data will be analysed using the trial data (unadjusted costs and effects) and using regression analysis (adjusted analysis).

Patients with bronchiectasis are expected to take the medication for life and as they age the disease mortality rate increases and at a higher rate for those with more severe conditions. It is, therefore, important to examine long term impact of treatment strategies on costs and benefits

for the NHS as well as the patients. We anticipate a Markov model will be developed to compare the cost-effectiveness of the different treatment strategies (the precise model form will be finalised during the model development). The model will be informed by advice from experts and will follow guidance for good practice in conceptualising an economic model [44]. Data to populate the model will come from the trial, HES and ONS data and relevant literature evidence. Mean estimates of costs and QALYs and parameters needed to define their respective distributions for the model will be based on data from the trial for the first year and extrapolated for the subsequent years based on literature evidence and expert opinion where appropriate. Transition probabilities between health states will be obtained from trial data and supplemented with literature evidence. Mortality rates will be based on the UK life table and disease specific mortality rates from the literature. The results of the model will be presented as mean costs and QALYs, incremental costs and QALYs and incremental cost per QALY for each intervention and will be discounted at an appropriate rate as per NICE guidance [45]. A probabilistic model will be developed which requires treating each input in the model as a distribution and using Monte Carlo simulation. The results of this will be presented using cost-effectiveness acceptability curves showing the probability that each intervention is cost-effective conditional on a range of possible threshold values that NHS decision makers attach to an additional QALY. Further deterministic analysis will explore other uncertainties such as different cost and QALY estimates and/or transition probabilities.

13 DATA HANDLING

13.1 Data Collection Tools and Source Document Identification

All data for an individual participant will be collected by each site's PI or their delegated nominees and recorded in the eCRF for the trial. Patient identification on the eCRF will be through a unique trial identifier number. A record linking the patient's name to the unique Participant ID will be held within each site's ISF stored in a locked room at their site, and is the responsibility of the site's PI. As such, participants cannot be identified from eCRFs. The CI or nominated designees will continually monitor completeness and quality of data recording in eCRFs and will correspond regularly with site staff with the aim of capturing any missing data where possible, and ensuring continuous high quality of data. A Source Data Agreement will be completed prior to the trial opening which will record what will be used as source data.

Consent will be sought from participants to perform long term follow-up via BronchUK, EMBARC, ONS and HES data (the collection of ONS/HES data is not applicable for Scottish sites), including collecting their NHS numbers to enable this (for ONS and HES data). Any NHS numbers required, alongside the participants corresponding unique participant ID Number, will be transferred to the NCTU by secure email (i.e. nhs.net to nhs.net or encrypted email) to nctu.dibs.conf@nhs.net. As Personal Identifiable Data, participants NHS number will be stored in line with Newcastle University Information Governance for Health Research, including a Safe Haven being set up to store the data and enrolling onto the Newcastle University's Data Security and Protection Toolkit (DSPT). Access to data will be restricted to members of the trial team who require it.

13.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with the General Data Protection Regulations 2018. Paper copies of trial-related documentation will be annotated, signed and dated, and filed in the medical records. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

13.3 Access to Data

Staff involved in the conduct of the trial, including the PIs, trial management team and NHS staff involved in screening and intervention will have access to the Investigator Site File.

The trial data and participant medical records may be looked at by NCTU during monitoring, the Newcastle upon Tyne Hospitals NHS Foundation Trust during monitoring or auditing and the Medicines and Healthcare products Regulatory Agency (MHRA) during inspection.

De-identified data from the trial will be shared with GlaxoSmithKline plc (GSK), including the following personal information:

- Age
- Sex at birth (female/male)
- Information about participants' bronchiectasis disease
- Ethnicity
- Participant identification number

Secure pseudoanonymised electronic data may be released to the Trial Statistician for analysis. The PI and trial sites staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Password limited access restricted to one's own particular role and site to the trial database will be granted to each site's PI and their delegated data entry personnel at that site. NCTU trial management team will have access to the trial database for monitoring purposes.

13.4 **Archiving**

All trial data will be stored for 5 years in accordance with UK GCP legislation and the Sponsor and NCTU SOPs.

14 MONITORING, AUDIT & INSPECTION

Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running of the trial and will consist of the CI, members of NCTU, statistician(s) and, as required, other members of the co-applicant team. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. TMG meetings will occur 4-6 weekly. Progress will be monitored proactively according to agreed trial timelines and any issues addressed. The TMG will liaise with the Trial Steering Committee (TSC), providing updates on trial progress and highlighting any issues arising.

Trial Steering Committee (TSC)

The TSC will be established to provide overall –independent oversight of the trial, and will oversee trial conduct and progress. The TSC will consist of an independent chair, together with at least two other independent members, two Patient and Public Involvement (PPI) representatives and the Chief Investigator. The TSC will meet approximately 6 monthly throughout the trial and meetings may be attended by non-voting observers including those from the NCTU, co-applicant team, Sponsor and Funder.

Independent Data Monitoring and Ethics Committee (IDMEC)

The IDMEC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The IDMEC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial. The IDMEC will meet approximately 6 monthly throughout the trial.

Principal Investigator

Each site will be led by a Principal Investigator who will be responsible for trial conduct. They will be supported by research nurses and all site staff will be GCP trained.

The Principal Investigator will be responsible for highlighting day-to-day trial conduct at site. The NCTU will provide day-to-day support for the site and training, site initiation visits and routine monitoring visits.

Monitoring

Quality control will be maintained through adherence to Sponsor and NCTU SOPs, trial protocol, GCP principles, research governance and clinical trial regulations.

Monitoring to ensure appropriate trial conduct and data collection will be carried out by the NCTU. Electronic data will be stored in secure, password-protected computers. NCTU staff will use a combination of central monitoring, off-site monitoring and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and the trial protocol.

The following will be monitored:

- Presence, validity and correct completion of completed original consent forms in the Investigator Site File (ISF) and copies in participants medical records.
- Comparison of original consent forms to the patient identification (enrolment) list.
- Reported serious adverse events, by verification against participant's medical records (source data verification).
- Presence of essential documents in the ISF and trial files
- Endpoint data, including for the primary endpoint, for a percentage of trial participants, by source data verification.
- Applications for trial authorisations and submissions of progress/safety reports, for accuracy and completeness, prior to submission.
- Eligibility data for a percentage of trial participants, by source data verification.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The site PIs and institutions will permit trial-related monitoring, audits, and regulatory

inspections, providing direct access to source data and documents relating to the trial. All data will be retained for 5 years.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol or urgent safety measures that occur during the trial. The Sponsor will notify the REC of any SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

15.2 Peer Review

This trial is funded by the NIHR Health Technology Assessment Programme and therefore has been subject to the NIHR peer review process for funding applications. This includes an external peer review followed by a review by the funding panel members.

15.3 Public and Patient Involvement

Patients have been involved throughout the trial concept and design phase. Funding has been provided for an expert patient representative to be involved on the TMG/TSC to ensure that the trial remains patient centred and to support engagement

15.4 Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU will support the CI in obtaining a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial (see sections 15.6, 10.10 and 10.4).

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial (see section 10.10).

The CI and NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

15.5 Protocol Compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI will retain overall responsibility.

Protocol deviations, non-compliances and breaches are departures from the approved protocol. Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events should be documented on the deviation tracking log (this will be provided as part of the ISF). NCTU will ask the site to provide copies of their deviation tracking log at intervals throughout the trial and before any monitoring visits. If no deviations have been identified during a particular interval, site are required to send an email to the NCTU to confirm this.

If a deviation constitutes a violation, the site must complete a protocol violation form (a blank template will be provided to the site as part of the ISF) and send a copy of this completed form to the Trial Manager in NCTU within 3 working days. The violation must also be entered on to the deviation tracking log.

Unintentional protocol deviations will be documented and reported to the CI and sponsor. Where necessary, Corrective and Preventative Actions (CAPA) will be implemented. These will also be documented and reported to the CI and sponsor.

Deviations found to frequently recur at a site are not acceptable and could be classified as a serious breach.

15.6 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The NCTU will notify the MHRA and the NHS REC within the required timelines in accordance with the sponsor and NCTU SOP.

15.7 Data Protection and Patient Confidentiality

Personal data will be regarded as strictly confidential. All data retained at site and sent electronically to the main co-ordinating centre will be sent securely and will contain a unique trial identifier number. The secure password-protected eCRF database will contain date of birth, ethnicity and sex at birth. This is essential for participant identification and verification. This information is also required for SAE reporting via secure email.

Participants NHS numbers (not applicable for Scottish sites) will be collected to allow for long term follow up where consent has been given for this. NHS numbers will be transferred to the NCTU by secure email (i.e. nhs.net to nhs.net or encrypted email) to nctu.dibs.conf@nhs.net. As Personal Identifiable Data, participants NHS number will be stored in line with Newcastle University Information Governance for Health Research, including a Safe Haven being set up to store the data and enrolling onto the Newcastle University's Data Security and Protection Toolkit (DSPT). Access to data will be restricted to members of the trial team who require it.

All personnel with access to trial data will be qualified and trained in, and will comply with ICH GCP.

A Participant Identification List will be the only document retained within the ISF, which contains full details of patients' hospital numbers, patient names and unique trial identifier numbers (participant ID).

The trial will comply with the General Data Protection Regulations, 2018. All trial records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access to those who are named on the delegation log.

15.8 Indemnity

The Newcastle Upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts for potential liability in respect of negligent harm arising from the conduct of the trial.

As Sponsor, the Newcastle upon Tyne Hospitals NHS Foundation Trust will provide indemnity in respect of potential liability and negligent harm arising from trial management.

Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by Newcastle University.

This is a non-commercial trial and therefore there are no arrangements for non-negligent compensation.

15.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor the Trial Management Group and Trial Steering Committee.

Substantial amendments will be submitted to the REC, HRA and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by the NCTU.

15.10 Post-Trial Care

Following the completion of the trial, trial participants will revert to clinician led care according to current guidelines.

15.11 Access to the Final Trial Dataset

Until publication of the trial results, access to the full blinded dataset will be limited to the Trial Management Group and to authors of the publication.

In line with General Data Protection Regulation (GDPR), explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur. In accordance with the NIHR position on the sharing of research data published in May 2019, which is in line with the UK Policy Framework for Health and Social Care Research, it is expected that valuable data arising from funded research should be made available to the scientific community. This must comply with participant consent and avoid inadvertent or deliberate identification of participants. Pseudonymised data from this trial may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the lead author/Chief Investigator and Clinical Trials Unit.

16 DISSEMINATION POLICY

To communicate with academics and medical professionals the intention will be to publish a number of scientific papers in peer reviewed publications and also to present lectures and posters at national and international academic conferences.

The full trial dataset must be created and uploaded for publishing through the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database as per the European Commission's guidelines on posting and publication of result-related information within 12 months.

The final report to funder will be published in the NIHR Health Technology Assessment (HTA) journal.

Authorship will be based on the ICMJE recommendations and it is expected that members of the Trials Unit that managed the trial will be invited to be co-authors. Recruiting sites are not automatically granted authorship but will be acknowledged "on behalf of the DIBS investigators".

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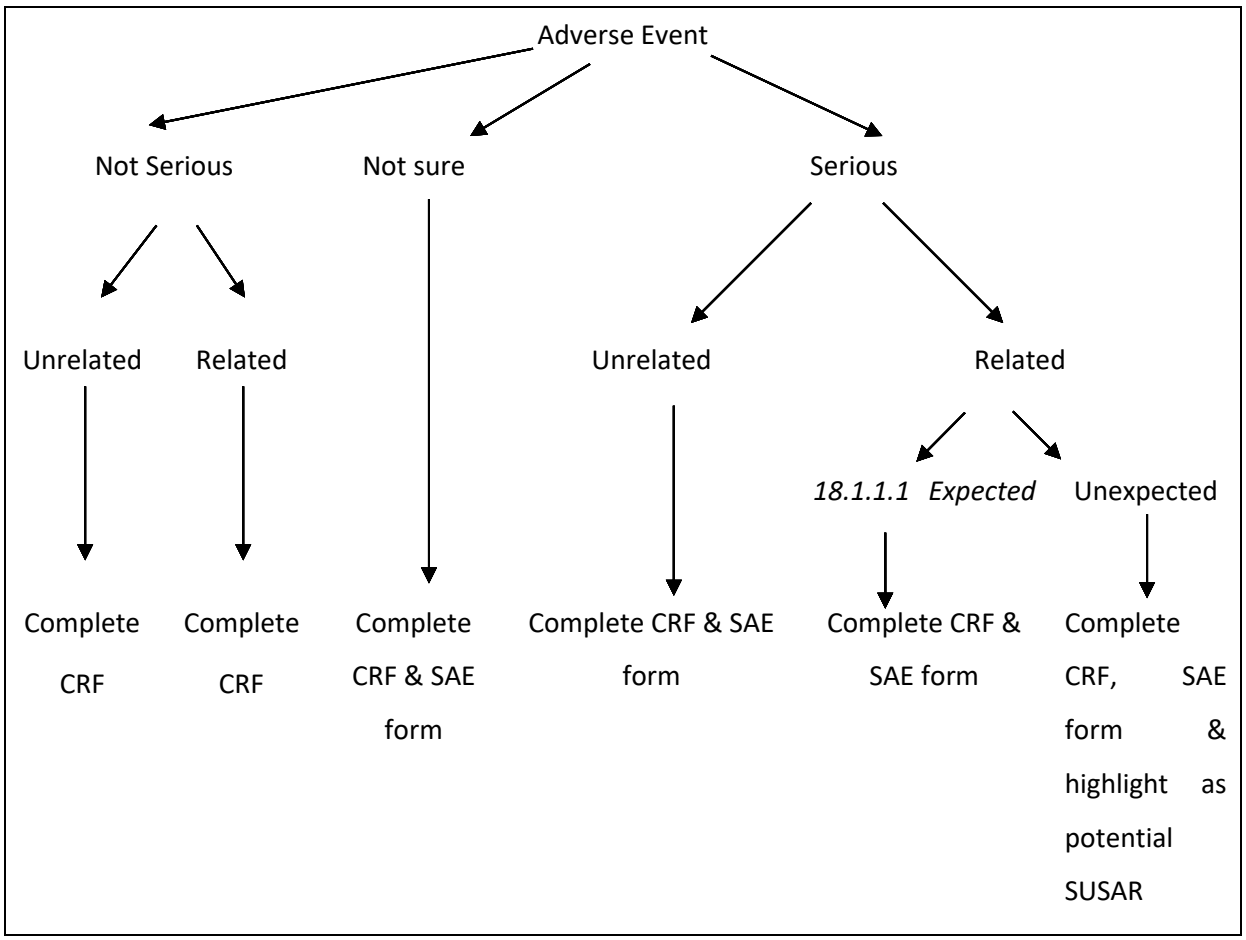
18 APPENDICES

18.1 Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs and SUSARs

Please send SAE form(s) via nctu.dibs.sae@nhs.net

18.2 Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Amendment 01	3.0	31st March 2021	Rebecca Wilson (Trial Manager)	• Clarification that one year of treatment with IMP is 365 days • Urea & Electrolytes and Liver Function Tests at screening/baseline removed • Timeframe to telephone participants to confirm receipt of IMP updated to within 3 days (+/- 1 day) of IMP posting • Removal of requirement for participants who do not take SABA as part of normal standard care to take a SABA prior to lung function tests • Clarifications made and typographical errors corrected
Amendment 02	4.0	4th May 2021	Miranda Morton (Trial Manager)	• Exclusion criterion number 12 updated for clarity • Sections 8.10.2 and 8.10.3: clarification of dates required to be recorded for past medical and medication histories
Amendment 06	5.0	22nd February 2022	Miranda Morton (Senior Trial Manager)	• Signatories, Trial Contacts, Co-Investigators/Co-applicants and Collaborators updated to reflect staff changes and contact detail changes • Internal pilot changes including extending from 6 to 12 month duration, recruitment target update, increase in the number of trial sites participating and change in progression criteria • Inclusion criterion number 2 updated to allow inclusion of patients experiencing 2 or more exacerbations within 12 months of each other in any two year period in the preceding 2 years • RSI updated in line with updates to SmPCs • Statistics section updated to include updated calculations accounting for the change in inclusion criterion number 2 • Clarifications made and typographical errors corrected throughout
Amendment 09	6.0		Richard Joyce (Trial Manager)	• Expansion of inclusion criterion number 4 (aimed at excluding patients with likely COPD) to allow patients with greater than 20 pack year history

				of smoking to enter the trial if there are no spirometric indications of COPD, i.e., an FEV1> 79% predicted • Exclusion criterion number 13 updated to enable patients with stable cancers to be included in the trial • Added clarification regarding SAE reporting timelines for those participants who have withdrawn from treatment • Staff updates