Liverpool University Hospitals NHS Foundation Trust

University Hospitals Birmingham NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

TRIAL PROTOCOL

STABILISE

A multicentre, randomised, parallel group, superiority trial to inveSTigAte the use of BCG vaccine In aLtering Immune reSponse and Exacerbation in chronic obstructive pulmonary disease (COPD)

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: ***2.0***

Version Date: ***30-Jan-2025***

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

Funding and support in kind

Funder(s)/Supporting Organisations	Financial and non-financial support given:
National Institute of Health and Care Research (NIHR)	£1,753,821
Funding scheme (if applicable)	Efficacy and Mechanism Evaluation (EME)
Funder's reference number	NIHR150098

The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the 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.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	STABILISE
Protocol version number:	Version: 2.0
Protocol version date:	30 / 01 / 2025
CI name:	Alice Turner
Signature and date:	Alice M. Turner 05 / 02 /2025

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham (acting as sponsor), confirm approval of this protocol.

Compliance statement

This protocol describes the STABILISE trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the STABILISE trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018, Human Tissue Act 2004 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the 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.

Trial name:	STABILISE
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_23-012
ISRCTN reference number	< ISRCTN reference number >
IRAS reference number	1007306

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Independent Members		
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Simon Barson	Patient representative	N/A
Ed Moran	Consultant in Infectious Disease	North Bristol NHS Trust
Christine Rollier	Professor of Vaccinology	University of Surrey
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Data Monitoring Committee		
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George Bouliotis	Associate Professor (Statistician)	University of Warwick
Susie Dunachie	Professor of Infectious Diseases	University of Oxford

ABBREVIATIONS

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
AECOPD	Acute Exacerbations of Chronic Obstructive Pulmonary Disease
BCG	Bacillus Calmette–Guérin
BCTU	Birmingham Clinical Trials Unit
CAC	Clinical Adjudication Committee
CAT	COPD Assessment Test
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
COVID 19	Coronavirus Disease
CRF	Case Report Form
CT	Computerised Tomography
DBS	Dried blood spot
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
EDC	Electronic Data Capture
EME	Efficacy and Mechanism Evaluation
EXACT	The Exacerbations of Chronic Pulmonary Disease Tool
FEV1	Forced Expiratory Volume in the first second
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HIV	Human Immunodeficiency Viral
HCP	Healthcare Professional
ICF	Informed Consent Form

IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGRA	Interferon Gamma Release Assay
IL1β	Interleukin-1 beta
IL6	Interleukin 6
IL-10	Interleukin 10
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IT	Information Technology
MHRA	Medicines and Healthcare products Regulatory Agency
MCID	Minimum Clinically Important Difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PBMC	Peripheral blood mononuclear cells
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and public involvement
PROBE	Prospective Randomised Open Blinded End-point
QOL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance team
RSI	Reference Safety Information
RSV	Respiratory Syncytial Viral

RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SMS	Short Message Service
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TNFα	Tumour necrosis factor
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom
UKAS	United Kingdom Accreditation Service
UKHSA	UK Health Security Agency
UoB	University of Birmingham
WOCBP	Woman of Childbearing Potential

TRIAL SUMMARY

Title

STABILISE: a multicentre, randomised, parallel group, superiority trial to investigate the use of BCG vaccine in altering immune response and exacerbation in chronic obstructive pulmonary disease (COPD).

Objectives

The primary objective of the trial is to determine whether the Bacillus Calmette–Guérin (BCG) vaccination reduces rates of moderate-severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) at 12 months in patients who have a clinical diagnosis of COPD, and a history of exacerbations in the preceding year.

The secondary objectives are listed in the protocol.

Trial design

A multicentre, two arm, parallel group, superiority, randomised controlled trial, with an internal pilot, a process evaluation, an acceptability study and embedded mechanistic work.

Participant population and sample size

Adults aged 18 or over who have a primary clinical diagnosis of COPD and have had ≥2 exacerbations in the last 12 months. 804 (402 in each arm) participants are required.

Setting

50 secondary and primary healthcare sites in the UK.

Eligibility criteria

Inclusion criteria:

- age ≥ 18 years
- a primary clinical diagnosis of COPD
- ≥2 acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in the last 12 months prior to screening

Exclusion criteria:

- exhibiting positive or indeterminate Interferon-Gamma Release Assay (IGRA)
- exhibiting immunosuppression
- received >20mg prednisolone per day for >14 days in the last 3 months
- known pregnancy
- previous experience of allergic reaction to vaccine
- Unable to give informed consent

Intervention and Comparator

A single dose of BCG vaccine vs no vaccine.

Outcome measures – at 12 months after randomisation for the control group/12 months after IMP administration for the intervention arm date unless otherwise stated

Randomised controlled trial (RCT) Outcomes

Primary:

- Rate of moderate to severe AECOPD (number per person per year)

Secondary:

- hospitalisation rate for infective exacerbations – equivalent to the rate of severe AECOPD
- quality of life (QOL), as defined by the COPD Assessment Test (CAT)
- total number of days of antibiotic therapy for AECOPD during follow up
- total number of days of oral steroid therapy for AECOPD during follow up
- type of exacerbation (as they occur (rate over time)):
    - defined by Anthonisen criteria
    - defined by a clinical adjudication committee (CAC), who will use sputum, viral and symptom data to determine aetiology of each event

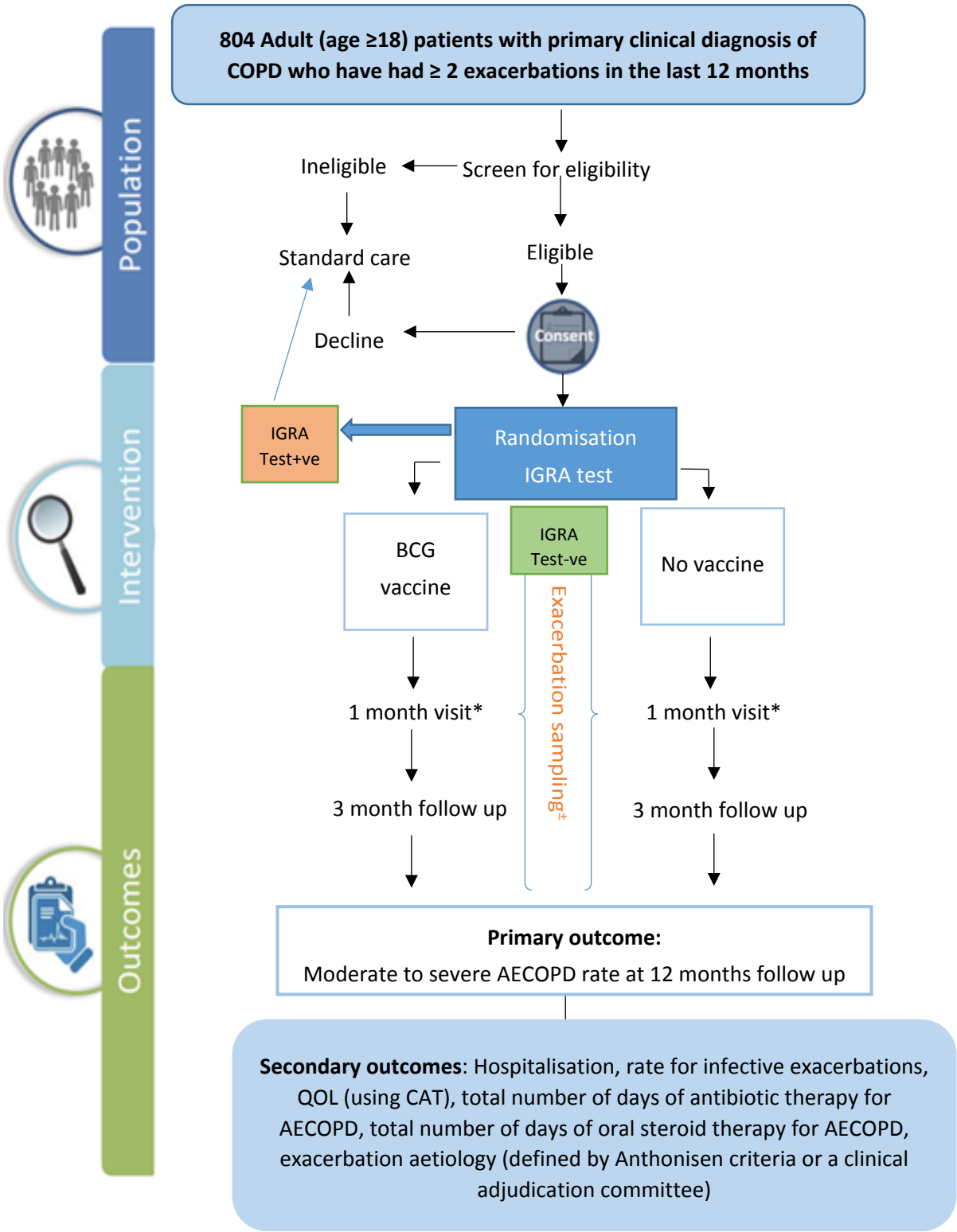
Mechanistic Analyses

BCG vaccine-specific responses comprised of trained immunity, gene expression analyses, cell phenotyping and functional screening.

- Based on analysis of dried blood spot (DBS) samples at baseline, 1, 3, and 12 months:
    - anti-BCG antibody responses
    - cytokine profiles (IL-1β, IL-6, TNFα, IL-10)
- Based on whole blood, dried blood spot (DBS), peripheral blood mononuclear cells (PBMC), neutrophils, serum, and PAXgene tubes at baseline, 1, 3, and 12 months:
    - antigen-specific B cell & antibody
    - trained immunity
    - serum cytokine analysis
    - transcriptomics
    - flow cytometry
- Based on sputum, saliva, nasal swab, and DBS samples following exacerbation:
    - microbiology profile (multiplex PCR, bacterial culture)
    - anti-pathogen antibody responses (Immunoglobulin G (IgG)/ Immunoglobulin A (IgA))
    - anti-BCG antibody responses
    - cytokine profiles (IL-1, IL-6, TNFα, IL-10)

TRIAL SCHEMA

STABILISE: a multicentre, randomised, parallel group, superiority trial to inve**ST**ig**A**te the use of **B**CG vaccine **I**n a**L**tering **I**mmune re**S**ponse and **E**xacerbation in chronic obstructive pulmonary disease (COPD)



*Mechanistic subgroup only

± Both groups to provide exacerbation samples unless patient opts out

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1. BACKGROUND AND RATIONALE

1.1 Background

Chronic obstructive pulmonary disease (COPD) is defined by fixed airflow obstruction. It frequently overlaps with other airways diseases (e.g. asthma, bronchiectasis), but it is normally possible to define a primary diagnosis, with any other airways' disease being secondary. Patients with COPD may be managed solely in primary care, with more complex/severe patients being seen in secondary care; this typically includes frequently exacerbating patients. Exacerbations, or flare ups, occur in all airways diseases and are associated with disease severity (1-3), blood eosinophilia (4, 5), poor quality of life (QOL) (1, 6, 7) and older age (7, 8). Current approaches to reduce exacerbation risk, whilst effective, do not completely abrogate risk, such that further treatments are needed. Current approaches include vaccinations, bronchodilators, inhaled steroids, mucolytics and prophylactic antibiotics. COPD affects 2 million people in the United Kingdom (UK) (9), causes breathlessness, cough and sputum production and results in over 140,000 hospital admissions/year (9). Given its prevalence and impact on the health service, optimising care is a priority for UK healthcare. This was highlighted by the British Lung Foundation, who noted that lung disease is one of the UK's biggest killers, alongside heart disease and non-respiratory cancers, killing 115,000 people/year, the equivalent of one person every five minutes (9). These mortality figures are roughly the same as a decade ago, whereas deaths from heart disease went down by 15% from 2008 to 2012 (9). Furthermore, the UK has the 4th highest mortality rate from lung disease in Europe (9). Despite current therapies, patients continue to exacerbate, and these are a significant cause of death – 38% will die or be readmitted to hospital within 90 days of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) (10) - such that more therapies targeting this trait are required.

Simple interventions which have the potential to alter immune response and through this prevent infection or inflammation are attractive additions to the current patient pathway; the Bacillus Calmette-Guérin (BCG) vaccine for tuberculosis (TB) is one potential intervention broadly applicable to all airways' disease patients. It is the most used vaccine in the world, with around 130 million children vaccinated every year. Soon after its introduction in Europe, epidemiological studies showed that BCG vaccination strongly reduced infant mortality, which could not be explained by a reduction in TB alone (11). Subsequent studies have shown an up to 50% mortality reduction in young infants due to protection against unrelated infectious agents, particularly respiratory tract infections (12). There is increasing evidence that 'trained immunity' is an important contributor to this phenomenon (13). The effects of trained immunity are evident on i) innate cell biology; ii) adaptive cell function; iii) immune cell metabolism; and iv) hematopoietic progenitor cells. An important factor is that the protective benefits persist for a year or longer.

During the COVID-19 pandemic, simple measures such as mask wearing, periods of isolation and hand hygiene have led to lower rates of admissions to hospital with AECOPD (14), and overall lower rates of viral infection (14). However, it has also been apparent in pre study patient and public involvement that further preventative measures are welcomed by patients. This is supported by positive intentions regarding SARS-CoV2 vaccination in patients with multiple medical conditions, or who have had the influenza vaccine previously, characteristics applicable to many airways' disease patients (15). Vaccines are already widely used in respiratory patients (e.g. annual influenza) such that incorporating

BCG vaccine into the clinical pathway is likely to be feasible, and since it costs little, may be cost-effective even if the effect size is small.

1.2 Trial rationale

Our *research question* is 'Does BCG vaccination reduce exacerbations in patients with COPD?'

Our *primary aim* is to determine whether BCG vaccination reduces rates of moderate-severe AECOPD up to 12 months in patients who have a clinical diagnosis of COPD, and a history of exacerbation in the preceding year. Our hypothesis is that the vaccine will reduce infectious exacerbations, and that there may be a greater effect for viral driven events.

1.2.1 Justification for participant population

In COPD a non-exacerbator phenotype is recognised, which is stable over time (4, 16), implying that a selection criterion which excludes these individuals could adequately enrich a trial cohort with exacerbators. We recognise that keeping inclusion as broad as possible, in order to ensure results are likely to be generalisable to the whole airways disease population in the UK, is desirable and for this reason, we have not included any other severity features (e.g. % predicted Forced Expiratory Volume in the first second (FEV1)) or prior treatment expectations as inclusion criteria, though we will gather data on severity features in order to describe the population accurately. Patients with more than one airway disease would commonly be excluded from drug trials, but they constitute a large proportion of the population in primary care; for example, 22% of COPD patients are also coded to have asthma (17) and 29% have bronchiectasis on computerised tomography (CT) scan (18). Such patients will not be excluded. Bronchiectasis occurs in around half of exacerbating COPD patients (18-20) and asthmatic features are observed in some COPD patients (21), such that including patients with these as secondary diagnosis in a COPD study represents real-life and improves feasibility of recruitment. Moreover, there is growing evidence that therapies, be they physiologically focussed, such as inhaled steroids and long-acting bronchodilators (22,23) or pathology focussed, such as the anti-IL5 mepolizumab (24,25), may work in multiple airways diseases to reduce exacerbations. This suggests, consistent with the long established 'Dutch hypothesis,' that there is a spectrum of airways disease, where conditions lie along a continuum and share aetiological factors (26), such that treatment strategies can be similar.

1.2.2 Justification for design

We have chosen a Prospective Randomised Open Blinded Endpoint (PROBE) design, powered to detect a 20% reduction, equivalent to 0.45 AECOPD/year in patients meeting our inclusion criteria. The primary outcome of the study is medically confirmed exacerbations of airways disease, treated with at least additional oral treatment (antibiotics or steroids); even though this moderate-severe AECOPD definition is a robust outcome commonly used in COPD trials, there is potential for bias to be introduced if the patient or clinician is aware they have received the vaccine. Despite the fact that a double blind design would be the most robust trial design with respect to bias, it have been proven to be exceedingly expensive and difficult to commercially produce matching blinded placebo vials. A PROBE study design maintains the benefits associated with a strict randomisation procedure, while the blinded end points help to eliminate bias. We will employ a group of clinical experts who are not responsible for recruiting participants into the trial to join an adjudication panel to determine the presence or absence of the exacerbation based on several sources of information. By doing this we will ensure that the primary outcome will be adjudicated independently. The panel will meet at different intervals and the review will be undertaken blinded to treatment allocation. Each panel

member will give their diagnosis and where there is disagreement, cases will be resolved by discussion. This addresses the problem of achieving a diagnosis from multiple sources of information and of subjective assessment of that information, as a diagnosis will be confirmed by consensus.

An alternative vaccine was not desirable as the trial concept is that non-specific immunity will be driven by BCG; another vaccine would only be an option if specific immunity were the outcome, or it was well known that an alternative vaccine did not have any non-specific immune priming, which is not the case.

The study is powered to detect the minimum clinically important difference (MCID) in AECOPD rate. The MCID in AECOPD rate is debatable, ranging from 4-20% in one review (27), but is likely closer to 20% (28), based on anchoring to QOL score. Anchoring is a method that relates MCID in one measure to change in another, in order to determine the MCID of the related item; whilst it is imperfect and could vary according to the measure chosen to anchor against, a subsequent systematic review has shown that a 20% reduction in moderate to severe AECOPD (i.e. those that require additional oral treatment or hospitalisation, equivalent to the primary outcome measure in this trial) relates reasonably well to both the MCID in FEV1 and the MCID in QOL (29). Furthermore, in a trial, clearly any reduction will vary with the included population's baseline rate. Frequent exacerbators are generally considered to be those with ≥2 AECOPD/year (1), hence a 20% reduction equates to 0.45 AECOPD/year – the exact amount by which macrolides (a common treatment strategy in people with COPD who frequently exacerbate) reduced AECOPD in the landmark trial (30), which informed our sample size calculation.

1.2.3 Justification for choice of intervention(s)

Beneficial effects of intradermal BCG on all-cause mortality have been observed at epidemiological level in children, putatively due to lesser rates of neonatal sepsis and respiratory tract infections (RTIs) (31). Observational studies show BCG vaccination may protect against respiratory syncytial viral (RSV) infection (32) and RTI in adolescents (33). In a study in elderly people, the BCG vaccine reduced infection rates from 42% to 25% of the cohort, with two categories of infection (RTI and viral RTI) having 95% confidence intervals clearly favouring BCG. The largest effect was seen for RTI of probable viral origin (hazard ratio 0.21, p=0.013) (34). However, this RCT included only 198 patients and these results were based on an interim analysis, thus the results are not conclusive. Furthermore, the study did not select for respiratory patients, nor for those at risk of infectious exacerbation, therefore a targeted study in such adults is warranted.

1.2.4 Justification of choice of primary outcome(s)

AECOPD are a significant burden to both the individual and the healthcare system and are not adequately controlled by existing therapies. Exacerbation reduction is also important to patients.

The primary outcome is moderate to severe AECOPD rate up to 12 months follow up. This is defined by healthcare utilisation (taking additional antibiotics and/or steroids, as recorded in the medical record, including prescription data), although we will collect symptom and treatment data from participants to infer if the event was infective. This will include all major and minor Anthonisen criteria (35), as well as whether antibiotics, steroids or antipyretics were taken.

2. AIMS AND OBJECTIVES

2.1 Internal objectives

The trial includes a 9-month internal pilot aiming to test recruitment strategies and processes across all sites opened during the pilot phase and to refine sample size calculation: Event rates at 3 months

follow up will provide an indication of the anticipated event rate, and if necessary, sample size adjustment. The DMC will review and advise on this.

2.2 Main trial objectives

2.2.1 Clinical aims and objectives

The primary objective of the trial is to determine whether BCG vaccination reduces rates of moderate-severe AECOPD over 12 months in patients who have a clinical diagnosis of COPD, and a history of exacerbation in the preceding year. Our hypothesis is that the vaccine will reduce infectious exacerbations, and that there may be a greater effect for viral driven events.

The secondary clinical objectives are to compare the rate of hospitalisations for infective exacerbations, QOL, total number of days of antibiotic and steroid therapy use during the follow up period between intervention and control groups and to determine the acceptability of the BCG vaccine.

2.2.2 Mechanistic aims and objectives

Specific exploratory immunology objectives are to:

- Characterise cellular and molecular immune responses induced by vaccination (BCG-specific and non-specific) and to pathogens identified during any exacerbations.
- To relate responses induced by BCG to the level of protection BCG affords against exacerbations.
- To relate exacerbating pathogen-specific response (if it occurs) to immune response induced by the BCG vaccine, in order to identify biomarkers that predict BCG-associated protection from exacerbations.

2.2.3 Qualitative acceptability study aims and objectives

The aims of the acceptability work are to explore understanding and acceptance of vaccines in general, and of this specific vaccine, by exploring and comparing uptake/acceptability to other exacerbation prevention strategies, for both patients and healthcare professionals. This includes exploring the concept of general uptake of preventive medicine, in the context of uptake of vaccines.

3. TRIAL DESIGN AND SETTING

3.1 Trial design

This is a pragmatic, multicentre, two arm, parallel group, superiority, individually (1:1) randomised controlled trial testing the efficacy of BCG vaccine to reduce exacerbations of COPD against no vaccine over 12 months. There is an internal pilot phase, a process evaluation, a qualitative acceptability study and embedded mechanistic work.

3.2 Trial setting

The trial setting is primary and secondary care sites in the UK. The aim is to open 50 sites across all settings, and we expect ≥70% of patients will be recruited from secondary care.

3.3 Qualitative acceptability study

The acceptability study aims to explore the understanding and acceptance of vaccines in general, that of the BCG vaccine used in this RCT and comparing the uptake/acceptability in this trial to other exacerbation prevention strategies, for both patients and healthcare professionals (HCPs).

3.4 Mechanistic/immunological study

The mechanistic/immunological study aims to assess the BCG vaccine-specific responses, heterologous trained immunity through antibody profiling, gene expression analyses, cell phenotyping and functional screening which will provide mechanistic insights into how BCG may modulate the host and provide non-specific vaccine effects over the course of this study.

3.5 Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: **Type A = No higher than the risk of standard medical care**

4. ELIGIBILITY

4.1 Inclusion criteria

- Age ≥18 years
- Any patient with a primary clinical diagnosis of COPD, confirmed by a medical record of post-bronchodilator Spirometry denoting obstruction
- ≥2 AECOPD in the last 12 months prior to screening.

4.2 Exclusion criteria

- Positive or indeterminate IGRA at enrolment
- Immunosuppressed in the opinion of the investigator (including, but not restricted to: Human immunodeficiency viral (HIV) infection, common variable immunodeficiency, chemotherapy, disease modifying agents for rheumatic diseases)
- Received >20mg prednisolone per day for >14 days in the last 3 months
- Known pregnancy
- Previous experience of allergic reaction to vaccine
- Unable to give informed consent

4.3 Co-enrolment

Co-enrolment in other mechanistic studies or observational work will be allowed.

5. CONSENT

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial related procedure. This task can be delegated by the PI to other members of the local research team, if local practice allows and this responsibility has been documented in the STABILISE site signature and delegation log.

5.1 Consent Procedure

All eligible participants will be approached about the trial by someone in the patient's direct medical care team; Participating sites are primary care centres and research active trusts with research embedded as part of their clinical care. Participants would, therefore, expect to be contacted about research studies they would be eligible for. If a patient expresses an interest in participating in the trial, the direct care team will introduce the potential participant to the local research team. Consent will be taken face to face, electronically at all research sites by the local research team. A paper version of the consent form will be available if a participant wants to complete a paper one. The

local team will be requested to post the paper completed ICF to the trial office at BCTU in a timely manner.

A Participant Information Sheet (PIS) will be provided to facilitate the consent process, which may be presented electronically or on paper. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the potential participant. They will also explain that participation is voluntary and that the potential participant is free to decide to take part and may withdraw from the trial at any time without this affecting their care. The potential participant will be given sufficient time, to read the PIS and to discuss their participation with others outside of the site research team. A paper copy of the PIS can be taken home to aid their decision making if required.

The potential participant will be given the opportunity to ask questions before electronically signing and dating the latest version of the Informed Consent Form (ICF). The PI or delegate will then electronically sign and date the ICF via the Electronic Data Capture (EDC) system.

5.2 Consent documentation

Consent will be taken electronically. A copy of the signed ICF will be given to the participant. Should participants wish to do so, they can receive a copy of the signed ICF electronically by consenting to provide an e-mail address, or alternatively a hard copy can be provided. A copy of the ICF will be filed in the medical notes and a copy placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. The participant's trial number will be linked against the consent form stored in the EDC system. In addition, there is a statement in the ICF to confirm that the participant understands and acknowledges that the signed ICF will be stored in the EDC system at BCTU for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Electronic copies of the PIS and ICF will be available from BCTU.

5.3 Ongoing consent

At each visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial, the participant will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.4 Additional consent

The ICF contains optional additional statements for the participant to:

- Agree for any remaining blood samples to be stored beyond the end of the trial to be used in future research which conforms to all relevant legal, governance and ethical requirements.
- Agree to be contacted by a researcher to discuss taking part in a research interview.
- Agree for their anonymised data from the trial to be shared with other Universities/third parties for research purposes.

- Agree to take part in the detailed mechanistic study (if the recruiting site is selected to recruit participants to the sub-study). See Section 0 for further details.

6. ENROLMENT AND RANDOMISATION

6.1 Identification

Patients will be identified by site PIs, or delegated individuals at that site, in conjunction with routine care teams. Patients may be identified by participating sites in any reasonable way for their practice/hospital and either invited directly or using the invitation letter. We anticipate primary care staff searching databases using search protocols developed by the lead Clinical Research Network, and inviting potential participants based on eligibility at this pre-screening stage (age ≥ 18 years, primary clinical diagnosis of COPD and ≥2 acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in the last 12 months). Searches of pre-existing, research databases, and prospective identification of patients in clinics may be used in any setting. Identifiable information will not be reviewed by people outside of the clinical care team without consent. Posters will be provided to primary and secondary care sites to exhibit in appropriate areas so that patients may self-refer. These posters will also be customised for web-based display via the trial's unit, patient support groups and other relevant social media, and will contain contact details for the trial's unit, so that patients can be connected to a site local to them, if available. Participant Identification Centres (PIC) sites may also be used to help identify potential participants e.g. ambulatory services linked to a main site taking part in the trial. Patients will be invited to participate in either the main trial or the qualitative acceptability study, or both.

Potentially eligible patients will be invited to take part in the trial by their usual care team via post, text or email using the invitation letter and a PIS to provide further information about the trial.

Patients may be contacted by short message service (SMS) text message via their GP Practice or secondary care provider (standardised text to be used for text messages will be provided). This could be as a follow up to the participant invitation letter (sent in the post) or as an initial recruitment approach. Patients will be asked to contact their usual health care provider if they have any questions or are interested in taking part in the trial. Where it is an initial recruitment approach, patients will be provided with the PIS before the usual consent procedure is followed.

Once adequate time has been allowed to consider the trial, a screening appointment will be scheduled which will take place either at their usual GP practice, secondary care site, over the telephone or via an online video link.

6.2 Consent and Enrolment

A single consent process is being employed for STABILISE. Consent will cover screening and randomisation into the trial. This will reduce the number of required visits for patients. After extended consultation, we opted for the approach of screening and randomisation before the IGRA results as this would be more convenient for volunteers since it would require fewer visits. In addition, given the typical demographic of patients with COPD in the UK, and with the UK being a low endemic country for TB, we expect the rate of positive or indeterminate IGRAs to be extremely low. Therefore, the need to alter randomisation following a positive IGRA result is likely to be highly infrequent.

Screening investigations will be completed in-person with patients at their hospital, by delegated doctors, nurses, and research nurses. The informed consent process will be documented in the patient's medical records. An electronic Screening Form will be completed for all patients who are assessed for eligibility and will be used centrally to monitor recruitment. Each patient will be assigned a screening number in lieu of a trial number being allocated when they are randomised.

Baseline data will be collected via CRFs completed at this visit. This will include asking additional questions regarding existing and potential pregnancy. Data collected includes Participant details, medical history, concomitant medications (refer to Section 9 – Trial Procedures). These data will be ideally added to the trial EDC system by delegated site staff before randomisation but if this is not possible, then as soon afterwards as is feasible.

Spirometry will be performed to assess COPD severity, if it has not been performed in routine care; if it is available in the routine care record in the last 12 months that may be used instead. Where spirometry is performed it should be done whilst the patient is taking their usual inhalers. Demographic data, smoking status and degree of past smoke exposure (pack years), medical history and current medications will be collected. These data will be added to the trial EDC system by delegated site staff once eligibility is confirmed by the local investigator, or as soon as possible after randomisation. If the patient is not eligible, any completed assessments and worksheets will be destroyed in line with local confidential waste disposal protocols.

All patients will be asked to provide a blood sample (used to perform the IGRA test), DBS sample, a sputum sample and complete a nasopharyngeal (nose and throat) swab (if they produce in the stable state). Participants will also be taught how to obtain their own DBS sample by a medically qualified member of staff as they will be asked to complete this at home at the specified follow up time points. A patient interviewer-administered questionnaire will be used to collect quality of life (CAT score) and exacerbation management in the last 12 months.

6.3 IGRA test results

Only patients with a negative IGRA test result from the blood sample taken at baseline are eligible to join the trial. If a participant's result is indeterminate, the site should contact the patient to ask them to provide a new sample of blood for testing. If the result of the second IGRA test is indeterminate, the patient will be deemed as ineligible. If the participants result is positive, they should be referred for assessment of TB status. Once a negative IGRA result has been received, the participant is eligible to receive the vaccine if they are allocated to the intervention arm. It is anticipated that the results from the IGRA test to be available within 1-2 days with a maximum of a week. Eligibility will be affirmed by a medically trained doctor. Patients with positive or 2 indeterminate IGRA will be informed by a letter from their recruiting site that their blood test results didn't meet the study inclusion criteria.

6.4 Randomisation

Patients will be randomised after eligibility, excluding IGRA result, has been confirmed by a medically qualified doctor. Randomisation will be provided by the Birmingham Clinical Trials Unit (BCTU) using a secure online system (available at https://*stabilise.bctu.bham.ac.uk*), thereby ensuring allocation concealment.

Unique log-in usernames will be provided to those who wish to use the online EDC system and who have been delegated the role of randomising patients into the trial as detailed on the STABILISE site signature and delegation log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online trial EDC system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the event of the online system not being available, a back-up telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

6.5 Randomisation process

After informed consent has been given and participant eligibility, excluding IGRA result, has been confirmed, the participant can be randomised into the trial using the online EDC system. Worksheets will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the online Randomisation Form must be answered appropriately prior to a potential participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the randomiser, local PI, local research nurse, trial mailbox, and the administrating site pharmacist. The local research nurse will inform participants of their allocation verbally.

The local research team should add the participant to the STABILISE Participant Recruitment and Identification Log which links participants with their trial number. The PI must maintain this document securely, which is not to be submitted to the Trial Office and should be held in strict confidence.

6.6 Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either BCG vaccine or no vaccine via a central secure web-based EDC system. A minimisation algorithm will be used within the randomisation process to ensure balance in the BCG vaccine allocations over the following variables:

- Age (<65 or ≥65 years)
- Prior BCG vaccination or TB infection (yes/no)
- Consent to participate in the detailed mechanistic sub-study (yes/no)
- Site

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.7 Blinding

STABILISE is a PROBE trial and will utilise a Clinical Adjudication Committee (CAC) to assess the primary outcome to determine the number of exacerbations after randomisation using all available trial related clinical information. The adjudication committee will be blinded to the allocated treatment arm. They will look at basic patient details, symptoms of the AECOPD (from the patient), treatment history including any hospital admission (from the GP/medical record/CRF) and the laboratory test results (i.e. the sputum, swab and DBS samples).

6.8 Informing the participant's GP and other parties

The participant's General Practitioner (GP) will be notified that they are in the STABILISE trial, using the STABILISE GP Notification Letter. No other parties outside of the trial team will be informed of the participant's entry into the trial.

7. TRIAL INTERVENTION

7.1 Trial intervention and dosing schedule

Participants will be randomised and those allocated to the intervention arm will receive the vaccine injection within 6 weeks from the date of randomisation. They will receive BCG vaccine (after reconstitution, 1 dose (0.1 ml) for adults contains Mycobacterium bovis BCG (Bacillus Calmette-Guerin), Danish strain 1331, live attenuated, 2-8 x 105 cfu). This is given as a one-off dose via the intradermal route of administration.

According to the manufacturer, the vaccine must be administered within 4 hours of opening the vial. Vials are only available to us in multi-dose vials, consequently batch delivery is required to avoid wastage. Sites can administer the allocated BCG to participants who gave consent in batches allowing them to make up one solution for delivery. We will be using administrating NHS hubs (organised by BCTU) where patients from 3-4 sites within the geographical area can travel to receive the BCG injection if they are within an hour travel. This will help to reduce the wastage of the vaccine. Patients will be reimbursed for the travel cost. Participants will be sent a letter for their vaccination appointment.

7.2 Reconstitution of the IMP

The IMP will be reconstituted by the administrating hub pharmacist or an HCP who will visually inspect the vaccine prior to administration. Each vial contains approximately 7-8 doses of the drug. To reconstitute the vaccine, 1ml of sterile water should be added to the vial and then carefully inverted a few times to re-suspend the lyophilised BCG completely, it should not be shaken.
Technique for Intradermal injection

The injection site should be clean and dry. If antiseptics (such as alcohol) are applied to swab the skin, they should be allowed to evaporate completely before the injection is made. The BCG vaccine should be administered by personnel trained in the intradermal technique. The vaccine must be injected strictly intradermally in the arm, over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm), as follows:

- The skin is stretched between thumb and forefinger.
- The needle should be almost parallel with the skin surface and slowly inserted (bevel upwards), approximately 2 mm into the superficial layers of the dermis.
- The needle should be visible through the epidermis during insertion.
- The injection is given slowly.
- A raised, blanched bleb is a sign of correct injection.
- The injection site is best left uncovered to facilitate healing.

7.2.1 Technical training and competency for the intervention

Some clinicians will already perform intradermal injections. However, some clinicians will not be familiar with the technique and all PI's and delegated staff performing intradermal injections will be offered remote, or where necessary, face-to-face training by a qualified TB nurse at University Hospitals Birmingham.

Written material on the technique will be provided to sites. Any clinician performing intradermal injections within the trial will be required to review the training material.

Given that intradermal injections are a simple procedure, only a self-assessment of competency and confirmation of training material review will be required. This will be recorded on a training log, which should be kept in the ISF and a copy forwarded to the STABILISE trial office. PI's will be responsible for approving trainee self-certification.

7.3 Overview of tissue sample collection

Blood samples will be collected from all participants of the trial at baseline. Some participants will be asked to provide additional blood samples at 1, 3 and 12 months. Participants will be asked to give consent to provide sputum samples, combined nasal and throat swabs at every AECOPD. Dried blood spot tests (DBS) will be completed at baseline, 3 months and 12 months follow up. Participants will also complete DBS test at every AECOPD if consented to do so.

Blood samples will be taken and processed at the local GP/NHS hospital sites. Samples will be frozen and stored at the GP/hospital site and then transported back to the Clinical Immunology Service at the University of Birmingham for longer term storage. Sample storage will be recorded in STABILISE lab file. Sputum, throat/nasal swabs and DBS tests will be sent directly to the Clinical Immunology Service at the University of Birmingham for receipt, processing and storage.

At the University of Birmingham, it is mandated that laboratories work to Good Clinical Practice.

Optional consent will be sought from participants to store any remaining blood samples after this trial for use in future research which conforms to all relevant legal, governance and ethical requirements. If consent for long term storage is not given, then these samples will be disposed of in accordance with the Human Tissue Authority's Code of Practice.

7.4 Drug interaction or contraindications

7.4.1 Permitted medication(s)/intervention(s) (including rescue medication)

There are no restrictions on permitted medication(s).

7.4.2 Concomitant medication(s)/intervention(s)

There are no restrictions on concomitant medication(s).

7.4.3 Prohibited medication(s)/intervention(s)

The are no prohibited medication(s).

7.5 Intervention modification or discontinuation

Since this trial has a one-off dose of IMP this is not applicable.

7.6 Continuation of intervention after the trial

There is no plan for repeated doses of IMP.

7.7 Intervention supply and storage

AJ Vaccines A/S are the marketing authorisation holder and manufacturer of the BCG vaccine AJV. The BCG vaccine will be sourced from a standard NHS stock supply, ring fenced for the trial. Each administering site will be responsible for maintaining the supply of BCG. Due to an international shortage of BCG, trial administering sites will be asked to purchase their BCG from UK Health Security Agency (UKHSA). UKHSA will send the trial stock of BCG vaccine directly to Trust pharmacy of the administrating hospital.

7.8 Packaging and labelling

As the IMP has a marketing authorisation in the UK, and are dispensed in their original packaging, there is a scope to reduce the labelling requirements. In compliance with Annex 13, as a minimum, trial labelling will include at least: name of sponsor and/or contract research organisation, name of trial, name of the principal investigator and name and address of the trial site.

Local sites will ensure the final labelling of the product meets the requirements above to protect the trial participant, allow full traceability, identification of the trial, identification of the product and

facilitate proper use of the IMP in accordance with Volume 4 of Good Manufacturing Practice, Annex 13 (Manufacture of investigational medicinal products 31 January 2010). BCTU will supply a template label but should sites wish to use their own label a copy should be submitted to the trial unit for Sponsor's approval prior to the opening of STABILISE at a trial site.

7.8.1 Drug storage

The BCG vaccine will be stored by Pharmacy under controlled ambient temperature. No additional temperature monitoring is required other than that required for general stock supplies held in the pharmacy for routine care. Please refer to the SmPC's for storage conditions for the BCG Vaccine.

7.8.2 Storage deviations

Storage including temperature monitoring of the drug will be as per the local trust guideline. In the event of excursions, local policies will be followed.

7.9 Accountability

Local pharmacy accountability logs will be completed in order to maintain traceability of the stock issued and returned within the trial.

7.10 Adherence

This is not applicable at the participant level since there is only a one-off dose administered by the site research team. The site research team will confirm on CRFs which participant's they administered the vaccine to once it has been given.

8. OUTCOME MEASURES

8.1 Internal pilot outcomes

An embedded internal pilot will run over a period of 9 months to assess site and participant recruitment and exclusion and primary outcome data completion.

The pilot outcomes are to:

Assess recruitment rate and exclusions: We aim for 20 sites enrolling at 9 months from study approval by the relevant authorities and target an overall recruitment rate of 1 patient per site per month. We will also examine reasons for non-inclusion of patients in the study; if high rates of exclusion occur due to patients declining, we will prioritise completion of qualitative acceptability work.

Assess primary outcome data completion: We aim for more than 90% of primary outcome data reported on the three month follow up form.

Assess an indication of the anticipated pooled AECOPD rate of the primary outcome: The pooled AECOPD rate at 3 months after date of treatment/randomisation will be used to indicate if the event rate is proceeding in line with what we would expect, such that the original sample size calculation remains accurate. The clinical adjudication committee will blindly review three-month AECOPD data collected directly from patients which will need confirmation via the routine care record (including data held on patient NHS App if necessary) at site, for the purposes of the 3-month review during the pilot. To meet the primary outcome of moderate to severe exacerbation, proof of antibiotic and/or steroid prescription (e.g. GP record of medication issue), and hospital admission (e.g. a discharge letter) respectively is required. Sites will be asked to confirm that such proof has been sent to be reviewed by the clinical adjudication committee.

We have considered Medical Research Council Hubs for Trials Methodology Research workshop guidance when determining stop/go criteria for the trial (43). Areas considered as suitable progression criteria include recruitment rate, protocol adherence (data completion) and outcome rate. A traffic

light system of green (go), amber (amend) and red (stop) was deemed preferable to a simple stop/go approach when specifying progression criteria for internal pilot studies, and they suggested recruitment progression criteria should be based on rates per centre per unit time that can be extrapolated, rather than specifying an absolute number by a specific date.

If sites overall have a recruitment rate of 1 participant per month, then recruitment will complete in 19-20 months across 50 sites. A recruitment rate of 1 participant/ month therefore represents green (go); if it is 0.5-0.9 participants/month this is amber (amend), and we will consider increasing the number of sites and enrolling patients after discharge from hospital due to an exacerbation, once 6 weeks have passed to allow stability; and if it is <0.5 participants/month this is red (stop).

Table 1 - Traffic light criteria

Green	≥20 sites open for recruitment
	Sites overall recruitment rate of 1 participant per month (on average)
	>90% of primary outcome data reported on the three month follow up questionnaire
Amber	5-19 sites open for recruitment
	Sites overall recruitment rate of 0.5-0.9 participant per month (on average)
	80-90% of primary outcome data reported on the three month follow up form
Red	<5 sites open for recruitment
	Sites overall recruitment rate of <0.5 participants per month (on average)
	<80% of primary outcome data reported on the three month follow up form

8.2 Main trial outcomes

8.2.1 Primary outcome(s)

The primary outcome is moderate to severe AECOPD rate over 12 months follow up from IMP administration date (or from the date of randomisation if no treatment was administered). This is defined by the clinical adjudication committee and will be based on an assessment of:

- basic patient details
- healthcare utilisation (taking additional antibiotics and/or steroids, as recorded in the medical record, including prescription data),
- patient-reported symptoms of the AECOPD
- laboratory results from patient-provided sputum, saliva, nose/throat swabs and DBS samples following an exacerbation

Severe events are defined by additional hospitalisation. Confirmation of events as stated in section 8.1, will occur via the CAC. Terms of reference for the CAC will be set.

8.2.2 Secondary outcomes

We will compare the following between intervention and control groups over 12 months follow up from IMP administration date (or after the date of randomisation if no treatment was administered), unless otherwise stated.

- Hospitalisation rate for infective exacerbations – equivalent to the rate of severe AECOPD.
- Quality of life (QOL), as defined by the COPD Assessment Test (CAT)

- Total number of days of antibiotic therapy for AECOPD during follow up, defined by patient self-report at each event, and confirmed by the site in the medical record (section 8.1).
- Total number of days of oral steroid therapy for AECOPD during follow up, defined by patient self-report at each event, and confirmed by the site in the medical record (section 8.1).
- Type of exacerbation (as they occur (rate over time)):
    - Defined by Anthonisen criteria, collected at AECOPD using patient self-report of symptoms. Type 1 being characterised by increased breathlessness, sputum volume and sputum purulence, type 2 by two of these three symptoms and type 3 by a single symptom.
    - Defined by the clinical adjudication committee (CAC), who will use sputum, viral and symptom data to determine aetiology of each event, categorising events as infectious (confirmed bacterial, confirmed viral, clinically likely but no organism identified) and non-infectious.

8.2.2.1 Qualitative acceptability study

Themes relating to vaccine acceptance and AECOPD prevention strategies in general, as obtained by the Framework method, described in section 3.3 constitute the outcomes of the qualitative work.

9. TRIAL PROCEDURES

9.1 Patient identification and invitation to participate

Potentially eligible patients will be identified and invited to take part in the trial (section 6).

9.2 Baseline visit

Patients screening and consent will take place at the baseline visit. The baseline visit will occur face-to-face at a participating research site (either primary or secondary care site). At the start of the baseline visit, patients will have an opportunity to ask questions about the trial before being asked to provide full informed consent (section 5). Once screening is completed and consent is obtained, site staff will then complete the baseline blood sample details CRF with patients and randomise participants, perform spirometry (if required i.e. if not available within the last 12 months), and the participant will provide a blood sample, sputum sample, nasopharyngeal swab and complete a dried blood spot (DBS) test. The blood sample will be sent to the research sites local laboratory and an IGRA test will be performed (section 6.3). Participants will be shown how to complete the DBS test themselves and given a test kit to take home to complete the DBS test themselves after each exacerbation and when their three month follow up is due. Site staff will also demonstrate to the participant how to take a sputum sample and perform a nasopharyngeal swab, as participants will be asked to send these samples to the main laboratory based at the QE hospital (UoB) if/when they experience an exacerbation at home.

Trial procedures and points to be collected at are:

- Confirmation of inclusion and exclusion criteria, excluding IGRA result
- Trial suitability
- Decliner questionnaire (if applicable)
- Informed consent
- Randomisation

The following baseline information will be completed:

- Demographic information including sex, ethnicity, date of birth
- Medical history & concomitant medications
- Smoking status
- Employment status
- Vaccine status
- NHS number
- Height and Weight
- Educational level
- Marital status
- COPD exacerbations
- Contact details – Address, email and telephone number
- COPD Assessment Test™ (CAT)
- Lung function test – spirometry
- Blood sample
- Dried blood spot test (DBS)
- Sputum sample + nasopharyngeal swab

9.3 IGRA result

Only participants with a negative IGRA result are eligible to take part in the trial. If the participant's result is indeterminate, the research site will arrange for a repeat blood sample to be taken and IGRA test performed. If the participant's result is positive, the participant will be informed that they are not eligible to take part in the trial and referred for assessment of TB status. For those randomised to the intervention arm, a treatment visit will be arranged to take place at the participant's local administrating hub site for them to receive the BCG vaccine.

Data point to be collected:

- IGRA blood results
- Affirmation of eligibility

9.4 Administration visit

Participants allocated to the intervention arm will receive a letter inviting them to a clinic at their closest administrative hub to receive the BCG vaccine (section 7.1). The visit and so vaccine administration to the participant, should be within 6 weeks of randomisation. The administering site will request that all women of childbearing potential (WOCBP) to arrive 10 minutes before their appointment for a pregnancy test to confirm pregnancy status. We refer to WOCBP as per Clinical Trial Facilitation Group (CTFG) guidance as "fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required."

If a woman is randomised to the BCG group and found to be pregnant after randomisation but before the administration of treatment, she will not receive the trial intervention. However, she will be followed up according to the protocol, and her data will be collected.

The administrative hub pharmacy will reconstitute the allocated IMP (section 7.2) and a delegated member of staff will administer the injection (section 7.3).

Data point to be collected:

- Pregnancy test results (where applicable)
- BCG vaccine accountability details

9.5 Follow up visits – One month and three months (mechanistic sub-group only)

If a participant has agreed to take part in the mechanistic sub-group, visits to their local research site will be arranged by the site at one and three months from the date the participant's BCG was administered for those in the intervention arm or from the date of randomisation for those in the control arm. Site staff will take additional blood samples from participants at these visits. During the three-month visit, questionnaires will be completed as for all other patients and DBS test performed. The DBS test will be sent to the main laboratory based at the QE hospital.

Data point to be collected:

- Venepuncture
- DBS
- Exacerbations since baseline
- Hospitalisations
- CAT test

9.6 Three month follow up visit (participants not taking part in the mechanistic sub-group)

Participants will be sent a link via email or SMS text message to access and complete their three month follow up questionnaire at home (paper copies can be posted if requested). This is sent to the participant automatically by the trial EDC system. Participants will also complete a DBS test at home and post the sample to the main laboratory based at the QE hospital. If a participant does not complete the questionnaire online after being sent the link three times on days 2, 3 and 5 from the missed due date, the trial team will send the questionnaire via post (paper) to the participant 7 days from the missed due date. The participant will be asked to complete and return the questionnaire to the trial team at BCTU, in the format it was received. If no response is received/completed after the attempts have been made, this data will be considered missing for this follow up time point.

Data point to be collected:

- DBS
- Exacerbations since baseline
- Hospitalisations
- CAT test

9.7 Twelve month follow up visit

Participants will be contacted by the research site to set up the twelve month follow up visit which will take place at the research site. Once the follow-up visit date/time is confirmed, the participant will be notified, i.e. verbally, appointment card, SMS text, email or letter. At the twelve month follow up visit, site staff will complete the twelve months follow up form with the participant and will perform a DBS test.

Data point to be collected:

- DBS
- Hospitalisations in the last 12 months
- CAT test
- Medical history over last 12 months
- Vaccination in the last 2 months
- COPD exacerbations over last 9 months
- Concomitant medications
- Prescriptions over the last 12 months
- Steroid use
- Smoking status

If a participant is unable to be contacted to arrange a twelve month follow up visit after three attempts, the site will send a letter or email to the participant. This letter/ email will remind the participant that their twelve month follow up is due and ask them to contact the research site to arrange their follow-up visit.

If the participant makes no contact, after approximately 14 days of last contact attempt, the trial team will send a twelve month follow up questionnaire out to the participant. This will be sent either by post (paper) or email (with online link to the questionnaire). The participant will be asked to complete and return the questionnaire to the trial team at BCTU, in the format it was received. If no response is received within 31 days of the twelve month follow up due date, this participant will be considered lost to follow-up and the data will be considered missing for this follow up time point.

9.8 Schedule of assessments

Table 2: Schedule of Assessments

Event	Baseline	IGRA test	Vaccine administered[1]	1 month +/-7 days[2]	3 months +/- 14 days[2]	12 months +/- 1 month[2]
Eligibility check	X					
Consent	X					
IGRA test	X	X[3]				
Demographics	X					
Medical history (including vaccine history)	X					X
Smoking status	X					X
Medications	X					X
Spirometry (FEV1/FVC)	X					
CAT score	X				X	X
Randomisation	X					
IGRA test results		X				
Pregnancy test (if applicable)			X			
BCG			X			
Exacerbation rate/symptoms/treatment	X			X		X
DBS (all participants)	X				X	X
Sputum sample	X			X		
Throat/nose swab	X			X		
DBS (exacerbation sampling)				X		

Venepuncture	X			X[4]	X[4]	X[4]
Follow up questionnaire					X	X
Adverse events					X	X

[1] *The vaccine, where allocated, should be administered to the participant within 6 weeks of randomisation.*

[2]*Follow up dates will be calculated using the date that the treatment was administered on for those allocated to the intervention arm and the date of randomisation for those allocated to the control arm.*

[3]*Further test required if result of first test is indeterminate*

[4]*Mechanistic subgroup only*

9.9 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process, and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post randomisation, for reasons other than to a positive or two indeterminate IGRA results, should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation. Participants found to be ineligible post randomisation due to a positive or two indeterminate IGRA results will not be followed up and we will not collect any further data.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits and/or undertake assessments in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

10. ADVERSE EVENT REPORTING

10.1 Definitions

Table 3: Adverse event reporting definitions

Severity Definitions	Mild Moderate Severe	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae. A sign or symptom, which interferes with the participant's usual activity. Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this intervention. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

		When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2 Adverse event recording – general

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the principles of GCP, and the Medicines for Human Use Clinical Trials Regulations 2004 (and its subsequent amendments). Definitions of different types of AEs are listed in Section 10.1 Definitions above. Patients will be questioned about Adverse Events at all follow up appointments. Exacerbations of COPD will not be reported as Adverse Events in this study as they are expected in this patient population and form the basis of the trial design.

The Investigator should document all AEs experienced by the trial participant in the participant's medical notes and assess the severity and causality (relatedness) with reference to Section 4.8 'Undesirable Effects' of the following Summary of Product Characteristics (SPC):

- BCG vaccine

Investigators will be provided with a copy of the most recent BCG SmPC at site setup and sites will be responsible for ensuring that this is filed in the Investigator Site File (ISF). Any subsequent updates to the SmPC will be provided by the STABILISE Trial Office and should be implemented immediately by the site and filed in the ISF; the previous versions should be marked as superseded.

All events will be documented in the medical notes from randomisation until the end of 12 month follow up period.

10.3 Adverse event reporting in STABILISE

The following non-serious AEs (and ARs) occurring from the time of trial treatment commencement until end of 12 month follow up should be reported in the relevant CRF but there is no requirement for specific reporting to the trial's unit beyond this routine data collection.

- Localised skin reaction to vaccine
- Fever
- Headache
- Injection-site abscesses
- Local reactions
- Lymphadenitis

The assessment of severity for AEs and ARs that do not meet the criteria for serious will not be collected due to the well understood safety profile of BCG. Assessment of severity of SAEs and SARs will be captured (see section 10.4 below).

10.4 Serious Adverse Advents (SAE) reporting in STABILISE

For all SAEs, the PI or delegate must do one of the following:

Record safety reporting-exempt SAEs in the medical notes but **not report** them to the trial's office on an SAE form 10.4.1Serious Adverse Events not requiring reporting to the Trial Office

Error! Reference source not found.Error! Reference source not found.

Report SAEs to the trial office in an expedited manner (within 24 hours of the site research team becoming aware of the event). 10.5SAE Reporting process

10.4.1 Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, from randomisation, to end of participant follow-up, the following are not considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.4.2 Admission for AECOPD

The population enrolling in STABILISE are expected to be admitted for COPD, and in this case admission for AECOPD is a study outcome. Duplication of data collection via SAE forms is therefore not planned. 10.5.2Assessment of expectedness of an SAE by the CI

Such events should still be recorded by the trial team in the participant's notes and as a trial outcome.

10.4.3 Serious Adverse Events requiring expedited reporting to the Trial Office

All SAEs not listed in Sections 10.4.1 and 10.4.2 10.4.1**Error! Reference source not found.**must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

10.5 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office as per the guidance in section 10.4.

To report an SAE to BCTU, the PI or delegate must complete, date and sign an SAE form via the STABILISE trial EDC system using the process described below in the timeline specified in sections 10.4.2 and any other relevant anonymised documents should be submitted to BCTU via the STABILISE trial mailbox (stabilise@trials.bham.ac.uk) to make BCTU aware that an SAE has been submitted, along with any other relevant anonymised documentation.

To report an SAE, submit the SAE Form to via the trial EDC system

Where an SAE form has been completed by someone other than the PI (or medically qualified delegate*)* initially, the PI must review and record confirmation of agreement with the causality and severity assessments on the SAE form.

SAEs will be recorded directly in the trial EDC system (on a single form per event) which can be edited to add additional information. On receipt of an SAE form, the trial Office at BCTU will allocate each SAE a unique reference number and notify the site via email as a proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

Site should also email the trial mailbox to inform BCTU that they have submitted an SAE. If the site has not received confirmation of receipt of the SAE within 1 working day of reporting, the site should contact the Trial Office.

Copies of the completed SAE form should be printed on resolution of the SAE and filed in the ISF.

10.5.1 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 4: Categories of causality) of the event. In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form.

As per Table 4: Categories of causality, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trial's office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 4: **Categories of causality**

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On completion of an SAE Form, the Trial Office will contact the Chief Investigator (CI) or delegate(s) and ask them to access the electronic SAE form and independently* review the causality of the SAE.

An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship ("Related" as per Table 4: Categories of causality) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

10.5.2 Assessment of expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in Table 5: Categories of expectedness.

Table 5: **Categories of expectedness**

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information (SmPC)
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the approved version of the reference safety information (RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR). The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.5.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information can be added to the same form the initial SAE was reported on.

10.5.4 Follow up of pregnancy outcomes for potential SAEs

Known pregnancy is an exclusion as there is a risk of congenital anomalies or birth defects in the offspring of patients as a result of their participant in the trial. Pregnancy in this patient population is possible and as such we will ask women at baseline if they are pregnant or planning to get pregnant in the next 6 weeks, which will mean they are ineligible. Woman of childbearing potential (WOCBP)will be asked to complete a pregnancy test to confirm they are not pregnant. If they are pregnant then they will be excluded from the trial.

In the unlikely event that a pregnant patient is randomised into the trial or becomes pregnant during the follow up period, this will need to be reported using the trial-specific Pregnancy Notification Form. This form will capture the pregnancy outcomes. Where the following outcomes are reported, they will also be defined as an SAE and should be reported to the STABILISE Trial Office according to the process described in Section 10.5:

- Induced abortion (medical reason)
- Miscarriage
- Stillbirth

- Birth defects
- Neonatal unit admission
- Neonatal death

10.6 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), and UoB Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). Additionally, the Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC, and RGT within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days of being notified.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7 Urgent Safety Measures

The Clinical Trials Regulations make provision for the Sponsor and PIs to take appropriate Urgent Safety Measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (MHRA in the UK) and ethics committees of all member states concerned.

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason they have been taken.

11. DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Table 6: **Source data in STABILISE**

Data	Source
Participant Reported Outcomes (Questionnaires) Baseline and 12 month follow up	Site staff will record the participants' responses directly into the trial database. The electronic record is the source

Participant Reported Outcomes (Questionnaires) 3 month follow up	Participants will be asked to answer the questionnaires directly into the trial database. The electronic record will be the source. If the participant requests to complete the questionnaire on paper, the paper questionnaires will be the source. The paper form will be transcribed into the database by Trial Office staff.
Lab results	The original lab report (which may be electronic) is the source data and will be kept and maintained, in line with normal local practice. Information will be transcribed onto the CRF.
Bronchodilator spirometry tests (if required at baseline)	The original records (which may be electronic) are the source data. They will be kept and maintained in line with normal local practice. Information will be transcribed onto CRFs.
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation detail will be recorded on the electronic form which is the source.

11.2 Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the following Forms (see Table 7: Case report forms in STABILISE7).

Table 7: Case report forms in STABILISE

Form Name	**Schedule for submission**
Screening CRF	At the point of screening
Decliner's form	At the point of screening and only for those who don't want to take part in the trial but happy to complete the decliner's form
Informed Consent Form	At the point of consent
Initial Visit Baseline CRF	As soon as possible after consent

Baseline blood sample details and results CRF	As soon as possible when the blood results are available
Participant contact details CRF	As soon as possible after consent
GP surgery details CRF	As soon as possible after consent
Randomisation CRF	At the point of randomisation
IGRA Test Results	As soon possible after first IGRA result available
IGRA repeat blood sample details and results Form	As soon as possible after receipt of indeterminate blood result
Vaccine Administration CRF	At the point of treatment administration
Sub-study blood sample CRF	As close to one, three and twelve months following the treatment administration date for the intervention arm and randomisation for the control arm.
Sub-study blood sample Lab CRF	As soon as blood results are available
Three month follow up questionnaire	As close to the three month follow up time point as possible
Twelve month follow up CRF	As close to the twelve month follow up time point as possible
Withdrawal and change of status CRF	At the point of change of status, withdrawal or death
Serious adverse event reporting form	At the point of being aware of an SAE
Pregnancy Notification Form	At the point of being aware of a pregnancy
Pregnancy Outcome Form	As soon as the pregnancy ends
Sputum sample, Nasopharyngeal (nose and throat) swab and finger-prick receipt patient completion form	To be provided as soon as an exacerbation occurs at home
Exacerbation symptoms and treatment - Participant completion	At the point of exacerbation
Sputum sample receipt, Nose/throat swab, DBS test Lab CRF (lab forms completed by lab staff)	All AECOPD episodes
Adjudication panel diagnosis confirmation	To be completed as soon as the adjudication committee meet every 3 months.
Qualitative sub-study participant consent form	At the point of enrolment into the qualitative sub-study
Qualitative Demographic Form (HCPs)	At the point of enrolment into the qualitative sub-study
Qualitative Demographic Form (patients)	At the point of enrolment into the qualitative sub-study

A CRF should be completed for each individual participant.

Data should be submitted according to section 11.4 in a timely manner i.e. within four weeks of submission schedule. If data has not been provided within four weeks of the submission schedule detailed in the above table, then a reminder email from the trial's team will be sent to sites. If data is consistently not provided in this timeframe, BCTU will directly contact the site to ascertain the reason for the delay. This may also be escalated to the site's senior management and can trigger a monitoring visit.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection. The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained initially via a site initiation meeting or by other trained members at each site to adhere to procedures.

All data (where possible) should be entered directly into the trial database.

The following guidance applies to data:

● Rounding conventions - rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. (e.g. 3.8 rounded to the nearest whole number is 4). If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. (e.g. 3.4 rounded to the nearest whole number is 3).

● Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied.

● Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible.

● Protocol and GCP non-compliances should be reported to BCTU on becoming aware.

11.3 Participant completed questionnaires

Participant completed questionnaires will be completed in clinic at baseline and twelve months by all participants, overseen by site staff. Questionnaires should generally be completed by the participant alone, however physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where any questions are unanswered, research site staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

At three months, either postal paper or electronic questionnaires can be completed at home by participants in all groups. If a participant is taking part in the sub-study, they can complete the questionnaires in clinic. If there is missing data on the participant completed AECOPD form (when reporting an exacerbation at home) regarding treatment taken, this will be followed up by a telephone call from site to the participant (or by the BCTU trial team), since this is required to allocate severity of AECOPD event. The telephone call may be omitted if remote access to the patient record is able to confirm this specific item, which is pertinent to the primary outcome. Where missing data pertains to a secondary outcome measure, sites should do their best to obtain it, but it is less critical to trial outcomes to obtain it.

11.4 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the site staff via a bespoke BCTU trial EDC system except for paper questionnaires completed by participants outside of clinic and sent to BCTU, which will be entered by BCTU staff. If online data collection is not possible for any reason, a paper version of the document will be completed and transcribed into the bespoke BCTU trial EDC system by the site.

The trial EDC system will conduct automatic range checks for specific data values to ensure high levels of data quality. Data queries will be raised via the trial EDC system, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested by the trial's team at BCTU.

11.5 Self-evident corrections

The below self-evident corrections will be permitted by the Trial Office:

- Contingent fields: When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk. E.g., Has the person had procedure "x"? If yes, state type. If the response to the first question is "no," yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.
- Changes to administrative notes and reference numbers: when new information becomes available such that a reference number does not accurately reflect the sequence of CRFs received e.g., an SAE form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no data queries have been raised using the original number. Similarly, any notes relating to the participant care which have an impact on the administration process, but not the data fields themselves, can be changed as appropriate.

11.6 Data security

The security of the EDC System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data (including the qualitative data) should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic information technology (IT) risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.7 Archiving

Archiving will be authorised by the STABILISE trial office at BCTU on behalf of the Sponsor following submission of the end of trial report.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

No documents should be destroyed without prior approval from the Trials Office.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and initiation

All local PIs will be asked to sign the necessary agreements including a STABILISE Site Signature and Delegation log between the PI and the Trial Office and supply a current CV and a valid GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a tele/video conference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan

12.2.1 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the STABILISE trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2 Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent data queries requesting missing data or clarification of inconsistencies or discrepancies.

12.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4 Notification of Serious Breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a "serious breach" is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial.
- the scientific value of the trial.

Sites are, therefore, requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of data queries. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC, MHRA and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample size

The sample size calculation is based on the primary outcome of moderate-severe exacerbation rate over a 12-month period. Poisson regression is often used to model count data. However, after reviewing trial and cohort studies in COPD (16, 50, 51, 52), we found that the variance of the counts of exacerbations is often greater than the mean, leading to over dispersion and hence a misspecification of the standard error under a Poisson model. A more appropriate approach, which allows for a more flexible mean-variance relationship, and which has been used to analyse COPD trials (53, 54), is to utilise a negative binomial model. We have outlined below how we have made our calculation with the expectation of using this approach.

Using the methods in Zhu and Lakkis (55), sample size calculations comparing two negative binomial rates require an estimate of the negative binomial dispersion factor. This in turn requires estimates of the following:

1) the standard error of the log exacerbation rate per patient per year (pp/year),
2) the total exposure time of study participants in the control group in person years, and
3) the mean rate of exacerbations pp/year.

We have estimated these parameters using data from the (theophylline with inhaled corticosteroids) TWICS trial (50) which has a similar population to our proposed study being limited to COPD patients with ≥2 exacerbations in the last 12 months. The estimates (rationale) are as follows:

1) 0.0331 (Mean number of acute exacerbations pp/year was reported as 2.23, with an associated 95% CI of (2.09 to 2.37). Then, SE(log(r)) = (log(2.23)-log(2.09))/1.96 = 0.0331),
2) 741 (Total exposure time of n=1536 patients is 1489 person years. Scaling by 772:764 ratio intervention: control gives an estimated duration, T, of 741 person years for control patients), and
3) 2.23 pp/year

Using equation 17 in (55), the over dispersion factor, ϕ, is estimated by ϕ=T×r×[SE(log(r))]2 = 741×2.23×[0.0331]2 = 1.81. Then, using equation 15 in (55), the negative binomial dispersion parameter, k, is estimated as k = (ϕ-1)/r = (1.81-1)/2.23 = 0.36. Thus, the estimate of the negative binomial dispersion parameter we have used is 0.36.

Our calculation has also required us to estimate the mean number of exacerbations pp/year in the control group. Again, based on a similar population studied in the TWICS trial (50), we will assume an overall mean exacerbation rate of 2.25 pp/year in the control arm (no vaccine). As noted in the 'Justification for design' section, a 20% relative reduction in the mean exacerbation rate pp/year equates to the likely MCID, is similar to other widely used therapies considered clinically meaningful to use in frequent exacerbators, and thus is an appropriate effect size upon which to base the power calculation. This reduction corresponds to an absolute decrease of 0.45 in the mean exacerbation rate pp/year from 2.25 in the control arm to 1.8 in the BCG arm. To detect this difference, comparing two negative binomial rates using the sample size formulae in (55), with 90% power, and a type 1 error rate of 5% (i.e. α=0.05), requires 361 participants per group to be randomised, or 722 participants in total. Assuming a loss to follow-up rate of 10% over a twelve-month follow-up period (see retention rate section), the study requires 402 per group to be randomised or 804 participants in total.

To allow for some uncertainty around our estimates, we have explored through sensitivity sample size calculations the impact of changing the parameters. Our proposed sample size is still likely to provide adequate power even if our estimates are not quite as expected. For example, for negative binomial dispersion parameters ranging from 0.65 to 0.3, and for mean exacerbation rates in the control arm ranging from 1.42 to 2.5, a sample size of 804 participants provides between 80% and 92% power to detect relative reductions of 20% in the mean exacerbation rate pp/year.

14.2 Analysis outcome

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to BCG vaccine versus those randomised to the control arm. In the first instance, all analyses will be based on the intention to treat principle, i.e., all participants will be analysed in the intervention group to which they were

randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups, e.g., incidence rate ratios, mean differences, relative risks, absolute differences will be presented, with 95% confidence intervals and p-values from two-sided tests also provided. Where possible intervention effects will be adjusted for the minimisation variables listed in Section ENROLMENT and RANDOMISATION , and baseline values (where appropriate and available). No adjustment for multiple comparisons will be made.

14.2.1 Primary estimand

The primary estimand is the rate of moderate to severe acute exacerbations of AECOPD in adults with a primary clinical diagnosis of COPD and will be measured as the rate per person per year. The estimand will follow the principal stratum strategy and those who will be randomised and then receive a positive or indeterminate result in their IGRA test will be excluded from all analyses.

The primary estimand can be summarised as follows:

Population: Adults with a primary clinical diagnosis of COPD and a negative IGRA test, ≥2 AECOPD in the last 12 months, who have not been Immunosuppressed and have not received >20mg prednisolone per day for >14 days in the last 3 months, have not previously experienced of allergic reaction to vaccine and are not pregnant, if they are female.

Treatment Conditions: BCG vaccine compared to no vaccine (see Section 7.1 for details on the intervention)

Outcome: Rate per person per year of moderate to severe acute exacerbations of AECOPD

Time: 12 months after randomisation in the no vaccine group and 12 months after receiving the BCG vaccine in the BCG group

Summary Measure: Adjusted incidence rate ratio and 95% confidence interval

Intercurrent Events and Strategies: The intercurrent events are: positive or indeterminate IGRA test; treatment non-receivers (those who randomised to receive but did not receive the BCG vaccine for any reason); withdraw consent for providing follow up data or lost to follow up; and death. All intercurrent events apart the first one (i.e. tested positive in their IGRA test) will be dealt with using the treatment policy strategy for the primary estimand as we want to evaluate the treatment effect as it would occur in normal practice. The intercurrent event, positive or indeterminate IGRA test will be dealt with using the principal stratum strategy because we are interested in the treatment effect in the principal stratum in which the intercurrent event would not occur.

Other strategies evaluating different estimands will be discussed in further detail in the SAP.

Rate of moderate to severe acute exacerbations of AECOPD will be analysed using a negative-binomial regression model, incorporating exposure time (person-years) and adjusting for the minimisation variables listed in Section 6.6 to estimate the adjusted incidence rate ratio and 95% confidence interval. The two-sided p-value relating to the intervention group parameter as generated by the model will be presented.

14.2.2 Secondary estimands

As per the primary estimand.

14.2.3 Secondary outcome estimands

Estimands for the secondary outcomes will deal with intercurrent events as per the primary estimand. All analysis models will adjust for the minimisation variables listed in Section 6.6. The differences between groups for the secondary outcomes will be presented along with 95% confidence intervals. Incidence rate outcomes (e.g. the hospitalisation rate for infective exacerbation

of airways disease at 12 months) will be analysed as per the primary outcome using negative-binomial regression models incorporating exposure time (person-years). Count outcomes (e.g. total number of days of antibiotics for AECOPD, total number of days of oral steroid therapy for AECPOD) will be analysed using Poisson regression models to calculate adjusted incidence rate ratios, unless there is compelling evidence of overdispersion, in which case negative-binomial regression models will be used. The chosen model will incorporate exposure time (person-years). The continuous secondary QOL outcome (using the CAT score) will be analysed using mixed effects linear regression models to calculate an adjusted mean difference accounting for the collection of QOL at multiple time points. Ordinal outcomes (e.g. type of exacerbation classified using two different approaches: i) a three-level classification based on Anthonisen criteria, and ii) a four-level classification based on clinical adjudication) will be analysed using mixed effect ordinal regression models to estimate the adjusted odds ratios.

14.2.4 Planned subgroup analyses

Subgroup analyses will be performed on the primary estimand only and limited to age (<65 or ≥65 years) and prior BCG vaccination or TB infection and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of these pre-specified subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.5 Missing data and sensitivity analyses

Every attempt will be made to collect full data to the end of the study on all study participants; it is thus anticipated that missing data will be minimal. Participants will be included in the primary analysis up to the time point they were last followed up. If no primary outcome data will be collected for a participant, they will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will consist of simulating the missing responses using a multiple imputation approach. Parameters used to simulate the missing responses will include the minimisation variables, intervention group, exposure time (person-years), and, if applicable, previous response at each time point. Full details will be included in the Statistical Analysis Plan.

14.3 Planned final analysis

The primary analysis for the trial will occur once all participants have completed the planned 12-month follow-up assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

15. HEALTH ECONOMICS

No Health Economic evaluation is planned for this trial.

16. QUALITATIVE ACCEPTABILITY STUDY

This is a trial of the world's most used vaccine, but it is not being given for traditional vaccine reasons, in that it is not being used to prevent TB, but to prevent more general infections (exacerbations) in COPD. The putative mechanism also differs from normal vaccines, so patients' understanding of this may be lower and thus take up of the vaccine in real-life might be poor. The aims of the acceptability work are to explore the understanding and acceptance of vaccines in

general, and of this specific vaccine, exploring and comparing uptake/acceptability to other exacerbation prevention strategies, for both patients and healthcare professionals. For example, patients may accept SARS-CoV2 vaccine to prevent coronavirus disease (COVID-19), or flu vaccine to prevent flu, but may have difficulty understanding BCG is being given for reasons other than TB. However, they take other medicines that are for generic infection/exacerbation prevention (e.g. macrolides (30), inhalers (22), so exploring their understanding of this concept, in the context of acceptability of the intervention would be relevant. Methods to enhance uptake will also be pertinent to elicit, and findings may be generalisable to other respiratory vaccines. We have systematically reviewed factors aimed at increasing vaccine uptake in COPD (37), and found that multimodal interventions, which target multiple aspects of evidence-based care and use both patient-focussed and clinician-focussed techniques, may have the greatest impact on vaccination rates. This will inform our topic guide, alongside the general literature (38) and patient and public involvement (PPI) input.

Data will be collected using individual interviews with up to 25 patients (including those who decline participation in the trial) and 15 healthcare professionals (HCPs). Interviews will be conducted virtually using an UoB approved platform account, on the telephone or by Voice Over Internet Protocol (VOIP) (e.g. Teams) and audio recorded using an encrypted voice recorder or the recording facility of the participants' chosen VOIP platform. All recordings will be transferred to one of the University of Birmingham's approved digital storage systems e.g. One drive.

Recordings will be transcribed clean verbatim by an external transcription service. Participant data files will be encrypted and transferred to the external transcription company via a University of Birmingham approved secure data transfer link e.g. Sharepoint. The transcription company will sign a full and comprehensive confidentiality agreement. Transcripts will be given an ID number by the qualitative team prior to transfer; transcribers will have not have access to any personal data regarding interviewees. No transcripts or recordings will be stored locally by the external transcription service. Transcripts will be stored on the University's secure cloud-based server.

Data will be managed and analysed using the Framework method. Interpretation of the data will draw on relevant theoretical concepts of risk work in the public encounter (to understand HCPs experiences of managing conversations about vaccines, vaccine hesitancy and preventative interventions generally) and organisational and interpersonal trust in relation to prevention and preventative interventions (to understand patient's responses) (39-42).

Those declining to participate in the main trial will have the option to express their views in an interview as described above. Alternatively, they can complete a brief survey either included in their invitation to participate in the main trial or provided directly by the research team e.g. in response to published adverts. Responses will be recorded on paper, online or over the phone. Before the survey is completed, patients will be informed that it is a one-off survey and that they are free to discontinue the survey at any point without their care being affected. Consent will be implicit by virtue of the fact that: a) they have chosen to contact us and b) that they choose to answer the questions. The researcher will not have access to any identifiable data from those completing the survey.

17. MECHANISTIC STUDY

17.1 Background

Briefly, the main study provides an oversight of the effects of BCG vaccination on a large population over time through a minimally invasive approach and correlation with clinical outcomes. Advantages include ease of unbiased sampling in the whole study population, simple processing, ability to detect specific anti-BCG responses, as well as general effects of vaccination on the host and the ability to revisit archived samples when other effects are identified. Collectively, the detailed mechanistic sub-study gives comprehensive assessment of BCG vaccine-specific responses, trained immunity, gene expression analyses, cell phenotyping and functional screening, thus enabling us to provide mechanistic insights into how BCG may modulate the host over the course of this study. Our experimental approach in the sub-study is focused to capture multiple aspects of immune responses in terms of relative "complexity". Thus, within our approach we can identify differences in soluble factors (e.g. antibodies, cytokines), epigenetic changes, gene expression and cellular phenotypes. This will allow integration across readouts captured from various platforms.

The mechanistic analysis will provide a comprehensive assessment of BCG vaccine-specific responses through differences in soluble factors (e.g. antibodies, cytokines), trained immunity, gene expression analyses, cell phenotyping and functional screening. Collectively, this will enable us to provide mechanistic insights into how BCG may modulate the host over the course of this study.

17.2 Objectives

To develop mechanistic insights into how BCG can modulate the risk of airway disease exacerbation.

17.3 Methods

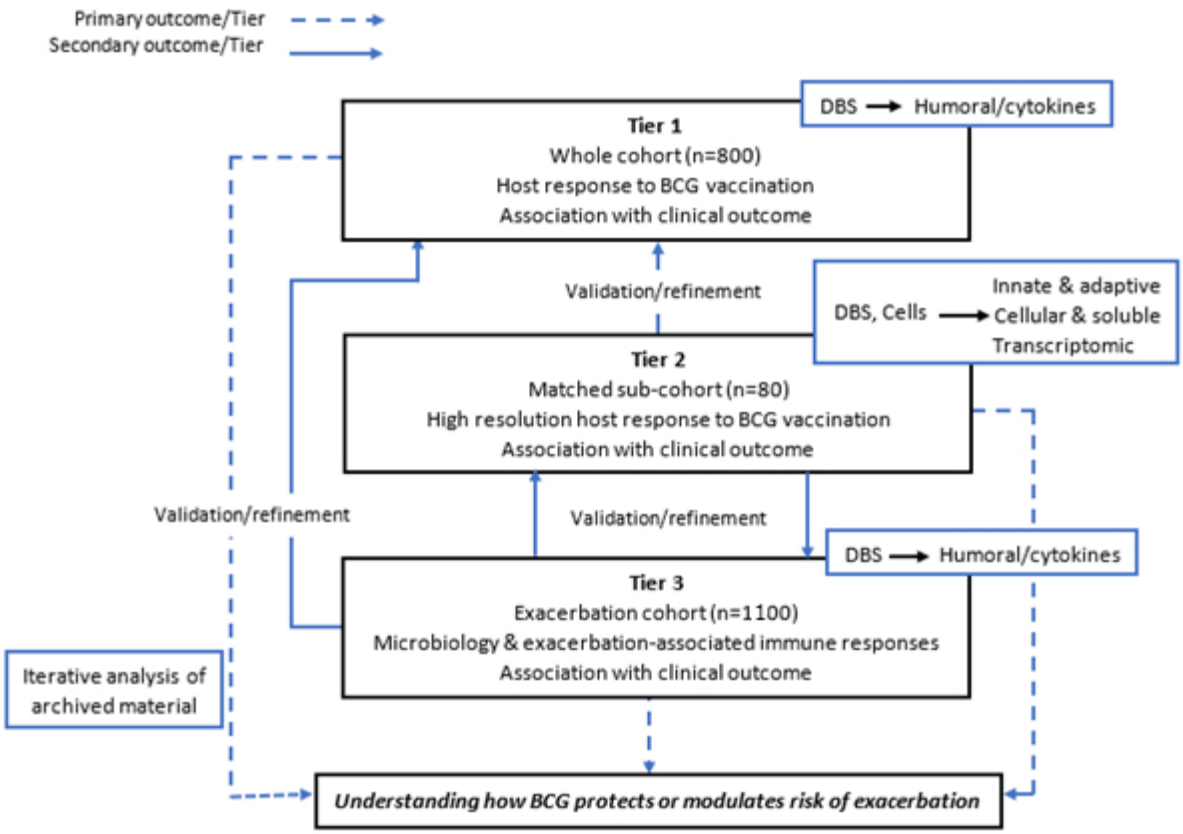
The mechanistic study consists of 3 tiers of testing:

1. Dried blood spot (DBS) sampling of all patients to assess humoral immunity.
2. Detailed mechanistic sub-study on 80 participants that involves more thorough assessment of humoral immunity by means of venepuncture.
3. Exacerbation sampling captures microbiological and immunological information at the start of exacerbations via patient submitted samples sent by post to the Clinical Immunology Service at the University of Birmingham.

All patients enrolled in the main study will have consented to provide DBS and exacerbation samples, and the 80 participants in the detailed mechanistic sub-study will be drawn from those who opt in at consent. Participants who gave consent to join the Mechanistic sub-study and were selected to take part will be notified by a letter. Local site team will contact those participants to arrange for one, three- and twelve-months visits.

The tiers are summarised in Figure 1 through a flow diagram that indicates the anticipated number of subjects sampled, the nature of the samples obtained and the assessments that will be made for each sample. More details on the tiers methods are included in Appendix A.

Figure 1. Laboratory plan for Tier 1-3 samples



Flow diagram of the laboratory plan for Tier 1-3 samples collected during STABILISE. n=800 has been shown for tier 1, though n=804 altogether, assuming a small rate of sample failure.

17.4 Outcomes

Mechanistic outcomes will be explored between individuals according to demographic and relevant minimisation data (e.g. prior TB vaccination), and as change from baseline in an individual.

17.4.1 Tier 1 outcomes (all cohort □ 800 participants)

All outcomes will be recorded at the pre-randomisation baseline visit and then at 1, 3 and 12 months post randomisation/vaccination (for the control/BCG vaccine groups respectively)

- Anti-BCG antibody responses, as obtained from ELISAs to detect IgG, IgA and IgM responses to whole BCG organism, proteinaceous (Ag85) and a non-proteinaceous (Lipoarabinomannan) antigen
- Cytokines: IL-1B, IL-6, TNFα and IL-10

17.4.2 Tier 2 outcomes (80 participants)

All outcomes will be recorded at the pre-randomisation baseline visit and then at 1, 3 and 12 months post randomisation/vaccination (for the control/BCG vaccine groups respectively)

- Antigen-specific B cell responses to BCG
- BCG antigens and relevant pathogens

- measures of trained immunity as determined by histone markers and heterologous cellular responses
- transcriptomics
- leukocyte, T and B cell phenotypes

17.4.3 Tier 3 outcomes (all exacerbations)

All outcomes will be recorded whenever a participant experiences an exacerbation and provides sputum, saliva, nose/throat swabs, and DBS samples.

Anti-BCG antibody responses, as obtained from ELISAs to detect IgG, IgA and IgM responses to whole BCG organism, proteinaceous (Ag85) and a non-proteinaceous (Lipoarabinomannan) antigen

- Cytokines: IL-1B, IL-6, TNFα and IL-10
- Type of pathogen present (bacteria, virus) and specific species
- IgG and IgA response to any identified pathogen

17.5 Sample Size

Tier 1 will consist of the whole cohort of 804 participants as for the main RCT.

Tier 2 will consist of the first 80 participants who have consented to provide samples for the detailed sub-study. Since consent to participate in the detailed mechanistic sub-study is a minimisation criterion, these 80 participants will be well balanced in terms of allocated treatment arm and the other minimisation criteria (see Section 6 – enrolment, randomisation and blinding).

Tier 3 will consist of all participants who experience an exacerbation and provide sputum, saliva, nose/throat swabs and DBS samples. We anticipate we will collect data on around 1300 exacerbations from the 804 participants.

17.6 Analysis of Outcomes

Analyses of mechanistic outcomes will be largely exploratory and completed by the laboratory team. In each Tier, summary measures of readouts from samples will be provided: means and SDs, or medians and IQRs as appropriate. Summaries will be reported separately for each time point and each treatment group, as well as pooled across treatment groups.

Subsets of sample readouts to include in the statistical models will be determined through clinical opinion and principal component analysis (PCA). Across the tiers, the longitudinal trajectories of the sample readouts will be analysed through linear mixed effects models. Associations between longitudinal samples and exacerbation rates will be explored through negative binomial mixed effects models. Model based estimates of time and treatment effects will be reported along with 95% confidence intervals and p-values from two-sided tests. Visual plots of fitted values will be provided to aid interpretation.

In Tier 2, additional analysis, through linear mixed effects models, will explore the associations between the DBS elute antibodies collected in Tier 2 and those in Tier 1. These analyses will include any new metabolites identified in Tier 2.

Associations between immune responses to BCG vaccination and exacerbations will be explored through negative binomial mixed effects models. Model based estimates of time and treatment

effects will be reported along with 95% confidence intervals and visual plots of fitted values to aid interpretation.

Exploratory identification of risk factors for exacerbation (classed as a binary yes/no outcome) will be performed using logistic regression modelling. Candidate predictors identified from clinical expertise and through analysis of samples in Tier 3 (and potentially Tiers 1 and 2) will be included in the model. Model performance will be reported through the C-index and Brier score. Calibration slopes will be plotted. Model overfitting will also be estimated, and optimism-adjusted estimates will be produced.

18. TRIAL ORGANISATIONAL STRUCTURE

18.1 Sponsor

The University of Birmingham will be acting as the sponsor for this study.

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

18.3 Trial Management Group

The Trial Management Group includes those individuals responsible for the day-to-day management of the trial, namely the CI, statistician, team leader, trial manager, data manager, qualitative researchers, other required clinical experts and patient representatives. Some co-applicants have roles specific to particular parts of the study, such as the qualitative acceptability analyses; these individuals will attend TMG meetings only when required based on the agenda. The role of the group is to 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. Meetings are planned to occur monthly but will vary according to the needs of the study.

18.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

18.5 Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the STABILISE trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

18.6 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a

minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

18.7 Clinical Adjudication Committee (CAC)

The Clinical Adjudication Committee will review the relevant medical history and trial data for each of the participants recruited into the trial to determine the incidence of COPD exacerbation within the patient cohort. The CAC will not be aware of the treatment allocation of the trial participants and trial data will be supplied in confidence by the trial office. The CAC's determination of the incidence of COPD exacerbation will serve as the primary outcome data for the trial.

The CAC will operate in accordance with the trial CAC Charter which will define the membership, roles, and responsibilities. The CAC will meet every three months with additional meetings arranged during periods when the volume of recruitment is higher than expected.

18.8 Finance

The research costs of the trial are funded by the National Institute for Health Research (NIHR), reference EME Project: NIHR150098 awarded to Professor Alice Turner at the University of Birmingham. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Statement of Activities. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004 and the Data Protection Act 2018.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments).

Participants will always be identified using their unique trial identification number on the Case Report Form in correspondence with the BCTU. Participants will give their explicit consent for the movement of their consent form if they use the paper form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party. Representatives of the STABILISE trial team and sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

21. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants. With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

23. POST-TRIAL CARE

All patients will continue to receive standard medical care following participation in the clinical trial. There are no interventions that participant's will be prevented from accessing after their participation in the trial has been completed.

24. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is

subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION PLAN

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

In all publications, authors should acknowledge that the trial was performed with the support of National Institute for Health and Care Research, University of Birmingham and BCTU. Intellectual property rights will be addressed in the external CI agreement and Clinical Study Site Agreement between Sponsor and site.

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27. Appendix A: Trial's tiers Methods

A1.1 Tier 1 Methods

DBS will be obtained from subjects at the pre-randomisation baseline visit and then at 1, 3 and 12 months post randomisation/vaccination (for the control/BCG vaccine groups respectively). DBS will be collected by capillary sampling onto forensic-grade 226 DBS cards (Ahlstrom Munksjo) with 8 spots collected at each time-point. The eluates from the main study will be obtained from the DBS using our established and standardised methods and soluble factors assessed (44). The eluates will be used to detect changes in anti-BCG antibody responses within individuals, over time by use of our established in-house ELISAs to detect IgG, IgA and IgM responses to whole BCG organism, proteinaceous (Ag85) and a non-proteinaceous (Lipoarabinomannan) antigen. Using this approach, we have shown that anti-BCG responses increase after vaccination (45). From this, we will be able to determine how well subjects respond to the vaccine and correlate these anti-BCG responses to other markers (risk of exacerbation, changes determined in the detailed mechanistic subgroup, exacerbation samples and markers determined from the main study). Eluates will also be used in ELISAs to determine whether baseline levels of cytokines most associated with pro-inflammatory effects (IL-1B, IL-6, TNF) and anti-inflammatory effects (IL-10) are modulated by BCG vaccination. Finally, depending upon what effects are found in studies performed in the mechanistic subgroup and from the exacerbation samples, DBS cards can be revisited, either during the course of this study or subsequently, to examine other effects of BCG vaccination (e.g. additional cytokines, epigenetics and clinical metabolomics).

A1.2 Tier 2 Methods

In this detailed mechanistic subgroup, we propose to undertake an in-depth study in the first 80 participants (50:50 vaccine: no vaccine) who have consented to provide samples for the detailed mechanistic study. Since consent to participate in the detailed mechanistic sub-study is a minimisation criterion, these 80 participants will be well balanced in terms of allocated treatment arm and the other minimisation criteria (see Section 6 – enrolment, randomisation and blinding). We will collect the following blood samples: whole blood, peripheral blood mononuclear cells (PBMC), neutrophils, serum and PAXgene tubes. Participants will have approximately 75ml of blood taken at each visit. This cohort will also provide samples at the pre-randomisation baseline visit and then at months 1, 3 and 12 months post randomisation/vaccination (for the control/BCG vaccine groups respectively). These blood samples will be compared to the DBS samples from the Tier 1 cohort and the exacerbation samples from the Tier 3 cohort. The following analyses will be conducted:

1. Antigen-specific B cell responses to BCG, BCG antigens and relevant pathogens. ELISAs to detect BCG-specific responses will be performed as for the main study alongside IgG isotype analysis, since in previous studies we identified an inverse correlation between IgG2 responses to BCG in infants and risk of a positive test for latent TB infection (46). Coupled to this we will perform ELISPOTs to determine Bmem responses by our standard approaches. Where relevant, if pathogens are identified in the exacerbation samples, this analysis will be expanded to assess antibody responses to these organisms +/- other pathogens. Such tests will be guided by whether any pathogens are identified in the exacerbation samples.
2. Assessment of trained immunity via histone markers and heterologous cellular responses. In addition to cytokine measurements, innate immunity will be assessed in vitro via methylation and acetylation modifications of specific histone markers at loci of pro-inflammatory genes. This will be performed using standard approaches at the Birmingham Centre for Genome Biology (47). Briefly, key cells (e.g. monocytes) will be isolated then fixed, sonicated and immunoprecipitated using antibodies against key histone targets (e.g.

H3K4me3, H3K9me3). Co-immunoprecipitated material will then be subjected to qPCR analysis using specific primers spanning the promoter regions of tumour necrosis factor α (TNFα), Interleukin 6 (IL6) and Interleukin-1 beta (IL1β). In addition, PBMCs isolated from participants' whole blood will be stimulated with mycobacterial (e.g. BCG, M. tuberculosis H37Rv) and non-mycobacterial heterologous antigens (e.g. heat-killed S. aureus antigen) and concentrations of IL-1β, IL-6, TNF-α and interferon gamma (IFN-γ) measured in supernatants.

3. Determining serum cytokine levels using multiplex cytokine cytometric bead array. To provide a broad screen of effects of BCG on subjects, we will use the Cytokine & Chemokine 34-Plex Human ProcartaPlex™ Panel 1A (Thermo Fisher) to detect cytokines and chemokines associated with different myeloid, T helper, inflammation and regulatory responses to give a comprehensive assessment of longitudinal alterations in subjects receiving BCG. IL-1β, IL-6, TNF and IL-10 are in this panel and enable cross-validation with DBS derived results and the validated bead array.
4. Transcriptomic analysis using standardised nanoString panels. In this element, we will use well-defined and established nanoString panels to identify transcriptional changes associated with BCG vaccination. These have the advantage of allowing comprehensive analysis of gene expression alongside an established analytical pipeline and can be undertaken locally in the University of Birmingham Tech Hub. We will employ three panels that provide a comprehensive analysis of genes expressed by myeloid cells (Myeloid Innate Immunity V2, 770 genes), immune responses to the vaccination (Host Response Panel, 785 genes) and core metabolic processes and immunometabolism (Metabolic Pathways Panel, 768 genes). Although there is some overlap on these panels, the strong focus on host susceptibility, homeostasis and adaptive immunity in the second panel complements the myeloid focus of the first panel. In addition, the third panel will provide a further complementary metabolic focus. From these three panels, we will derive a comprehensive overview of the effects of BCG vaccination on these subjects.
5. Flow cytometry immunophenotyping of leukocyte populations. We have developed a range of (up to 17 colour) standardised flow cytometry panels to enable a comprehensive assessment of the phenotype of different leukocyte populations longitudinally. We have used such panels in a broad range of patients including those with active and latent M. tuberculosis infection and secondary immunodeficiencies (e.g. chronic kidney disease) (48,49). We will include chemokine/homing markers (e.g. CD49a, CCR9, CD103) and CXCR3 associated with homing to the lung to enable the identification of standard CD4/CD8 T cell (including NKT cells and CD28null cells), B cell/plasmablast/cell and NK cells. A particular focus of this element will be myeloid populations and the changes within these that are associated with BCG. Dendritic cell, monocytic-lineage cells and neutrophils (including CD11b, CD14, CD15, CD66b, HLA-DR, CD84 to help identify cells with a suppressor-like phenotype) and eosinophils from whole blood and PBMC will be assessed. Depending upon our findings, we can use myeloid cells obtained from later time-points in standard assays to determine changes in phagocytic uptake, activity, NET formation and suppressor activity. These will be performed using established protocols within the group or standardised kits available commercially (e.g. PhagoTestTM and PhagoBurstTM assays). As necessary, differentially expression of cytokines and genes identified in 2 and 3 above will be confirmed.
6. Deeper surface and intracellular phenotyping of T and B cells. In addition to the above cytokine, gene and phenotypic analyses, we will perform intracellular cytokine (+/- CD3/CD28 or purified tuberculin/CD28) and transcription factor analyses, paired with surface phenotype marker analysis to identify T and B cell subsets (e.g. Th1, Th2, Th17, Treg, IL-4, IFN-γ, TNF, IL-17, FoxP3, CD25, CCR4, CXCR3 and CD28, KLRG1 for senescence, Beff/reg cells classic markers and CD24, CD80/86) coupled with markers associated with mucosal homing and tissue residency (e.g. CD103, CD69).

A1.3 Tier 3 Methods

This tier is focused on participants who experience an exacerbation and have provided sputum, saliva, nose/throat swabs and DBS samples, and is designed to capture microbiological and immunological information from these participants. PCR for respiratory viruses and standard culture for bacterial pathogens will be performed in United Kingdom Accreditation Service (UKAS)-accredited NHS clinical microbiology laboratories. IgG and IgA responses to any pathogen identified will be assessed in saliva and sputum, in parallel with antibody testing in matched DBS eluates. DBS eluates will be used in assays to determine anti-BCG and cytokines as described in Tier 1. If necessary, eluates will be tested further, based on signatures identified in the detailed mechanistic sub-study.