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PARTICIPANT INFORMATION SHEET

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)

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This information sheet is provided in English. Birmingham Clinical Trials Unit (BCTU) can help with language translation if needed. If you would like access to a translation service, please contact STABILISE@trials.bham.ac.uk

Thank you for taking the time to read this information leaflet about a research trial (also known as a clinical trial) for patients with COPD. Joining the trial is entirely up to you. If you choose not to take part, you will continue to receive the normal standard of care at your GP practice and/or local hospital.

To help you decide, this information leaflet explains why the research is being done and what will be involved. A member of the research team from your local hospital or GP practice will go through this Information leaflet with you to help you decide whether or not you would like to take part, and to answer any questions you may have.

Part One *of this Information leaflet tells you the reasons for doing this trial, what will happen to you if you take part, and any potential risks or benefits that you should be aware of.* ***Part Two*** *gives you more detailed information about how the trial is being run and how your data will be used.*

Trial Summary

- Chronic obstructive pulmonary disease (COPD) is the name for a group of lung conditions where it's difficult to breathe air out of the lungs. Flare ups of lung disease are usually called exacerbations, and are mainly (but not always) due to infection.
- Preventing exacerbations in people with lung disease is particularly important because frequent infections can cause lung disease to progress, and every time an infection happens quality of life may get worse.
- The vaccine for tuberculosis (TB) (Bacillus Calmette–Guérin, BCG) has been in use to prevent TB for over 70 years. More recently, it has been shown that the vaccine may result in other health benefits, including helpful changes within the immune system that can protect against many other infections.
- STABILISE aims to investigate whether the BCG vaccine can help reduce the rate of exacerbations in people with COPD.
- Participants will be randomly allocated to either receive the BCG vaccine or no vaccine.
- Participants will be followed up at 1, 3 and 12 months.

PART ONE

1. Background to the research

Chronic obstructive pulmonary disease (COPD)

COPD is a common lung condition which leads to a decline in lung function, and symptoms of breathlessness, cough and/or phlegm that often get worse over time. Your condition means that at certain times your COPD symptoms may get worse, and this is called an exacerbation. All patients with COPD should receive advice so they know how to spot when they are having an exacerbation and what they should do about it.

At the moment the standard advice and treatment is to tell you the signs to look out for, and to provide you with antibiotics and steroids so that you can manage your condition.

Bacillus Calmette–Guérin (BCG)

The vaccine for tuberculosis (Bacillus Calmette–Guérin, BCG) has been in use to prevent TB for over 70 years in the UK and is considered safe for use. It is made from a weakened strain of TB bacteria. Because the bacteria in the vaccine is weak, it triggers the immune system to protect against the infection but does not give you TB.

There are some expected reactions to the vaccination which can include:

- a slight swelling, redness and tenderness at the injection site followed by a local lesion
- some weeks later this lesion evolves into a small ulcer
- after some months this ulcer will heal leaving a small, flat scar
- a slight swelling of the lymph nodes in the armpit may be experienced

Like all medicines, the BCG Vaccine AJV can cause side effects, although not everybody gets them:

- Severe allergic reactions (such as redness of the face and neck, swelling of the face, throat or neck, skin rash, breathing difficulties and collapse) may occur in rare cases (less than 1 in 1,000). You will need to contact your doctor if you require medical attention.

Other side effects include:

Uncommon side effects (may affect up to 1 in 100 people)	**Rare side effects (may affect up to 1 in 1000 people)**
Fever	Abscess at the injection site
Swelling of lymph nodes in the armpit larger than 1 cm across	Infection with the bacteria from the vaccine can occur. The infection can spread throughout the body, including the bones
Inflammation of lymph nodes, sometimes with oozing ulcers and pus	
An oozing ulcer at the injection site	
Headache	
Fainting, seizures and convulsions among patients receiving injections have been observed	

2. What is the STABILISE trial trying to find out?

BCG vaccine vs standard care

It has been shown that giving the BCG vaccine can result in other benefits apart from protecting against tuberculosis, including helpful changes within the immune system that can protect against many other infections, and may prevent hospital admissions. The main additional benefit of the BCG vaccine seems to be on rates of chest infections, which are more common in people who have a lung disease already, such as COPD, asthma, or bronchiectasis. Flare ups of lung disease are usually called exacerbations and are mainly (but not always) due to infection. Preventing exacerbations in people with lung disease is particularly important because frequent infections can cause lung disease to progress, and every time an infection happens quality of life may get worse.

We want to find out whether the BCG vaccine reduces rates of respiratory exacerbations in patients who have COPD and a history of exacerbations in the previous year.

Randomisation

Participants will be put into two different groups, and this will be decided 'randomly' using a computer. This is a little like 'tossing a coin' to decide who gets which treatment and is a very standard way that research trials are run. This is really important so that the two groups for the STABILISE trial have a similar mix of participants in them. Having a similar mix means that we know that if one group of participants does better than the other, it is very likely to be because of the treatment used and not because there are differences in participants who happened to be in each group. There is an equal chance of being given either the BCG vaccine or not.

3. Why have I been asked to take part in the trial?

To enable us to answer our research question, we plan to recruit 804 participants who have COPD and have had at least two exacerbations in the last 12 months.

You have been asked to take part because your usual medical team have identified that you have been diagnosed with COPD and may be eligible for this trial as shows in your medical records. They might have searched their pre-existing database or might have identified you in their own clinic either in your GP or the

hospital. Identifiable information is not reviewed by people outside of the clinical care team without consent.

4. What would taking part involve?

Pre-screening: You will have either been approached directly by your health care provider (HCP), received a letter of invitation or an SMS text message asking if you would like to take part in the trial. You might have also seen our STABILISE Trial poster provided in your GP practice/ hospital and decided to join the trial. If you would like to take part or have any questions, please contact the HCP who sent you the invitation or your usual HCP for more information. Your suitability to join the trial will be checked and an appointment for the initial visit will be booked. If you have been given this information sheet whilst you are at a participating hospital, this pre-screening check and initial visit appointment booking may happen face to face at the hospital.

Initial visit (baseline): This will be held in person at your local hospital or GP practice (depending on who invited you to take part) and will take roughly 1-2 hours. You will have the opportunity to ask more about the trial. Your healthcare provider will confirm your eligibility to take part in the trial and, if you decide to take part, you will be asked to sign a consent form. HCP will ask you questions and record your answers in the trial database. This will include information about your demographics, medical history (including past vaccines received), current medications, smoking status, degree of past smoke exposure and exacerbation rate/symptoms/treatments. You will then be asked some questions related to the impact of COPD on your life, and how it changes over time. Participants need to get Interferon-Gamma Release Assay (IGRA) to test their TB status and only those who are negative will be eligible for the trial. As part of this eligibility check, you will be asked to provide a sample of blood (approximately 60 ml in volume (which is equivalent to 4 tablespoons)) which will be used to perform a TB blood test. A TB blood test is used to measure a person's immune response to the bacteria that causes TB. The test will be sent off to a local laboratory for analysis. You will be randomized to receive one of the two treatments which are described:

- **Treatment arm one:** participants who are assigned to this treatment will receive the BCG vaccine.
- **Treatment arm two:** participants who are assigned to this treatment will not receive the vaccine.

You will also be asked to complete some simple tests, outlined below:

1. **Spirometry** – if you haven't done this in the last 12 months, you will be asked to blow into a device called a spirometer, which will measure how much air you can blow out and how fast. You will be asked to take a common short acting bronchodilator (e.g. Salbutamol) given by an inhaler through a spacer device and then to rest for at least 20 minutes before doing the test. This is only needed if you have not done the test within the last 12 months.
2. **Finger-prick blood test (dried blood spot test (DBS)) –** a single-use safety lancet will be used to prick your finger to obtain several drops of blood, which will be applied to a filter paper. You will be taught how to complete the finger-prick blood test by your healthcare provider (HCP) as we will require you to do this on your own at home and to post the sample back to the trial main laboratory based at the Clinical Immunology Services at the University of Birmingham using the address that will be provided to you after you have been in the trial for one month, 3 months and every time you experience an exacerbation. Everyone will do this test.
3. **Sputum sample-**you will be asked to provide phlegm by coughing up and spitting in a clean container that will be given to you. You will be taught how to give the sample by your HCP as we will require you to do this on your own at home and to post the sample back to the trial main laboratory using the address that will be provided to you every time you experience an exacerbation.

Trial suitability and vaccine administration:

Once your HCP receives the results from your TB blood test, they will contact you to let you know if you are suitable for the trial or not (only participants with a negative result are eligible to take part). If your test result is 'indeterminate', you will be asked to provide another blood sample for testing. If your test result is 'positive', your HCP will refer you for assessment of TB status. If your blood test results show that you are not eligible to take part in the trial, we will store the data that we have collected to confirm your eligibility. These will include relevant details from your medical information, and the results from your blood tests. We will not use this information and the data will be securely archived. No other data will be collected from you and your participation in the trial will end. If you are eligible for the trial, you will receive a letter informing you of your treatment allocation.

Participants who will be allocated to the BCG vaccine group will be given details on the appointment to receive the injection. This could be up to 6 weeks after your initial baseline visit. The vaccine appointment might be in a local hospital, and you will be reimbursed for the travel costs up to a maximum of £15. Please make sure to keep any relevant supporting documentation regarding your expenses, such as receipts.

Women aged between 18 and 55 years will be asked to arrive 10 minutes before their appointment for a pregnancy test if they are not taking contraception and there is no other reason that they could not be pregnant.

Exacerbation:

During your participation in the trial, you will be asked to provide a sputum sample, a combined throat/nose swab sample and to complete a finger-prick blood test if/when you experience an exacerbation at home. Please make sure to email the trial team at Stabilise@trials.bham.ac.uk to inform the trial team to expect the samples. Some participants will also be invited to provide additional blood samples at various time points during their involvement in the trial (as detailed in the follow up schedule below). This is optional and you can still take part in the main trial if you would prefer not to provide extra samples.

Scheduled follow up: After the baseline visit, you will be contacted at up to three further time points:

- **1 month:** You will be asked to complete a finger-prick blood test at home and to return it to the trial main laboratory based at the Clinical Immunology Services at the University of Birmingham in the post**.** If you agreed to provide additional blood samples when you completed the consent form, your HCP will contact you to schedule an appointment for you to provide a sample at your hospital or GP practice. If you were not asked or did not agree, you will not be contacted at this time point.

- **3 months:** This will involve completing a questionnaire and providing details about any exacerbations, your symptoms and any treatments you received. You will also be asked to complete a finger-prick blood test at home and to return it to the trial main laboratory based at the Clinical Immunology Services at the University of Birmingham in the post. If you agreed to provide further blood samples, your HCP will contact you to schedule an appointment for you to attend your hospital or GP practice to provide a sample and you will be asked to complete the questionnaire and blood spot test whilst you are there.

- **12 months:** This will be held at your local hospital or GP practice. This appointment will take roughly 1-2 hours. The trained member of the research team will ask you questions about your medical history, current medications, smoking status, exacerbation rate/symptoms/treatments and complete a short questionnaire with you. You will also be asked to complete a finger-prick blood test

(DBS). You will be also asked to give some blood sample if you have agreed to provide additional blood samples when you completed the consent form.

Information will also be collected from your existing GP record where it is relevant to you taking part in this research, and information about hospital admissions will also be collected from electronic NHS records of all admissions, A&E attendances and outpatient appointments at NHS hospitals in England. This information is collected and will be submitted to STABILISE trial database. STABILISE trial clinical committee will review this information and decide if you had a true exacerbation or not.

Optional interview study: If on your consent form, you agreed to be contacted about the interview study, one of our researchers will contact you during the trial. If at this time you are still happy to take part, they will arrange a time for you to talk about your experiences of COPD and the health care you have received. They will ask about your perceptions of different treatments to help manage COPD, including your experiences and views on vaccinations.

Optional Mechanistic sub-study: This sub-study will check how the immune system responds to the BCG vaccine. We aim to recruit only 80 randomly selected participants for this sub-study. If you agreed to take part and were among the 80 participants selected, this will require you to visit your local research site at one, three and twelve months. The visits will be arranged by the research site, and you will be asked to provide additional blood samples during these visits.

5. What are the possible benefits of taking part?

We cannot predict whether you will benefit directly from taking part in this trial, but the information we get from carrying out this trial could potentially change the way people with COPD are treated. Many of the tests and treatments used in hospitals today have been developed with the help of people who took part in research.

6. What are the possible disadvantages and risks of taking part?

The BCG vaccine is considered safe for use but like all vaccines it can cause side effects which are outlined in question 1 of this information leaflet. If you have any concerns during your time in the trial, please do not hesitate to talk to the clinical care team or research team at your GP practice or local hospital.

PART TWO

7. Who is organising and funding this trial?

The STABILISE trial is a national trial run by the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham. The University of Birmingham is the Sponsor of the trial (the group legally responsible for its conduct) and BCTU is responsible for the day to day running of the trial. The trial is being run in partnership with Liverpool University Hospital NHS Foundation Trust and the University Hospitals Birmingham NHS Foundation Trust. The trial is funded by the National Institute for Health and Care Research (NIHR) and Efficacy and Mechanisms Evaluation (EME) programme.

8. How have patients and the public been involved in this trial?

Public members sit on the panel which reviewed and agreed to fund the trial. We have consulted a group of service users during the design of this trial. We have dedicated patient and public (PPI) representatives on

both our Trial Steering Committee and Co-Applicants Group who have helped to ensure all information provided to participants is clear and understandable. PPI input will continue to be an integral part of the trial.

9. Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC), to protect your interests. This trial has been reviewed and given favourable opinion by the London - Hampstead Research Ethics Committee**.** This trial has also undergone rigorous review by a multidisciplinary group on behalf of the trial funder as part of the funding review process.

10. What happens to my research data after the study??

If you agree to take part in this trial, your details and any information collected about you for this research will be handled, stored and destroyed in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018.

The University of Birmingham take great care to ensure that personal data is handled, stored, and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law.

Any physical paperwork containing identifiable data will be kept in an access-controlled and secured room inside a locked filing cabinet.

In relation to this study, all questionnaire answers that you provide for the study will be kept anonymous and stored in a protected computer database on physically secure servers at the University of Birmingham. This database will be password protected and accessible only by certain members of the research team on a need-to-know basis.

If you agree to give your research data from this study for future research. Sometimes this future research may use research data that has had your name and NHS number removed. Or it may use research data that could show who you are. You will be told what options there are. You will get details if your research data will be joined up with other information about you or your health, such as from your GP or hospital.

Once your details like your name or NHS number have been removed, other researchers won't be able to contact you to ask you about future research.

Who will have access to my data?

The Birmingham Clinical Trials Unit (Data Processor), and the University of Birmingham which is the legal Sponsor for the trial (Data Controller) will have access to your data.

What information will be accessed about me?

We will ask for your consent to collect the following:

When you first join the trial: Contact details, education level, NHS number, Date of Birth, sex, ethnicity, employment status, height and weight, education level, medical history (including vaccine history), smoking status, smoking history, medication you are taking at the time you join the trial, COPD history in the previous 12 months (including hospital admission, results of any lung function tests or previous exacerbations), how often you have accessed medical care for your exacerbations, and which service you accessed. We will also record the results of any medical and laboratory tests or questionnaires that are completed during this visit, including a questionnaire to assess your quality of life.

At the vaccine appointment: results of pregnancy test from relevant participants who are assigned to the vaccine arm and needed pregnancy test before receiving the vaccine.

During exacerbation: Exacerbation duration, treatment you received, radiology images and if there is any hospital admission. We will also record the results of any laboratory test

At one month follow up: We will record the results of finger-prick blood test. We will also record the results of any laboratory tests if you agreed to give extra blood sample.

At the 3 month follow up: You will be asked to complete a questionnaire which will assess your quality of life, exacerbations history in the last 3 months and any vaccine you received in the last 3 months. We will also record the results of any laboratory tests.

At the final visit: Medical history (including vaccine history and hospitalisations in the last 12 months), smoking status, any medications you are currently taking, COPD exacerbation in the previous 9 months, any symptoms you are experiencing, treatments you have received will be collected and you will be asked to complete a questionnaire to assess your quality of life. We will record the results of any laboratory test if you agreed to give extra blood sample.

You will not be identified by name and will be identified by a unique 'Participant Number' allocated during the randomisation process. The only identifiable information supplied to us by your hospital will be your date of birth and initials, which may be used in routine communication between us and your GP practice or hospital, as well as during the randomisation process.

Involvement of General Practitioner

You might have been invited to take part in the trial by your registered GP practice as they are helping us to find participants that are suitable for this trial. If you are interested in taking part, an initial visit appointment will be booked that will take place face-to-face at your GP Practice. The appointment will be with your usual medical team and they will take your written consent and assess if you are suitable to be included in the trial.

12 months later, your GP will arrange a follow up appointment with you which will take place face-to-face at your GP practice. Here, we will make sure you are still happy to be part of the trial.

If you are invited to take part in the trial by your local hospital, with your consent, we will let your GP know that you are taking part in the STABILISE Trial. Your GP will be provided with a summary of the trial but will not be aware of which group you are randomised to.

What will happen to the samples I give?

Prior to taking any samples we will require your consent to do so. Any blood samples you provide will be processed at your local GP practice or hospital and some will be frozen and stored at the GP practice or hospital and then transported back to the University of Birmingham labs for analysis. Blood spot samples and sputum/throat swab samples collected from you will also be sent to the University of Birmingham labs. We will ask for your permission to store any remaining blood samples after this trial for use in future research for up to 10 years which conforms to all relevant legal, governance and ethical requirements. Those samples will need to be transferred to the Human Biomaterials Resource Centre (HBRC), University of Birmingham, Birmingham once the End of the Study Declaration is submitted.

How will my information be stored and used?

All information about you will be securely stored and only people working on the trial, or working to ensure the trial is running correctly, will have access to the data. The University of Birmingham are responsible for looking after your information and using it properly. Information collected about you will be kept for at least 25 years after the trial has finished. This allows the results to be verified if needed.

Occasionally, we may need to check your medical records to make sure that the information provided about you is accurate. This will be done either by clinical staff or by designated trial personnel. Under no circumstances will you be identified in any way in any report, presentation or publication arising from this or any other trial. Any data stored long-term would not identify you as an individual.

Will anyone else have access to my data?

It may also be necessary to allow authorised personnel from Government regulatory agencies and/or NHS bodies to have access to information about you. This is for your protection and is to ensure that the research trial is being conducted to the highest possible standards. In addition, we may share anonymised data collected through the STABILISE trial with other research collaborators; you would not be identified by name in any data shared with other interested parties who are not part of the trial.

How will we use information about you?

We will need to use information from you, from your medical records and test results for this research project. This information will include your:

- your NHS number
- your name and
- contact details

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

International transfers

Your data will not be shared outside the UK.

What are your choices about how your information is used?

- you can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have
- you have the right to ask us to remove, change or delete data we hold about you for the purposes of the study. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

How long will my personal data be kept?

Your data will be retained for 25 years. If you withdraw from the trial, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible.

Where can you find out more about how your information is used?

You can find out more about how we use your information, including the specific mechanism used by us when transferring your personal data out of the UK.

- by visiting https://www.birmingham.ac.uk/privacy/index.aspx
- by asking one of the research team
- by sending an email to dataprotection@contacts.bham.ac.uk, or
- by ringing us on +44 (0)121 414 3916.

You can also find out more from www.hra.nhs.uk/information-about-patients/ and by reading the information available here www.hra.nhs.uk/patientdataandresearch

11. What if something goes wrong?

If you have a concern about any aspect of this trial, you should ask to speak to a member of the research team who will do their best to answer your questions. Please contact the STABILISE trial team by email at STABILISE@trials.bham.ac.uk or by phone 0121 415 9123. If you remain unhappy and wish to complain formally, you can do this through your GP/hospital's Patient Advice and Liaison Service (PALS) team (you can find their contact details at the bottom of the last page of this document) or via the independent NHS Complaints Advocacy Service. Details can be obtained from: https://www.nhs.uk/nhs-services/hospitals/what-is-pals-patient-advice-and-liaison-service/

If you have any questions or concerns about taking part in research you can also contact NHS England: Tel: 0300 311 2233, email: england.contactus@nhs.net

In the unlikely event that you were harmed by taking part in this research trial, there are no special compensation arrangements, if the care offered was appropriate. However, as with standard healthcare, if you were harmed by care that was felt to be negligent, then you may have grounds to consider legal action. The normal National Health Service complaints mechanisms will be available to you in the same way as they are for standard clinical care.

12. What if I change my mind?

It's up to you to decide whether or not to take part. If you do decide you want to take part you will be given a copy of this information sheet to keep and will be asked to sign a consent form.

You may change your mind about taking part in any aspect of the trial at any time (before the start of the trial or even after you have commenced the trial) for whatever reason, without having to justify your decision and without any negative impact on the care you will receive. You can withdraw by contacting the STABILISE trial team by email at STABILISE@trials.bham.ac.uk. If you change your mind and withdraw from the trial, your care will continue in the usual way at your GP practice or hospital.

Data and samples collected up until withdrawal will be kept and used, as part of the trial analysis.

13. What will happen to the results of the research study?

Once the research is complete we aim to publish the results in reputable medical literature. Confidentiality will be ensured at all times and you will not be identified in any publication. A link to the published results, together with a short lay summary of the study results will be provided on our website when available. It may take several years to complete recruitment and analyse the trial results.

We will send every participant in the study a short summary of the results in a way that will be clearly understood with its implications for the future treatment of COPD.

Thank you for taking the time to read this information leaflet and for considering taking part in the STABILISE trial.

Contact Information

If you would like more information or have any questions about the STABILISE trial you can talk to:

Stabilise trial team: telephone number: 0121 415 9123 email: STABILISE@trials.bham.ac.uk

Support can also be found through the NHS Patient Advisory and Liaison Service (PALS)

(Site Local PALS telephone number: <number>, email: <email address>)

Contact details for the STABILISE Trial Office at the Birmingham Clinical Trials Unit:

Website: www.birmingham.ac.uk/STABILISE email: stabilise@trails.bham.ac.uk

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