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# Volunteer Information Sheet

## TB046: A clinical study comparing the immune response to revaccination with intradermal BCG and aerosol BCG in previously BCG vaccinated healthy adult volunteers with and without Type 2 Diabetes

Thank you for showing an interest in this study. The first page of this information sheet sets out a brief summary. The rest of the document provides more detail. You can ask us for more information at any point.

| Condition Studied | Research Study Length | Number of visits |
|---|---|---|
| Tuberculosis (TB) | Six months | Nine to ten |

### What will the study involve?

- A screening visit (2-3 hours) to check you are healthy and can take part
- Vaccination with BCG either as an injection or by breathing it in
- Completing a diary of your symptoms
- For some people a bronchoscopy (looking into the airways with a small camera and taking samples)
- 8-9 further visits with blood tests
- Regular Throat Swabs

### Could I be eligible to take part?

You must
- Be aged 18-65 years old
- Be in good health
- Know whether or not you have a diagnosed Type 2 Diabetes
- Live in or around Oxford
- Have previously had the BCG vaccine

You must not
- Be pregnant or breastfeeding
- Have any breathing problems e.g. asthma
- Be a current smoker, including vaping
- Have lived in a rural area of the tropics for more than 12 months

**We are looking to recruit both people *with* Type 2 Diabetes and those *without* Diabetes.**

### Why take part?

Information gained from this study may help in developing a more effective Tuberculosis (TB) vaccine and understand why people with diabetes are more likely to get infections.

There is no known direct benefit to you from taking part in this study.

You will be compensated for your time, travel and inconvenience.

### Are there risks?

There are always risks with taking part in any study.

Common local side effects include muscle and arm ache, short-lived cough, sore throat, shortness of breath and chest tightness. These are described fully below.

There is absolutely no risk of contracting TB in this study.

**Dear Volunteer,**

Thank you for showing an interest in taking part in this research study. Before you make a decision, it is important you take the time to understand why the research is being done and what it would involve. Please read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish.

- Part 1 tells you the purpose of the study and what will happen to you if you take part
- Part 2 tells you more information about how we run (conduct) the study, including what happens to samples and the data you provide

Please ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not to take part. **Taking part is entirely voluntary.**

Volunteer Recruitment Coordinator
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# Contents

# Part 1 – What Happens in This Study

### 1.1 What is the purpose of this study?

We are a tuberculosis (TB) vaccine research group. We are working on ways to protect people from getting infected with TB. The purpose of this study is to 1) explore whether we can make BCG more effective by giving it in a different way and 2) explore if there are difference in response to re-vaccination in healthy volunteers with and without Type 2 Diabetes.

**Key Concept – What is BCG?**

BCG stands for Bacillus Calmette-Guérin. It is a type of bacteria (bacillus = a type of bacteria) named after the two French scientists (Calmette and Guérin) who developed it. They did this by taking the bacteria that usually causes TB in cattle (but can also cause TB in humans) and weakening it. This created bacteria that are too weak to cause any disease in healthy humans. However, because the bacteria are similar in structure to those that cause TB, they activate the immune system to recognise and fight off TB-like bacteria and develop faster responses if the person came into contact with TB in the future. This is how the BCG works when used as a vaccine injected into the arm.

TB is a disease caused by a bacteria (*Mycobacterium tuberculosis*). TB disease remains one of the top 10 causes of death worldwide. BCG, given as a single dose under the skin, is the only vaccine currently licenced for use against TB, but it is not always protective. The BCG vaccine works well against disease in childhood, but it is not good enough at protecting against disease in adulthood, which is when majority of TB deaths occur. We are working on developing better vaccines schedules against TB in the hope of providing greater protection than currently recommended single dose.

There has been recent interest in giving a second dose ("booster") of BCG by a different route which might make it work more effectively than an injection. One other way vaccines can be given is by turning them into an aerosol (fine mist) and breathing them. One area this study is going to look at is whether this way of giving a second dose of the BCG vaccine gives a stronger immune response compared to a conventional injection.

### 1.2 Why are people with Diabetes needed for this study?

Diabetes is caused by the body losing its ability to process sugars. There are different types of the condition, but they all involve problems with the way a hormone called insulin is produced and works. It is a common condition worldwide and the number of people affected is predicted to continue to increase.

People with Diabetes are at an increased risk of a range of medical conditions, and they are also more likely to develop infections. There is particularly strong evidence that Diabetes increases risk of developing, and becoming sick from, Tuberculosis infections. Therefore, improving vaccines which protect against TB is particularly important in this group of people. To achieve this, it is important to understand how responses to TB vaccines is different in people with diabetes.

### 1.3 What is an aerosol and how is it given?

An aerosol is a fine mist of very small liquid particles. They are produced by a special device called a nebuliser (similar to an inhaler) which takes liquids and squeezes them through a very fine mesh using sound waves. The mist is inhaled into the lungs.

Many medicines for asthma, emphysema, and other respiratory diseases are already given by inhalation. In three other studies conducted by our research group, TB041, TB043 and TB044 we have given BCG to volunteers by aerosol inhalation with no safety concerns.

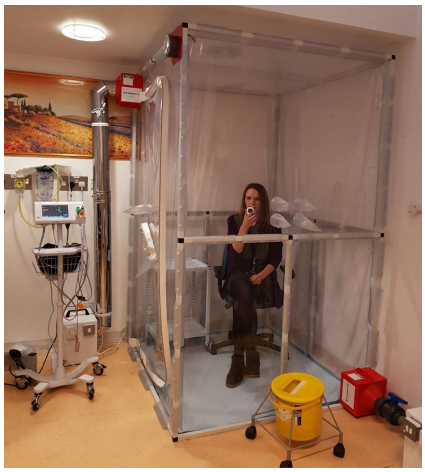

*Photo 1. Volunteer receiving aerosol BCG vaccination*

Breathing in the aerosol of BCG in this study is not uncomfortable, it takes about 5 minutes and you sit in a specially designed tent while you do it. (See photo 1)

### 1.4 Will everyone in this study get aerosol BCG?

This study is split into different groups (see figure 1), only one group will get an aerosol BCG booster, while the other volunteers will have their BCG booster vaccination as an injection. The BCG injection will be given in the same way as your original vaccination, the injection is made under the top layer of skin, this is called an "intradermal" injection. The group you are entered into will depend upon whether you have diabetes or not.

To understand how the body's immune system is responding to the vaccinations all volunteers will have blood tests taken at follow-up visits. Volunteers without diabetes also have washings taken from their lungs in a procedure called a bronchoscopy. The bronchoscopy will take place 14 days after the BCG booster and is explained below.

We will then use the lung washings and the blood samples which we collect during the study to compare between the groups. This will help us to understand both how aerosol BCG affects the immune system and also how having Diabetes affects the immune response to BCG booster vaccination. Throat swabs may also be taken throughout the study to investigate the 'normal' bacteria which live in and on our bodies (the microbiome). These bacteria can be helpful in training our immune system to work and can protect us from bacteria which cause infections.

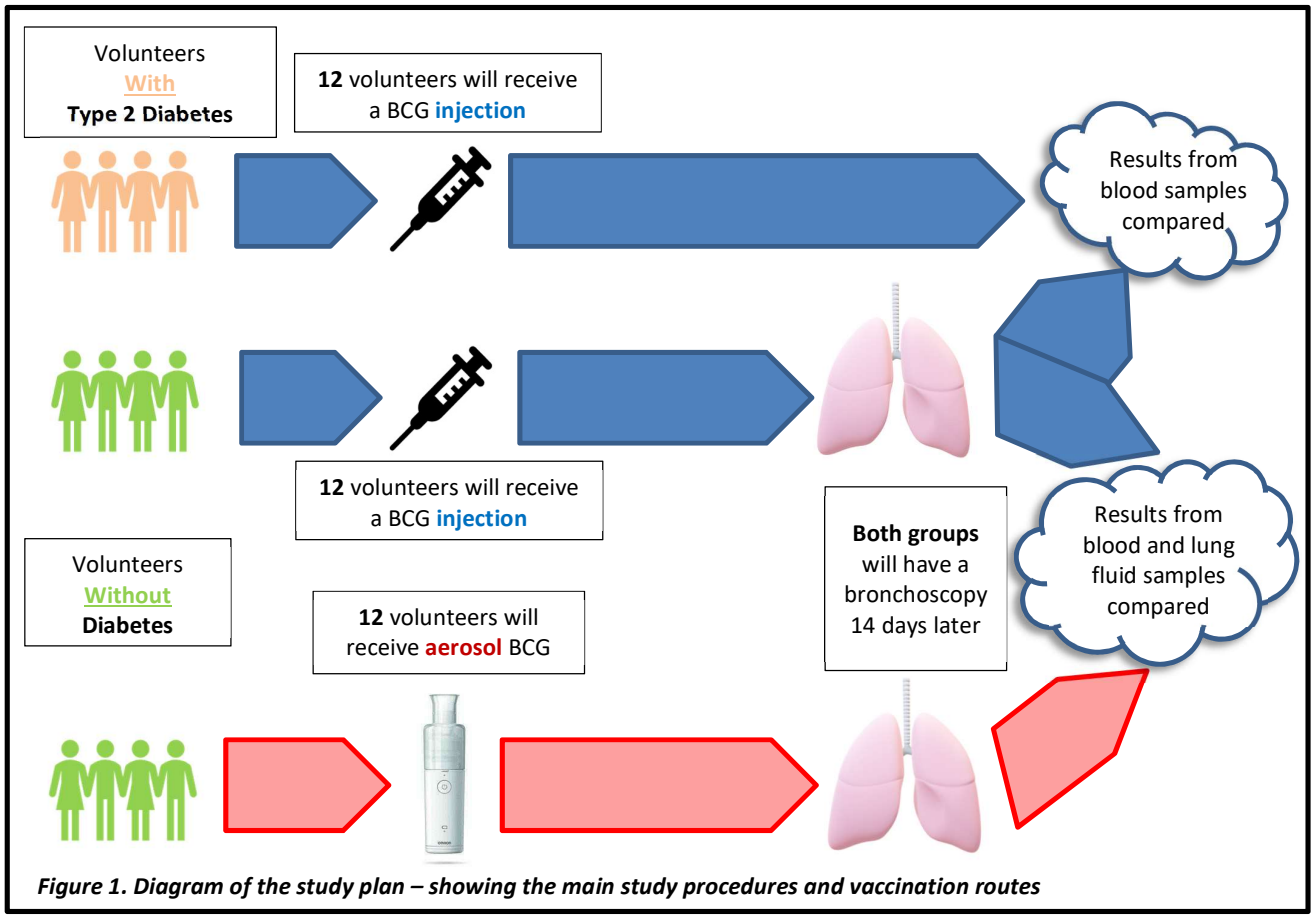


***Figure 1. Diagram of the study plan – showing the main study procedures and vaccination routes***

### 1.5 Can I take part?

We will ask you to complete an initial online pre-screening questionnaire to assess key aspects of your eligibility to take part in the trial. If you meet these initial eligibility criteria, we will contact you via email and may arrange a pre-screening telephone call (lasting around 15 minutes) prior to inviting you for a formal face-to-face screening visit.

In order to take part in the study you **MUST**:

- Be an adult aged between 18 and 65 years with no significant findings in your medical history (other than diabetes) or identified during physical examination
- Live in or near Oxford (approximately within a one-hour drive) for the duration of the study period
- Give written informed consent to take part in the study
- Allow the investigators (researchers) to discuss your medical history with your General Practitioner (GP) and/or to access your electronic medical records
- Allow the investigators to register you on The Over-volunteering Prevention System (TOPS), a confidential database set up to prevent people entering into multiple studies at the same time
- Refrain from blood donation during the course of the study
- Practice continuous effective contraception for the duration of the study (people of child bearing potential only)
- Be willing to be tested for evidence of SARS-CoV-2 infection and allow public health notification of the results if needed
- Be able and willing (in the investigator's opinion) to comply with all the study requirements including BCG vaccination, blood tests, lung function tests, throat swabs and bronchoscopy (if being performed)
- Be previously vaccinated with BCG at least 12 months prior to entering the trial. You **will need** to provide evidence of this; EITHER by a visible scar OR documentation in medical or occupational health records

Additionally, for people with Type 2 Diabetes, you **MUST**

- Have been diagnosed with Diabetes more than 12 months ago and be taking a medication plan which includes Metformin

You **CANNOT** take part in this study if:

- You have a significant history of allergies or severe allergic reactions, including to vaccines or other medications including anaesthetics that are required during the study
- You have a significant history of heart problems, gut problems, liver, kidney, hormone gland (other than diabetes), skin or neurological diseases
- You have any significant problems with your immune system
- You have previously been diagnosed or treated for TB disease or latent TB infection or any of these are found on your screening tests
- You have ever received an experimental TB vaccine
- You have had more than one BCG vaccine or had aerosolised BCG in the past
- You have hepatitis B, hepatitis C or HIV infection
- You are taking any tablet or inhaled steroid medication or other drugs working on your immune system or have done so for more than 14 days in the past 6 months
- You have had immunoglobulins or any other blood products (such as blood transfusion) in the 3 months before your involvement in this study
- You have a history of cancer (except basal cell carcinoma or carcinoma in situ)
- You have a history of any serious psychiatric (mental health) condition which may affect your taken part in the study (including previously having to be admitted (stay overnight) in a psychiatric care facility)
- You have a history of significant drug or alcohol abuse
- You are pregnant, breast-feeding or trying to become pregnant during the study
- You have previously lived for more than 12 consecutive months in a rural area of a tropical climate (due to possible increased exposure to different types of bacteria that may affect the study results)
- You have taken part in another research study involving receipt of an investigational product in the 30 days before your involvement in this study
- Your body mass index (BMI) is lower than 18.5 or greater than 45
- You plan to take part in another study of an investigational product at the same time as this study
- Any significant abnormality is seen on your screening chest X-ray, lung function tests, blood tests, urinalysis or clinical examination

Additionally, for people without Type 2 Diabetes you **CANNOT** take part if:

- You have any respiratory (chest/lung) disease, including asthma
- You are a current smoker or have smoked in the last 3 months (including e-cigarettes)
- You are taking any substances or medications through the nose or via inhalation including cocaine or other recreational drugs
- You have any nose, mouth or throat abnormality that would affect undergoing a bronchoscopy
- You share a household with someone with clinically significant problems with their immune system

### 1.6 Do I have to take part?

No, taking part is entirely voluntary. It is up to you to decide whether or not to take part. Your decision will not result in any penalty, or changes to your standard medical care. If you do decide to take part, you will be given this information sheet to keep (or be sent it electronically) and will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason, but you may be asked to return to the clinic for a safety follow up.

The University of Oxford does not urge, influence, or encourage any employees or students of the institution to take part in this research study. Your decision to not take part in the study, or a decision on your part to withdraw from the study, will have no effect whatsoever on your employment/student status at the University if applicable.

### 1.7 What will happen if I decide to take part?

If you decide you would like to take part in this study, you will need to attend a screening visit lasting two to three hours. The screening visit, BCG vaccination and all follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM).

At the screening visit, you will be met by one of the investigators who will go through this information sheet with you to ensure you understand what to expect, the risks involved and what side-effects you might experience. You will also have the chance to ask any questions that you might have about any aspect of the study.

Once you feel that you understand what the study involves, and the investigator is satisfied that you have understood everything, you will be asked to sign a consent form that will be kept at the study site. You will be given a copy of this consent form to take away and keep. You will be asked to allow the investigators to contact your own doctor (GP) to obtain your medical information, to make sure there are no medical reasons why you should not take part. You will be asked to agree to being registered on a confidential database (The Over-volunteering Prevention System TOPS), which is designed to prevent people entering into multiple studies at the same time.

*Photo 2. Breathing into a lung function machine*. Lung function tests are done at the screening visit and after BCG vaccination

Having signed the appropriate forms, the investigator will go through a few questions for administrative purposes and detailed questions related to your health. This will be followed by a medical examination of your skin including looking for evidence of a previous BCG scar, heart, lungs, abdomen and glands. Your blood pressure, pulse, temperature and oxygen levels will be recorded. We will record your weight and height. You will also be asked to provide a urine sample to check for any problems and for people of child bearing potential a pregnancy test will be performed.

A number of blood tests will be carried out which include tests for anaemia, your blood sugar levels, any blood clotting problems, tests to see how your liver and kidneys are functioning, a test to see if you have come into contact with TB without realising, and tests for HIV (the virus that leads to AIDS), Hepatitis B and Hepatitis C (viruses that affect the liver). In the event of you testing positive for any of these infections, we would inform you of the result and, only with your permission, offer you referral for medical review and further investigations as necessary.

To check that your lungs are healthy, we will measure your lung function and arrange an X-ray of your chest. The lung function test is done by taking a deep breath and then breathing out through a mouthpiece attached to a machine which gives us readings. You will also be asked to breathe in air mixed with very small amounts of gases (helium and carbon monoxide), hold your breath for about 10 seconds and then breathe out slowly. (see Photo 2)

A chest X-ray is a routine medical test that shows us the appearance of your airways and lungs. This may be performed at the same time as your screening visit or you may be required to attend on a separate visit to the hospital in Oxford.

If all your test results have been checked and there are no problems, you will be contacted to arrange a date to start the study.

**1.8 What will happen at the different study visits?**

Based upon whether or not you have a diagnosis of diabetes and the time that you join the study, we will assign you to one of the groups below. All of the groups will be recruited at the same time, and we plan to recruit 36 people in total (see Table 1). You will only enter one group. Figure 2 shows the number of visits and what they involve for the different groups.

| Group | Diagnosis of Type 2 Diabetes | Number of Visits | Route of BCG Vaccination | Number of Volunteers |
|---|---|---|---|---|
| A | No | 9 | Intradermal BCG injection | 12 |
| B | No | 9 | Aerosol BCG | 12 |
| C | Yes | 9 | Intradermal BCG injection | 12 |

*Table 1. Study groups including number of doses of the novel vaccine and days of follow-up.*

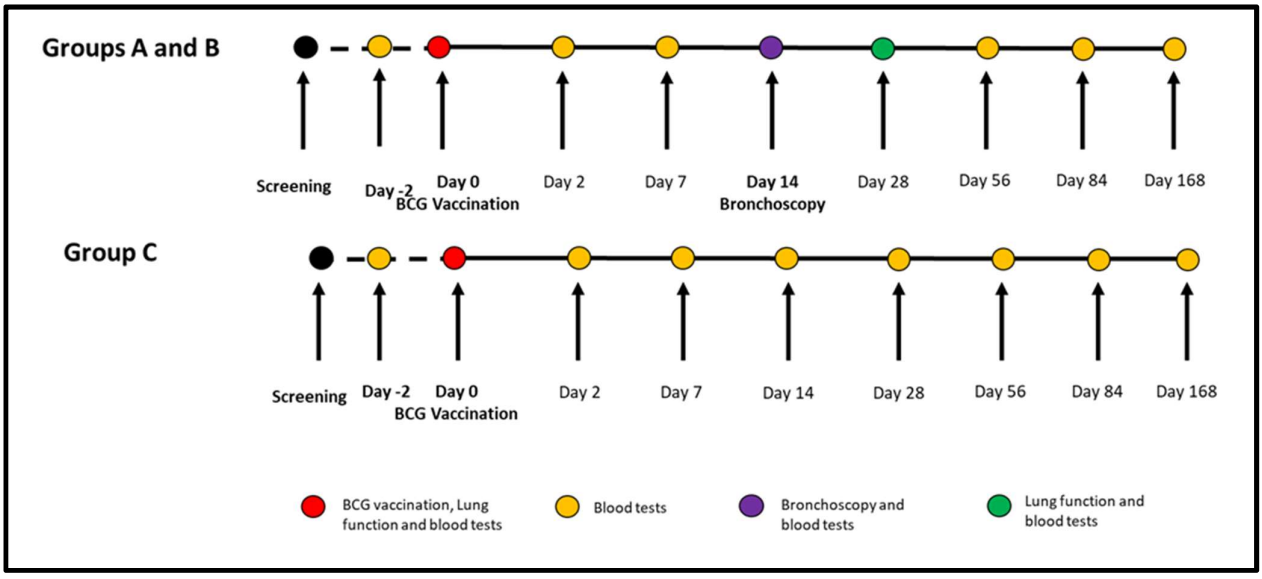


*Figure 2. The timing of key visits for the different TB046 trial groups*

***Day 0 – BCG Vaccination***

On the day of your vaccination you will be asked a few questions to check there have been no changes since screening. Your observations (blood pressure, pulse, oxygen levels, temperature) will be checked and blood samples taken and you may have a throat swab performed. If you are a person of child bearing potential, a urinary pregnancy test will also be performed, and you will have an extra visit 2 days prior to vaccination for a serum pregnancy test.

*Intradermal BCG vaccination visit (Groups A and C)*

You will be given the vaccine into your arm. After the vaccination your observations will be checked and then you will be asked to wait in our unit for 30 minutes. Observations will be checked again and you will then be given a thermometer (to measure your temperature) and an electronic symptom diary (eDiary) for you to record these readings and your symptoms over the next 14 days. This needs to be filled in online, using either your smartphone or your personal computer (a paper diary alternative can be provided if required). Overall the vaccination visit will take about one hour.

*Aerosol BCG Vaccination (Group B)*

The inhaled dose of BCG will be given using a nebuliser attached to a mouthpiece that you place between your lips, and the BCG is inhaled by breathing normally for about 5 minutes until the full dose has been administered.

After the vaccination your observations will be checked and then you will be asked to wait in our unit for 60 minutes. After this, observations will be checked again and your lung function may be measured again. You will then be given a thermometer (to measure your temperature) and an eDiary account for you to record these readings and your symptoms over the next 14 days. This needs to be filled in online, using either your smartphone or your personal computer (a paper diary alternative can be provided if required). Overall, the vaccination visit will take about one and a half hours.

***Day 14 – Bronchoscopy visit (Groups A and B Only)***

On the day of your allocated bronchoscopy visit, you will not be able to eat or drink from midnight before the procedure. For this procedure, you will need to be with us for several hours and you should plan to have the day off from work. In the morning, before the procedure, we will complete routine checks and go through any symptoms that you have. A small plastic tube called a cannula will be inserted into your arm (for giving medication, see below), we will take blood samples and you may have a throat swab performed to look at the 'microbiome'. A urinary pregnancy test will be completed for people of childbearing potential.

A member of the NHS respiratory team will discuss the bronchoscopy procedure with you and ask you to sign a separate consent form before proceeding. For the procedure itself, if you wish, you will be given some medications via the cannula that make you feel sleepy (also called sedation). Your throat will be numbed with a local anaesthetic spray, which tastes bitter. You may be given some extra oxygen with a plastic tube next to your nostrils, and an oxygen sensor will be placed on one of your fingers.

Once you are sedated, the bronchoscope (a thin flexible telescope) will be passed through your mouth or occasionally your nose, down the back of your throat and into the windpipe. The airways will be examined and digital images/photographs of your airways may be recorded. See *figure 3.* Samples are then obtained by flushing a small volume of salty water through the bronchoscope into the lungs, and sucking it out again, thus removing cells for analysis. For these a small pair of

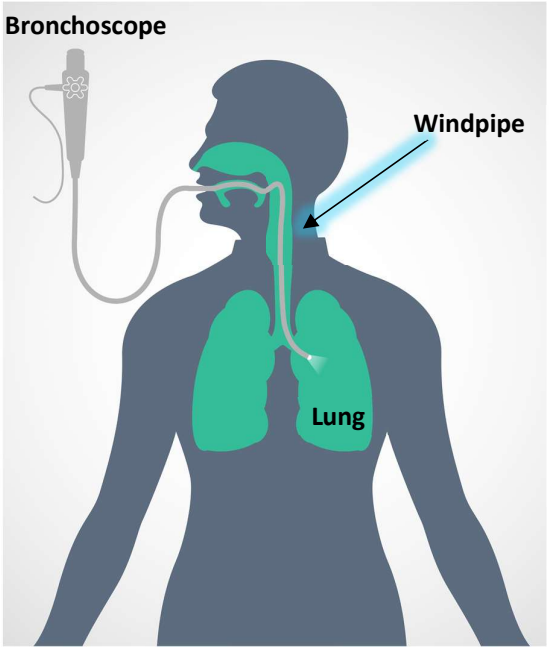


*Figure 3*. A diagram of bronchoscopy showing how the bronchoscopy camera is inserted into mouth and through the windpipe into the lung where the washings are taken.

tweezers (called forceps) or a very small brush may be passed down your airway on the end of a wire and very small pieces of tissue taken. In total, the procedure usually lasts around 20 minutes.

Afterwards you will be sleepy and will need to rest in bed for a while in the unit. Because the local anaesthetic throat spray affects your swallowing, you will not be allowed to eat or drink anything for at least half an hour. We may ask you to provide a sputum (phlegm) sample after your procedure by gently coughing and spitting into a sample pot. The hospital staff will test your swallowing, remove the cannula, and check you are fine before they discharge you. It is essential that somebody accompanies you home as you will not be allowed to drive or to depart alone if you have received any sedation. You should also not be alone overnight after your bronchoscopy, in case you feel unwell. For 24 hours after the bronchoscopy you should not drive, return to your workplace, operate machinery, drink alcohol, sign legal documents or be solely responsible for small children.

***Other follow up visits.***

These visits will last 30-45 minutes. In addition to a short check-up and blood tests you may have a throat swab performed. For those in groups A and B, your lung function tests will be repeated on your day 7 and day 28 visit, and these may be repeated at other follow up visits if we think it is needed.

You will remain in the study for approximately 3 months in total.

### 1.9 What will happen if I want to leave the study after I start?

Taking part in the study is entirely voluntary. You have the right to withdraw at any time. Additionally, volunteers may rarely be withdrawn from the study at the discretion of the Investigator. This may be due to:

- concerns for the volunteer's health and well-being
- ineligibility discovered during the study or retrospectively
- significant protocol deviations
- volunteer non-compliance with study requirements
- adverse events requiring discontinuation
- confirmed pregnancy during the study.

The study may be put on hold for any event(s) that may risk the safety of volunteers or the reliability of the data.

### 1.10 What should I avoid during the study?

You should not donate blood during the study or take part in other studies that involve blood sampling or the administration of drugs or vaccines. If during the study you require any vaccinations for health, travel, or occupational reasons, you should inform the investigators who can advise you if and when it is safe to receive them.

People of child bearing potential should use an effective contraceptive method (such as the oral contraceptive pill, a contraceptive hormonal implant or injection, an intra-uterine device, an occlusive cap with spermicide or condoms) for the whole of the study. Exceptions to this are allowed if the person of childbearing potential is truly abstinent from sex and this is in line with their preferred and usual lifestyle (periodic abstinence and withdrawal are not acceptable methods of contraception), they exclusively engage in same sex intercourse or if their sole partner has undergone a vasectomy.

Even though no harmful effects of BCG on the foetus have been observed, there have not been studies to prove its safety. Pregnant volunteers, those who are planning to become pregnant during the study and those who are breastfeeding must not take part in this study. Volunteers who are of childbearing potential will be asked to have a urinary or serum pregnancy test at screening 2 days prior to BCG vaccination, on the same day as BCG vaccination (prior to vaccination), and on the same day as bronchoscopy (prior to bronchoscopy (if being performed)).

Any volunteer who becomes pregnant during the study should immediately tell their research doctor. If you were to become pregnant, any baby born may need to be followed up. We would not routinely take blood from a pregnant volunteer unless there is clinical need.

### 1.11 Is the BCG vaccine safe?

BCG is one of the most widely used vaccines in the world. Several billion people have received the BCG vaccine over the past 100 years and no serious side effects have been seen in healthy people. BCG is usually given as an intradermal injection (injection under the skin) and it is not licensed as an aerosol. However, it has been given into the lungs in three previous trials in the 1960s and 70s, and we have given aerosol BCG in our previous studies (TB041, TB043 and TB044) with no serious side effects.

### 1.12 Are there any risks from taking part in the study?

The risks and side effects of the study procedures are detailed here:

***BCG Vaccination***

BCG has limited side effects and is given safely to millions of people every year as an infection. As with any vaccination, you may experience general symptoms such as headache, tiredness, muscle aches and pains, nausea, feverishness or a low-grade fever. If they occur, these symptoms usually resolve within 48 hours.

Rare side effects: Theoretically, infection with the bacteria in the BCG vaccine can spread through the body, including to the bones. However, this is extremely rare in people who are otherwise healthy and there is no increased risk in people who have diabetes. If infection occurred it would need to be treated in a similar way to TB, with a prolonged course of antibiotics.

*Specific Intradermal BCG Vaccination side effects*

The most common side effects of vaccination are swelling and redness, this can form a small ulcer some weeks later at the site of vaccine injection. This usually heals over a few months and leaves a small flat scar (on both arms in this study). It is also possible to develop some swelling of glands in the armpit, but less than one centimetre across. These are natural reactions to the vaccine. Uncommonly, (less than one in a hundred people) swelling of glands in the armpit to more than 1cm across or an ulcer that leaks fluid at the injection site may occur. If this happens, the ulcer should be allowed to dry and tight clothes should be avoided. Rare side effects (less than one in a thousand people) include inflammation of glands, sometimes with abscesses (collections of infections) and leakage of fluid from the swellings.

*Specific Aerosol BCG Vaccination side effects*

Inhalation is a safe route for giving medicines. All of the side effects seen in our previous studies TB041, TB043 and TB044 were non-serious and of short duration. Potential local side effects include a sore or tickly throat, shortness of breath, wheezing, chest pain, chest tightness, dry cough or cough with phlegm. Side effects could occur within the first few days of the aerosol BCG vaccination but can also occur later. In previous studies which we have completed, in a small number of people we detected brief changes in the lung function tests after they have had aerosol BCG. These changes were small and those who have had them have not noticed feeing more breathless or any other symptoms. We will continue to monitor these lung tests throughout the study if you are given aerosol BCG. A doctor will be available throughout aerosol BCG administration and the clinic room is equipped with oxygen and medications to treat any other symptoms.

***Bronchoscopy***

Bronchoscopy is a widely used routine medical procedure for diagnosing and treating illnesses of the lungs and airways, it has also been used in many research studies involving healthy volunteers. It will be performed at the Oxford University Hospitals NHS Foundation Trust by an experienced respiratory doctor. The specific risks of the procedure will be discussed with you beforehand by the respiratory team. These include post-procedure flu-like symptoms for 1-2 days, hypoxia (low oxygen levels), air leak (called a pneumothorax) requiring insertion of a special tube into the chest (less than 1 in 1000), low blood pressure, abnormal heart rhythm (less than 1 in 1000), and risk of death (less than 1 in 5000). These figures quoted are for all people undergoing bronchoscopy for any medical indication and it is likely that the risk for young, healthy volunteers is even lower, however risk can never be completely removed for any invasive procedure.

When using sedative drugs to make you sleepy, just as in a general anaesthetic, the rate of breathing can sometimes be decreased, but this is uncommon and we will monitor this closely. We sometimes give you extra oxygen during the procedure to ensure you have adequate oxygen levels. As with all medicines, the local anaesthetic and sedatives can cause allergic reactions from mild to severe.

The effect of the sedative medication is to reduce feelings of anxiety and it also makes you sleepy. A side effect of this is that afterwards you may not remember all of the procedure itself. The small volume of saline flushed into the lungs is safe and well tolerated. A small amount of bleeding from the airway may occur so your sputum (phlegm) may be slightly blood stained for a day or two. During the procedure, there is a risk of damage to the lung or significant bleeding but this is extremely low. Spasm of the vocal cords causing cough occurs rarely. At the end of the procedure, you will feel sleepy for a short while. You may have a slight cough and discomfort in your throat or chest lasting a day or two.

On the evening of bronchoscopy, approximately 10% of people have a fever for several hours but this goes away without treatment. After any invasive procedure like this, there is a small risk of infection. We would detect any infection during the follow up period and treat you if necessary. We will discuss all the risks fully at your screening appointment.

***Chest X-ray***

If you take part in this study you will have a chest X-ray. This procedure uses ionising radiation to form images of your body and/or provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you by about 1 in a million

All chest x-rays will be reported by an NHS radiologist and any abnormal findings will be appropriately followed up, with referral to appropriate specialists where required and with your permission.

***Blood samples***

Taking blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. Very rarely, blood taking can cause soft tissue infection to develop. During the course of the study we will need to take up to a maximum 73.5 ml of blood at a single visit. We take around 23mls at the screening visit. The total amount we will take over the study could be as high as 541ml, and is similar to the amount that you might give during an NHS blood donation.
As we are taking this amount of blood for the study, you should not donate blood during the study, or take part in any other studies where you give blood.

***Lung function test***

This is a very safe test, which sometimes causes a short period of lightheadedness or coughing as you breathe out vigorously into the mouthpiece. The gases you will be asked to breathe in are harmless at the low levels used.

***Throat Swabs***

These are not painful but can be uncomfortable. Swabbing the back of the throat can cause individuals to cough or gag.

### 1.13 What are the possible benefits of taking part?

You will not necessarily gain any direct benefit from the study. There is currently no clear evidence that having a second dose of BCG gives more protection against TB than having one dose, so we would not suggest that taking part in this study changes the way that you live in the long term.

During pre-study assessment you will get information about your general health including results from a medical examination, blood tests, urine tests, chest x-ray and lung function measurement. You may also get information about your health from the bronchoscopy. However, these assessments are not carried out for diagnostic purposes and should not be considered a substitute for a doctor's visit.

Information gained from this study may aid in the development of more effective vaccination programmes to prevent TB worldwide.

### 1.14 Will my General Practitioner/family doctor (GP) be informed of my wish to take part?

As part of the consent process, you will be asked to allow the investigators to contact your own doctor (GP) to obtain your medical information. This is to make sure there are no medical reasons why you should not take part.

Sometimes test results may be "out of range", which means the results do not fall within the usual ranges for healthy individuals. In this case, you would be asked to return for a repeat test so that it can be checked again. If the test results are still out of range, or if the chest x-ray shows a significant abnormality, this will mean you cannot take part and we will ask your permission to contact your GP or a specialist doctor, whichever is the most appropriate, to ensure the abnormality is followed up. *At no point will your test results be divulged to anyone outside the study team without your permission.*

### 1.15 Will I be reimbursed for taking part?

You will be compensated for your time, inconvenience and travel expenses. You are not anticipated to incur any additional expenses due to your involvement in the trial. Due to the different type of appointments, the total amount compensated will depend upon which group of the trial you join.

- People in groups A and B will receive approximately £1095
- People in group C will receive approximately £765

If you are required to have any repeat or extra visits then you will be compensated proportionately in addition to this payment. However, there is no additional reimbursement for travel, as these are included in the above values.

Study reimbursement will be made by bank transfer, usually within six to eight weeks of you completing the study. Please bring your bank details with you to your screening visit; no cash payments can be made. Should you decide to withdraw from the study before it is completed, you will receive a proportion of the total amount based upon the parts of the study you have completed.

**We will not pay tax or National Insurance from the money due to you. It is your responsibility to pay these and to check how any compensation received from taking part in the study affects any state benefits to which you are entitled. Contact HM Revenue & Customs for information (http://www.hmrc.gov.uk/ or telephone 0300 200 3300).**

Please note that there are some situations where we are required to tell the authorities about your payments if we are asked to.

# Part 2 – How the Study is Conducted

### 2.1 What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue, you would be asked to sign an updated consent form. Upon receiving new information, your research doctor might consider it to be in your best interests to withdraw you from the study.

### 2.2 What will happen if I don't want to carry on with the study?

Taking part is entirely voluntary and you are free to withdraw at any time, without needing to provide a reason. If you withdraw, we would not perform any more research procedures, although we might need to offer you a follow up visit to, for example, check a blood result for safety reasons. With your permission, we would like to store the samples already collected but if you did not want this, we would discard them. Please note that if samples have already been used in research testing, they cannot be withdrawn and any resulting data will be retained. If you choose to withdraw from the study, your standard medical care will not be affected.

### 2.3 What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your taking part in this study. In the event that something does go wrong and you are harmed during the research,

and this is due to someone's negligence then you might have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. NHS indemnity operates in respect of the clinical treatment and procedures, undertaken as part of the study and if you needed to be admitted to hospital. At any time during the study, you will be entirely free to change your mind about taking part, and to withdraw from the study. This will not affect your subsequent medical care in any way.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient during your X-rays or bronchoscopy. PALS is unable to provide information about this research study. If you wish to contact the PALS team please call 01865 235855 (Churchill Hospital), 01865 221473 (John Radcliffe Hospital), or by email at PALS@ouh.nhs.uk

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you can contact the Chief Investigator, Professor Helen McShane on 01865 617973 or helen.mcshane@ndm.ox.ac.uk. Alternatively, you may contact the University of Oxford Research Governance, Ethics and Assurance Team (RGEA) office on 01865 616480 or the head of RGEA via email: RGEA.Sponsor@admin.ox.ac.uk.

**2.4 What tests will be done on my samples?**

The blood tests which we will perform at the screening visit have already been described in Part 1. At screening and at various points in the study we will take about 7ml of blood to test your blood counts as well as your kidney and liver function. These are taken to monitor how different organs are responding.

The immunology blood tests (60 ml at each visit) that will be done throughout the study will look at your body's response we will also measure blood sugar levels (4ml) to investigate how this impacts your immune system function. If you are in a group which has a bronchoscopy (groups A and B), we will look to see if the vaccine has triggered any response in the immune system of the lungs. We might use the samples from the bronchoscopy to explore the bacteria in the lung including any evidence of BCG.

During the study visits we may also take swabs of the throat see how the normal bacteria (microbiome) of the airways changes in people who have been vaccinated. If felt to be relevant by the study team we may need to take swabs to look for SARS-CoV-2 RNA (either the genetic material or antigens (proteins) made by the virus that causes COVID-19 disease).

Some of the samples will be processed at the University of Oxford, while other samples will be transported for processing in collaborating research centres outside the University of Oxford. All samples will remain pseudonymised throughout – this means that although samples will not have your personal details directly attached to them, it would be possible for members of the study team to link them back to the correct volunteer if necessary. The link to your personal details will not be available to anyone other than the clinical members of the team in the CCVTM.

**2.5 What will happen to leftover samples?**

If you consent, your leftover samples may be stored indefinitely at the Oxford Vaccine Centre Biobank and may be used for further related research, including into tuberculosis, the human body's immune response, vaccine research and/or your safety. More information around the procedures for long-term storage of your samples is available in the Oxford Vaccine Centre Biobank information booklet and you will be asked to sign a separate biobank consent form if you agree. Your involvement in this study will not be affected by your decision regarding storage and future use of your leftover samples in the biobank.

**2.6 Will any tests be done on genetic information?**

We will do genetic tests on your blood samples to look at the patterns of genes that regulate your own individual immune response (these are called Human Leukocyte Antigen genes). Doing this helps us to work out which aspects of the immune response to vaccines are due to genetic differences between individuals. We may also try to identify and study the genes that appear to be important in response to BCG or in protecting against TB. We will only look at specific areas of interest, not your whole set of genes. We will not perform analysis called

whole genome sequencing on fresh or stored biospecimens. Samples will be tested in anonymised form; however, your DNA is unique to you so it can never be completely anonymous.

**2.7 Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the study will be kept strictly confidential. Blood tests will be sent under a pseudo-anonymised trial number. Your chest X-ray, bronchoscopy procedure and any Covid-19 PCR tests are done under your NHS number. Data is available to the study team, the NHS trust staff who are involved in your care, regulatory agencies and the sponsor (The University of Oxford), who can ask to assess the study. Responsible members of the University of Oxford or NHS trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Your GP will be informed about your involvement, as mentioned in Part 1. Every effort will be taken to maintain confidentiality. Information about you may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the research site. Pseudonymised data, including safety data, may be shared with the funder.

**2.8 What will happen to my data?**

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you and your hospital and GP records, in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.

The University of Oxford will keep identifiable personal information about you for 5 years after the study has finished. We may store any research documents with some personal information, such as consent forms, securely at the University of Oxford for at least 25 years after the end of the study, as part of the research record. However, such personal information will be limited only to the minimum necessary. The need to store study data will be reviewed every 5 years.

If you agree to your samples being used in future research, your consent form will be held securely until the samples have been used up. Files will be confidentially destroyed when storage is no longer required.

Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

For any positive COVID-19 PCR tests performed, we are required by law to share your result and personal data (including your name, contact details, and postcode) with UK Health Security Agency.

The Oxford University Hospitals NHS Foundation Trust may use your name and contact details to contact you about NHS appointments within the study only. They will keep identifiable information about you from this study in your medical records, in line with their NHS Trust policy.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at [https://compliance.web.ox.ac.uk/individual-rights]. You can also find out more about how we use your information by contacting the Chief Investigator – helen.mcschane@ndm.ox.ac.uk.

**2.9 Who is organising and funding the research?**

This study is funded by UK Research and Innovation (UKRI) as part of a grant from Horizon Europe, through which a subcontract is awarded to the University of Oxford under the direction of Professor Helen McShane. The study is designed and organised by the investigators. Neither your GP nor the researchers are paid for recruiting you in this study.

**2.10 Who has reviewed the study?**

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect volunteers' interests. This study has been reviewed and given favourable opinion by _____Research Ethics Committee (ref xxxxx).

Use of the aerosol BCG as a vaccine in this study has also been looked at by the Medicines and Healthcare products Regulatory Agency (MHRA). This agency is responsible for giving permission for experimental medicines and vaccines to be used in clinical trials. The use of this vaccine was reviewed and given a favourable opinion by _____ (ref xxxxx).

### 2.11 What will happen to the results of the research study?

The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until one or two years after the study is completed. A summary of published reports will be available on request to all trial participants for their information and interest. We are not able to provide individual results to volunteers. You will not be identified in any report or publication. Data from this study may be used as part of a student post-graduate degree, for example an MD or DPhil. The anonymised data from this study will be shared with our collaborating partners who are organising and funding this research. Data from this study may be used to file patents, licence vaccines in the future or make profits in other ways. You will not be paid for any part of this.

### 2.12 Further information and contact details

Thank you for your interest in the trial, we hope this information sheet has answered all of your questions. If you would like further information about taking part in research please visit the following website: [http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx]. For independent advice about taking part in this study you may wish to contact your GP. If you would like to speak to one of our study doctors or Professor Helen McShane (Chief Investigator) to discuss any aspect of this study, or if you would like to take part in this study, please contact:

Volunteer Recruitment Coordinator
Centre for Clinical Vaccinology & Tropical Medicine
Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Telephone: 01865 611424
Email: vaccinetrials@ndm.ox.ac.uk

If you have any medical problems during your participation in this study, please contact 01865 611424: (9am-5pm Mon-Fri), or 07990 431010: (24 hour emergency number). Alternatively, if your query is not urgent you can email vaccinetrials@ndm.ox.ac.uk.