



Participant Information Sheet: TB044

Studies of TB vaccines in healthy adults

“A clinical challenge study to evaluate controlled human infection with BCG administered by the aerosol inhaled route in historically BCG-vaccinated healthy adult volunteers”

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



Tuberculosis (TB)

Research Study Length



Six months

Number of visits



Nine-Thirteen

What will the study involve?

- A screening visit (2-3 hours) to check you are healthy and can take part
- Visits for COVID-19 swabs (as required during COVID-19 pandemic)
- Breathing in the BCG
- Completing a symptom diary
- A bronchoscopy (looking into the airways with a small camera and taking samples)
- 7 further visits with blood tests
- Wearing a droplet-collecting mask for 30 minutes on 7 occasions across study visits
- Inhaling salty water to produce phlegm (may not always occur during pandemic)

Could I be eligible to take part?

You must



- Be aged 18-50 years old
- Be in good health
- 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

Why participate?

Information gained from this study may help in developing a more effective TB vaccine.

There is no known direct benefit to you from participating 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 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 the conduct of the study

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. **Participation is entirely voluntary.**

Volunteer Recruitment Coordinator
vaccinetrials@ndm.ox.ac.uk

Part 1

What is the purpose of this study?

We are a tuberculosis (TB) vaccine research group. We are working on developing booster vaccines that can be given after BCG immunisation in the hope of providing greater protection against TB. The purpose of this study is to confirm that it is safe to give inhaled BCG to people who have previously been vaccinated with the BCG.



Key Concept



The BCG stands for *Bacillus Calmette-Guérin*. It is a type of bacteria (baccillus = 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 stimulate the immune system to recognise and fight off TB-like bacteria. This is how the BCG works when used as a vaccine injected into the arm.

In this information sheet, we will give some background information about the BCG in its role as a vaccine. For the purpose of this study however, **we are using the BCG as a type of weak bacteria to mimic an infectious response**. This study does not use virulent (infectious) TB bacteria at all and there is no risk of getting TB.

TB is a disease caused by a bacterium (*Mycobacterium tuberculosis*). TB disease remains one of the top 10 causes of death worldwide. BCG is the only vaccine currently licenced for use against TB, but it is not always protective. BCG works well against disease in childhood, but it is not good enough at protecting against disease in adulthood, which leads to the majority of TB deaths. We are working on developing better vaccines against TB in the hope of providing greater protection than that given by the BCG alone.

It is difficult to develop new TB vaccines, as it is not easy to determine which ones will work well and which will not. In vaccine studies against other diseases, such as influenza and malaria, it is possible to experimentally infect volunteers with the disease in question to see if the vaccine being studied is effective. This is called a “challenge” and is possible where the disease being studied is self-limiting or where safe, effective and short treatment regimens exist. This is not the case with TB, which requires a minimum of 6 months of treatment with multiple medications. However, using a related but far less infectious bacteria is a feasible alternative.

We have developed a challenge model, where we give the BCG as an infectious agent to healthy volunteers as a mimic for TB infection. The BCG consists of a live attenuated (weakened) strain of the bacteria that causes TB in cattle, which is called *Mycobacterium bovis*. The bacteria in the vaccine are still alive but, because they are weakened, they do not cause disease in healthy individuals. However, as the BCG and TB bacteria are similar, studying how the body's immune system responds to and "fights off" BCG can give us important information about how well a new TB vaccine might work. It also helps us to understand more about the body's immune response to this type of infection.

When BCG is given as a licensed vaccine, it is given by an injection into your arm. However, in this study we will use the BCG as an infectious agent, by giving it as an aerosol inhalation into the lungs. We know that the lungs have a very well developed and specialised immune system. We also know that *Mycobacterium tuberculosis*, the bacterium that causes TB, infects people by being breathed into the lungs. Therefore, inhaled BCG more closely imitates TB infection than an injection of BCG in your arm. A nebuliser device (similar to an inhaler) will turn the BCG liquid into a very fine mist (aerosol) which can be breathed in (inhaled). Many medicines for asthma, emphysema, and other respiratory diseases are already given by inhalation. In two other studies in our group, TB041 and TB043, we have also given BCG to volunteers by aerosol inhalation with no safety concerns thus far.

Until now, we have only given the inhaled BCG to people who have not previously been vaccinated with the BCG. In this study, we want to confirm that it is safe to give inhaled BCG to people who have already been vaccinated with the BCG (via the standard injection route) in the past. We also want to see whether prior vaccination with the BCG alters the body's response to the inhaled BCG infection (or challenge).

To understand how the body's immune system responds to and "fights off" the BCG in the lungs, all volunteers in this study will have a bronchoscopy. The bronchoscopy will be 14 days after the BCG administration (challenge). As explained below, a bronchoscopy is a routine medical procedure performed under light sedation, where a thin flexible telescope is passed into the main airways within the lungs to examine them and obtain samples.

Is BCG safe?

BCG is the one of the most widely used vaccines in the world. Several billion people have received the vaccine over the past 90 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 as an aerosol in three previous trials in the 1960s and 70s, as well as in our group's studies (TB041 and TB043) with no serious side effects. In TB041, 31 healthy volunteers received aerosol BCG and have completed their 6-month follow-ups without any safety concerns. Our TB043 study is still ongoing, but so far 42 volunteers have received aerosol BCG, again with no serious side effects. This will be the first time we are giving the inhaled BCG to people who have previously received the BCG vaccine, so part of the study is to make sure aerosol BCG challenge is safe in this situation.

Do I have to take part?

No, participation 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 participate 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.

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.

You may be invited to take part in this study if you are a healthy volunteer and have had a BCG vaccine in the past.

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

- Be a healthy adult aged between 18 and 50 years with no clinically relevant findings in your medical history or identified during physical examination
- Have received the BCG vaccine in the past, at least 12 months prior to enrolment in the study (with evidence such as a visible scar or documentation in medical/occupational health records)
- Be resident in or near Oxford (approximately within a one hour drive) for the duration of the study period
- Give written informed consent to participate in the study
- Allow the investigators 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 (women 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
- Be able and willing (in the investigator's opinion) to comply with all the study requirements including BCG challenge, blood tests, lung function tests, mask-wearing, induced sputum (if being performed) and bronchoscopy

You cannot participate in this study 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 have had confirmed COVID-19 disease or a high clinical suspicion of COVID-19 disease in the 3 months preceding enrolment.
- You have a significant history of allergies or severe allergic reactions, including to vaccines or other medications including local anaesthetics that are required during the study
- You have a significant history of cardiovascular, gastrointestinal, liver, kidney, endocrine, skin or neurological disease
- You have any significant autoimmune conditions or 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 hepatitis B, hepatitis C or HIV infection
- You are taking any oral, inhaled or systemic steroid medication or other immunosuppressive drugs 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 preceding 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 that may affect your participation in the study
- You have a history of significant drug or alcohol abuse
- You are taking any substances or medications through the nose or via inhalation including cocaine or other recreational drugs

- You have any nasal, pharyngeal or laryngeal (nose, mouth or throat) abnormality that would affect undergoing a bronchoscopy
- You are pregnant, breast-feeding or trying to become pregnant during the study
- You have previously lived for more than 12 months in a row in a tropical climate (due to possible increased exposure to different types of bacteria that may affect the study results)
- You share a household with someone with clinically significant problems with their immune system
- You have participated in another research study involving receipt of an investigational product in the 30 days preceding your involvement in this study
- Your body mass index (BMI) is lower than 18.5 or greater than 45
- You plan to participate 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

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 for around two to three hours. The screening visit, BCG challenge visit and all follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM). The bronchoscopy visit will be performed at the Oxford University Hospitals NHS (National Health Service) Foundation Trust in Oxford.

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 if you take part, the risks involved and what side-effects you might experience. You can of course expect to receive full and comprehensive answers to any questions you may have.

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 participate. 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.

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, chest, abdomen, mouth and the lymph glands in your upper body. 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 women of child bearing potential a pregnancy test will be performed.

A number of blood tests will be carried out which include tests for anaemia, any blood clotting problems, tests to see how your liver and kidneys are functioning, a test to measure your immune response to TB, and tests for HIV (the virus that leads to AIDS), Hepatitis B or Hepatitis C (viruses that affect the liver). In the event of you testing positive to 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 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. A chest x-ray is a routine medical test that shows us the appearance of your airways and lungs. These tests may be performed at the same time or may require you to attend on a separate visit to the hospital in Oxford.

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 participate 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.*

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.

How is the study going to work?

We plan to recruit 12 people into four groups (see *Table 1*).

The first three people will be in group 1, the second three people in group 2, the third three people in group 3 and the final three people in group 4. The study visit timeline is detailed in *Figure 1*.

- Group 1: Volunteers will receive a very low inhaled dose of BCG and 14 days later undergo a bronchoscopy
- Group 2: Volunteers will receive a higher, but still low, inhaled dose of BCG and 14 days later undergo a bronchoscopy
- Group 3: Volunteers will receive a medium dose of inhaled BCG and 14 days later undergo a bronchoscopy
- Group 4: Volunteers will receive a higher (standard) dose of inhaled BCG and 14 days later undergo a bronchoscopy. This is the standard dose of inhaled BCG we are using in our current study TB043.

The doses of the inhaled BCG are expressed in “colony forming units” or cfu. This is the standard way amounts of bacteria are expressed and is a representation of the number of live bacteria.

Group	Intervention Dose	Sample size
1	Very low dose (1×10^4 cfu) aerosol inhaled BCG + bronchoscopy	3
2	Low dose (1×10^5 cfu) aerosol inhaled BCG + bronchoscopy	3
3	Medium dose (1×10^6 cfu) aerosol inhaled BCG + bronchoscopy	3
4	Higher(standard) dose (1×10^7 cfu) aerosol inhaled BCG + bronchoscopy	3

Table 1: Study Groups

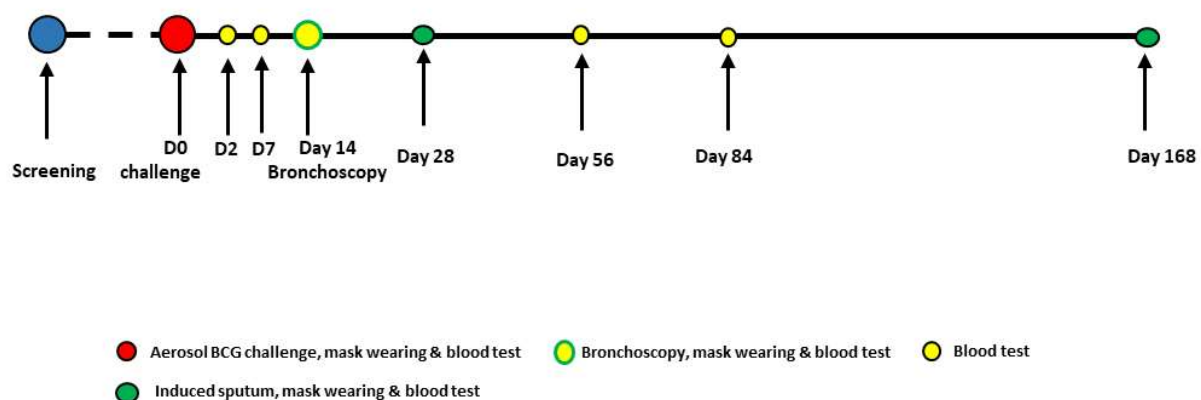


Figure 1. Study timeline. SARS-CoV-2 testing may be performed 2 days (+/- 2 days) prior to D0, bronchoscopy and any Induced Sputum procedures.

Day 0 Challenge:

Please note, during the COVID-19 pandemic you will be asked to attend 2 days prior to your planned D0 challenge to have an additional screening test for COVID-19 infection. If the test is positive, you will not be enrolled at that time and enrolment will be postponed for at least 3 months. We are legally required to inform the relevant public health authorities of all COVID-19 test results (see “COVID-19 additional information” sheet for more details).

If you qualify to be in the study, you will be asked to attend in the morning on the day of BCG administration - Day 0 "Challenge". You will be asked a few questions to check there have been no changes since screening. Your blood pressure, pulse, oxygen levels, temperature (observations) will be checked and blood samples taken. If you are a woman of child bearing potential, a urinary pregnancy test will also be performed.

We want to capture and analyse the droplets coming from your lungs. To do this you will be asked to wear an adapted face mask containing strips that captures droplets as you breathe out. You will be asked to do this for 30 minutes prior to receiving aerosol BCG. We think this could provide a simple way to detect tuberculosis bacteria and other lung infections in the future.

You will then receive the aerosolised BCG challenge at the dose indicated by your allocated group. The inhaled dose of BCG will be given using a nebuliser attached to a mouthpiece that you place between your lips. The nebuliser creates a fine mist, which is inhaled by breathing normally for about 5 minutes until the full dose has been administered. This will take place in a designated clinic room or inside a specially designed isolation tent.

After the BCG challenge your observations will be checked and then you will be asked to wait in the out-patient area for one hour. During this time, we will again ask you to wear an adapted mask again for 30 minutes. After one hour, observations will be checked again and your lung function will be measured. You will then be given a thermometer (to measure your temperature) and an ed diary account for you to record these readings and your symptoms over the next 28 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 challenge visit will take about two and a half hours. You will be asked to attend for a series of follow-up visits as detailed in *Figure 1*.

Follow up visits - day 2, day 7, day 56 (2 months), day 84 (3 months):

On these visits, you will come for a short check-up that will last 30-60 minutes to ensure everything is fine, to check your symptoms and have blood tests. At day 2 and day 7 we will ask you to again wear an adapted face mask for 30 minutes to allow us to capture and analyse droplets from your lungs. We will also repeat the lung function tests at the day 2 and day 7 visits and at any subsequent visits if felt necessary by the study team.

Bronchoscopy visit day 14:

Please note, during the COVID-19 pandemic you will be asked to attend 2 days prior to your planned bronchoscopy visit to have an additional screening test for COVID-19 infection. If the test is positive, you will not undergo a bronchoscopy at that time. The bronchoscopy will be postponed for at least 28 days (from onset of symptoms or a test date if asymptomatic) or may not be able to be undertaken. We are legally required to inform the relevant public health authorities of all COVID-19 test results. (see "COVID-19 additional information" sheet for more details)

On the day of your allocated bronchoscopy visit, you will need to fast from midnight. 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 perform routine checks and go through any symptoms you have. During these checks, we will ask you to repeat wearing the same type of adapted face mask you wore at your Day 0 visit. A small plastic tube called a cannula will be inserted into your arm (for giving medication, see below) and we will take blood samples. A urinary pregnancy test will be performed for female volunteers.

All bronchoscopy procedures are performed by an experienced respiratory consultant at Oxford University Hospitals NHS Foundation Trust, Oxford. A member of the 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. Samples are then obtained by flushing a small volume of saline through the bronchoscope into the lungs, and sucking it out again, thus removing cells for analysis. We may also use other methods to collect samples, including endobronchial biopsies or brushings. For

these a small pair of 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. 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 work, operate machinery, drink alcohol, sign legal documents or be responsible for small children.

Follow up visits: day 28 (1 month) and day 168 (6 months):

These visits will last 45-90 minutes. In addition to a short check-up and blood tests, we will ask you to again wear an adapted face mask for 30 minutes to allow us to capture and analyse droplets from your lungs.

We may also collect some phlegm to send for analysis. To help bring up enough sputum (phlegm), you will be asked to inhale salty water via a nebuliser. This procedure is called *Induced Sputum* and is a non-invasive procedure. We will first check your lung function and give you two puffs of a medication called salbutamol. This medication has a very good safety profile, though some people find it makes their heart beat a bit faster. You will then inhale sterile salty water through a nebuliser for 20 minutes and be asked to try to cough up some sputum. As we will be encouraging you to cough, for your own comfort we would advise you not to do strenuous exercise or have a large meal just before coming in for the procedure. We may not routinely perform Induced Sputum during the COVID-19 pandemic and if we restart we may require you to have an additional COVID-19 PCR test 2 days prior to the procedure, similarly to the enrolment and bronchoscopy visits, or a COVID-19 lateral flow test on the day of the procedure.

After the last visit, study participation is complete. In total, you will spend about 24 weeks (6 months) enrolled in the study.

Premature discontinuation of the study

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

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

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.

Women 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 a woman 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 inhalation on the foetus have been observed, there have not been studies to prove its safety. Pregnant women, women who are planning to become pregnant during the study and those who are breastfeeding must not take part in this study. Female volunteers

will be asked to have a urinary pregnancy test at screening, prior to receiving the BCG and prior to the bronchoscopy.

Any woman who becomes pregnant during the study should immediately tell her 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.

Are there any risks from taking part in the study?

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

Blood samples

Drawing 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 69 ml of blood (approximately 4 tablespoons) at a single visit. We take around 20mls at the screening visit. The total amount we will take over the 6-month period of the study is 523ml, which is just slightly more than a single blood donation at the blood bank. 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.

Testing for COVID-19 infection

Detailed information about the testing process can be found in the "COVID-19 additional information" sheet.

Aerosol inhalation of BCG

Inhalation is a safe route for giving medicines. All the side effects seen in our previous study TB041 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 BCG infection and/or a week or two later. We have not given the inhaled BCG to people who have previously been vaccinated with the BCG before but we do not anticipate any serious complications. A doctor will be available throughout the BCG challenge and the clinic room is equipped with oxygen and medications to treat any other symptoms.

As with a vaccination, following BCG challenge, you may also experience more generalised symptoms such as headache, tiredness, generalised aches and pains, nausea, feverishness or a low-grade fever. If they occur, these symptoms usually resolve within 48 hours following BCG administration.

Rare side effects: Theoretically, infection with the bacteria in the vaccine can spread through the body, including to the bones. However, this is extremely rare in people who are otherwise healthy. This would need to be treated in a similar way to the treatment of TB.

As with other experimental procedures, medications, and vaccines, there is a possibility of some completely unexpected side effect. Serious allergic reactions may occur. In case of this unlikely event, medication for treating allergic reactions is available in the clinic room and the investigators are appropriately trained. If you experience unexpected events or become in any way concerned during the study you should call the emergency contact number at 07990 431010. A qualified study doctor from the CCVTM is available at all times on this number.

Bronchoscopy

Bronchoscopy is a widely used routine medical procedure for diagnosing and treating illnesses of the lungs and airways and in research studies involving healthy volunteers. It will be performed at the Oxford University Hospitals NHS Foundation Trust by a consultant respiratory physician. 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 (<0.1%), low blood pressure, abnormal heart rhythm (<0.1%), and risk of death (<0.02%). These figures quoted are for all people undergoing bronchoscopy and it is likely that the risk for young, healthy volunteers is even lower but risk cannot be completely removed in any invasive procedure.

The cannula (small, thin plastic tube) which is inserted into a vein in your arm before the procedure can sometimes cause slight pain and bruising. The local anaesthetic spray at the back of your throat tastes bitter and also affects the coordination and safety of your swallowing muscles for a short while. We will not let you eat or drink again until it is safe to do so. 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.

As a result of the sedative medication, you may not remember all of the procedure itself. The small volume of saline flushed into the lungs is safe and well tolerated. As we may be taking biopsies, a small amount of bleeding from the airway may occur so your phlegm (sputum) 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% 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

The chest x-ray is a routine medical examination that uses a dose of radiation approximately equal to 3 days of natural background radiation. The additional risk of cancer attributable to one chest x-ray is about one extra case in every 900,000 people. 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, with your permission, where required.

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.

Induced sputum (not during peak of COVID-19 pandemic)

This is a simple and safe non-invasive procedure. The salty water causes a cough (to help bring up the phlegm). For some people this may lead to coughing spasms. You will be asked to stay in clinic until any coughing stops. Very rarely the salty saline may cause your airways to spasm. This is extremely unlikely in people with no history of asthma and is quickly reversible with medication. A sensation of shortness of breath may rarely be experienced during induced sputum procedures. You may be required to have an additional COVID-19 test prior to induced sputum procedures.

Adapted mask wearing

It is possible that if you suffer with significant claustrophobia, adapted mask wearing may not be suitable for you. The masks contain polyvinyl alcohol collection strips. They are designed so these do not touch your face, but we will ask you if you about any potential allergies or problems with skin irritation at your screening visit.

What are the advantages of taking part?

You will not necessarily gain any direct benefit from the study, however, 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 a more effective vaccination programme to prevent TB worldwide.

Will I be paid for taking part in this study?

You will be compensated for your time, inconvenience and travel expenses. You are not anticipated to incur any additional expenses due to your participation in the trial. The total amount compensated will be approximately **£705-£750**. If you are required to have any repeat or extra visits then you will be compensated pro rata in addition to this payment.

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, payment will be pro rata (you will receive a proportion of the total amount). Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

Part 2

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.

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

Participation 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.

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 participation 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, which may be provided 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 United States National Institutes of Health (NIH), the funder, does not have a mechanism to provide direct compensation for research related injury.

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 the time of your 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: ctr@admin.ox.ac.uk.

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 participation, 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. Pseudo-anonymised data, including safety data, may be shared with the funder and this will be outside of the UK and European Economic Area.

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. The baseline and safety blood tests on day 0, 7, 14 and 28 involve taking about 5mL of blood to test for the levels of your blood cells as well as your kidney and liver function. The immunology blood tests (60mLs at each visit) that will be done throughout the study will look at your body's response to the challenge agent you have been given. We will look for evidence of activation of your immune system, to see if the infection has triggered any response specifically against TB-like bacteria, and how it differs compared to previous studies. We will also do this analysis on the lung samples taken during bronchoscopy, and will look at lung fluid and droplet samples to see how much BCG can be found after challenge. During the COVID-19 pandemic, tests will be taken to look for SARS-CoV-2 RNA (the genetic material of the virus that causes COVID-19 disease) or antigens (proteins).

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 participation in this study will not be affected by your decision regarding storage and future use of your leftover samples in the biobank.

Will any genetic tests be done?

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 HLA 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 challenge, vaccination 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.

Who is organising and funding the research?

This study is funded by the National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases (NIAID), parts of the U.S. Department of Health and Human Services, 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.

Who has reviewed the study?

This trial has been ethically reviewed by South Central Oxford A Research Ethics Committee (ref: 20/SC/0059).

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 we perform in the public interest. The University of Oxford is the data controller and is responsible for looking after your information and using it properly. We will be using information from

you in order to undertake this study and will use the minimum personally-identifiable information possible. Pseudo-anonymised safety data may be shared with our funder.

We will keep identifiable information about you such as contact details for a maximum of 7 years after the study has finished. For new uses of BCG that may be licensed, we may store research data securely at the University of Oxford for up to 15 years after the end of the study, subject to adjustments in clinical trials regulations. In addition to the de-identified scientific data, we will also store documents containing personal information that you provide when registering for the trial (including contact details), medical information and signed consent forms during this archiving period. Your bank details will be stored for 7 years in keeping with University of Oxford financial policy. If you completed an online pre-screening questionnaire but were not enrolled on the trial either because you were not eligible after screening or decided not to take part, then any data collected will be kept until the end of the trial.

For any 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 HSA.

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.

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 sent to all trial participants for information purposes. We are not able to provide individual results to participants. 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, including NIH and NIAID. 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.

Further information and contact details

We hope this information sheet has answered all of your questions. If you would like further information about participating in research please visit the following website: : <https://www.nhs.uk/conditions/clinical-trials/>. For independent advice about participating 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.