

From:
Prof Helen McShane FRCP PhD
FMedSci
Chief Investigator, TB Vaccine Trials
Jenner Institute, University of Oxford



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

Volunteer Information Sheet

Studies of TB vaccines in healthy adults

“A human challenge study to evaluate innate and adaptive immune responses to a controlled human infection with BCG administered by the intradermal or aerosol inhaled route in healthy, BCG-naïve, UK adult volunteers” (TB043)

Dear volunteer,

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

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more details about how this study will be conducted

A further information sheet entitled “COVID-19 additional information” will be provided to accompany this information sheet during the COVID-19 pandemic.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

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Part 1

What is the purpose of this study?

Tuberculosis (also known as TB) is a disease caused by a bacterium (*Mycobacterium tuberculosis*) that is responsible for more deaths worldwide than any other infectious disease. BCG (Bacille Calmette-Guérin) is the only vaccine currently in 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 booster vaccines that can be given after BCG vaccination in the hope of providing greater protection against TB. However, it is not easy to work out which vaccines work well and which do not. To help determine this, we have developed a ‘challenge model’, where we give the BCG vaccine to healthy volunteers as a mimic for TB infection to see how their body reacts to it.

BCG is a live attenuated vaccine of a strain of the bacteria that causes TB in cattle, which is called *Mycobacterium bovis*. The bacteria in the vaccine are still alive but weakened and do not cause disease. 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 we could make a vaccine that helps the body's immune system fight off a TB infection. In this study, you will only receive BCG Danish 1331, which is the strain of BCG used for routine vaccinations in the UK.

BCG vaccine is licensed to be given by an injection in your arm. However, in another study in our group, TB041, we have given BCG to volunteers by inhalation, and in this study we will also give BCG by inhalation. This means that an inhaler or nebuliser device 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 in this way. 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. We will be giving some people in the study BCG via the standard injection route, together with inhaled saline (sterile salty water). This will allow us compare the immune response and amount of BCG recoverable from the lungs by different routes. Inhalation of saline is planned together with the BCG injection, as it is possible that inhalation of any substance, however inactive, may alter the body's immune response to the BCG injection in some way. To find out 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 either 2 days, 7 days, 14 days, 1 month or 2 months after the BCG administration (we call this BCG challenge), depending on the group into which you are enrolled. As explained below, the bronchoscopy is a routine medical procedure performed under light sedation whereby a thin flexible telescope is passed into the lungs to examine them and obtain samples. Most volunteers who have had a bronchoscopy as part of their study previously have said that based on their experience of having had a bronchoscopy, they would be willing to have another one.

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 and is not licensed as an aerosol, although it has been given as an aerosol in three previous trials in the 1960s and 70s, as well as in our group's trial (TB041) with no serious side effects. The TB041 study has recently finished and 31 people inhaled the BCG and completed 6 months of follow up with no safety concerns identified. The main purpose of this second study is to collect information about your body's immune response; however, we will also collect safety data about aerosol BCG challenge to supplement the information from the TB041 study.

Can I take part?

If you are aged between 18 and 50 years, live in or around Oxford, are in good health, have not had coronavirus disease (COVID-19) in the last 3 months and have not previously received BCG, you may be eligible to participate. People with respiratory conditions including asthma, a significant history of allergy or current smokers may not take part. You must be able to comply with all of the study requirements (including BCG challenge, blood tests, bronchoscopy and potentially sputum collection) and be able to attend all of the follow up visits. You must agree to be tested for SARS-CoV-2 - the virus that causes COVID-19 disease. Before you can enter the study, you will need to attend a screening visit where a full medical history and examination will be performed. Participation is voluntary and at the discretion of the investigators, and you are free to withdraw at any time. Women who are pregnant or who are trying to become pregnant should not take part in this study. Those with a history of allergy to vaccines may not be able to participate.

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 about two to two and a half hours. The screening visit, challenge visit, and all follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM). The bronchoscopy will be performed at the Oxford University Hospitals NHS 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 the consent form. You will be provided with a copy of the consent form for your records. You will be asked to agree 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 also be asked to agree to being registered on the confidential TOPS (The Over-Volunteering Prevention System) database, which is set up to prevent people entering into multiple studies or trials 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 also be recorded.

A number of blood tests will also 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 to see if you have been exposed to 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, offer referral for medical review and, with your permission, confirm the result and arrange treatment as necessary. You will also be asked to provide a urine sample to check for any problems and for women a pregnancy test will be performed.

We will arrange an x-ray of your chest to check for any abnormalities. A chest x-ray is a routine medical test that shows us the appearance of your airways and lungs. For those receiving any aerosol substances, we will measure your lung function to check that your lungs are healthy. 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. 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 these 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.

Please note, if you are required to undertake a test for COVID-19 infection as part of the study (see below), then we will need to notify all results to the relevant public health authority (see below).

How is the study going to work?

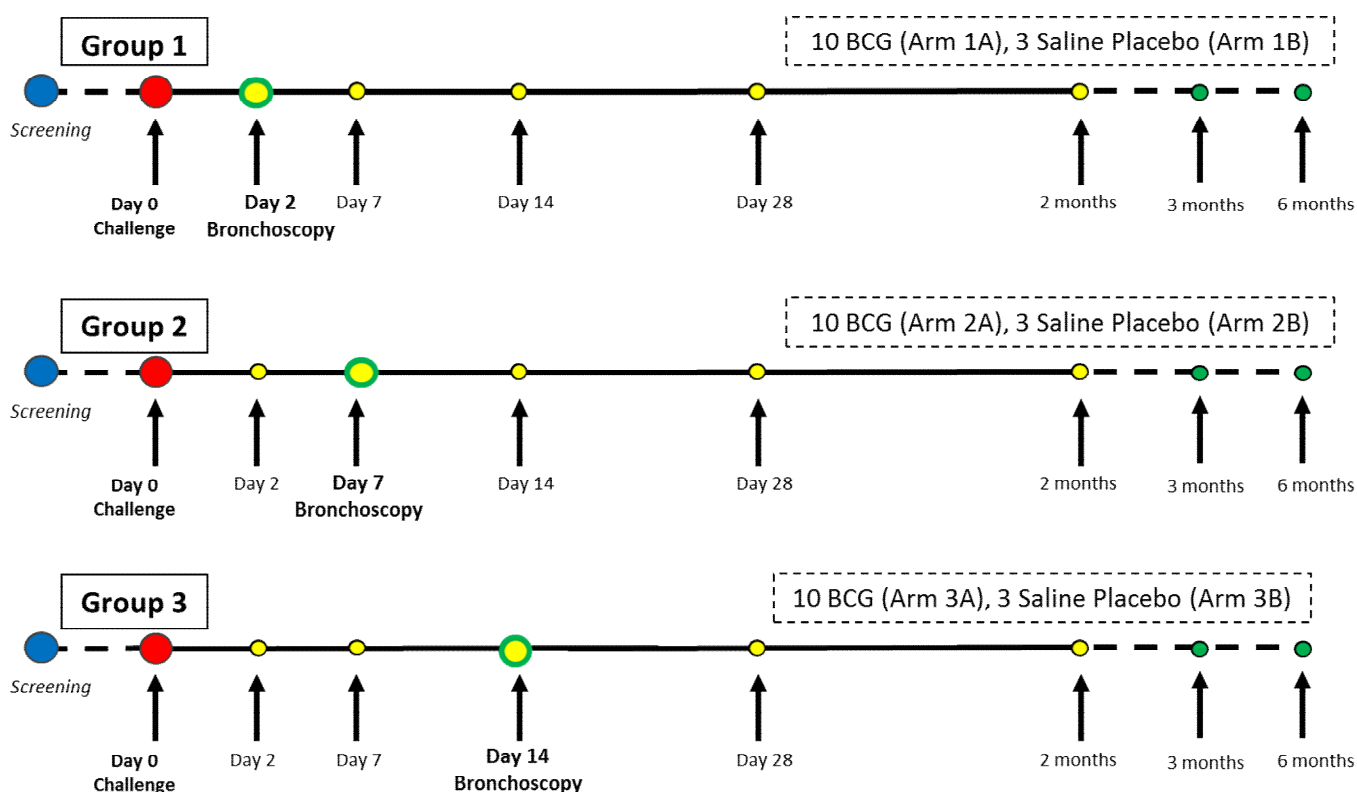
Overall, the study will recruit 81 people into seven groups. We are recruiting volunteers for groups 3, 4, 5 and 7 (see table 1 below). You may be able to choose which group you prefer to be in, depending on your schedule and availability of bronchoscopy and other visit slots. If you are assigned to group 3, 4 or 5, you will be randomly allocated to either inhale BCG (Arm A) or to inhale saline (Arm B). Saline is sterile salty water. You will not know which of these arms you are in – we call this blinding. In group 7, all volunteers will inhale BCG. Volunteers in group 7 will also be asked to wear specially adapted sample collection masks at certain time points (see below). If you feel uncomfortable with wearing a collection mask, you may be able to choose to be in an alternative group, again depending on scheduling availability. We can show you an example of the mask at your screening visit if you wish.

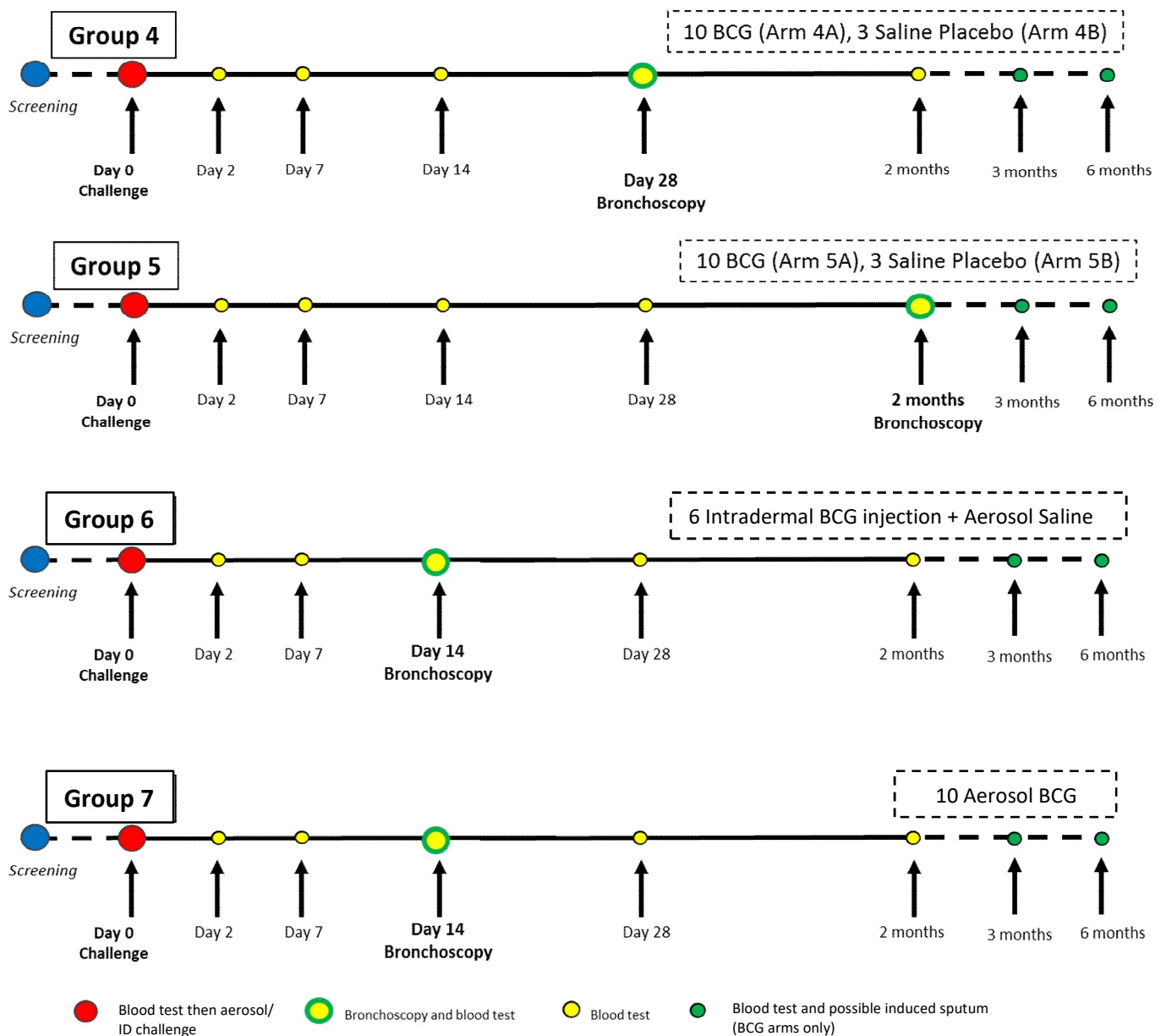
Group 1 volunteers will then have a bronchoscopy on Day 2 post challenge. Group 2 will have the bronchoscopy on Day 7 post challenge, Group 3, Group 6 (intradermal injection) and Group 7 on Day 14 post challenge, Group 4 at 1-month post challenge and Group 5 at 2-months post challenge (Table 1).

Table 1: Study Groups

Group	(Randomised) Intervention	Sample size
Group 1: Bronchoscopy Day 2 post challenge Fully enrolled	Arm 1A BCG: Aerosol inhaled BCG	10
	Arm 1B Control: Aerosol inhaled normal saline placebo	3
Group 2: Bronchoscopy Day 7 post challenge Fully enrolled	Arm 2A BCG: Aerosol inhaled BCG	10
	Arm 2B Control: Aerosol inhaled normal saline placebo	3
Group 3: Bronchoscopy Day 14 post challenge	Arm 3A BCG: Aerosol inhaled BCG	10
	Arm 3B Control: Aerosol inhaled normal saline placebo	3
Group 4: Bronchoscopy Day 28 post challenge	Arm 4A BCG: Aerosol inhaled BCG	10
	Arm 4B Control: Aerosol inhaled normal saline placebo	3
Group 5: Bronchoscopy Day 56 post challenge	Arm 5A BCG: Aerosol inhaled BCG	10
	Arm 5B Control: Aerosol inhaled normal saline placebo	3
Group 6: Bronchoscopy Day 14 post challenge Fully enrolled	Intradermal BCG Injection + aerosol saline	6
Group 7: : Bronchoscopy Day 14 post challenge	Aerosol Inhaled BCG	10

Figure 1: Trial Timeline**





COVID-19 testing will be performed at D0 minus 2 days and bronchoscopy minus 2 days during COVID-19 pandemic and may also be included prior to any induced sputum procedures if indicated

***Volunteers in groups 3, 6 and 7 may be asked to attend for an OPTIONAL extra follow up visit at 12 months*

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. 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/saline administration (Day 0 Challenge). You will know in advance what group you have been allocated to and what day your bronchoscopy will be. You will be asked a few questions to check there have been no changes since screening. Your temperature then blood pressure, pulse, and oxygen levels (observations) will be checked and blood samples taken.

Volunteers in group 7 will be asked to wear a specially adapted collection face mask prior to and just after the inhalation. This is to allow us to capture and analyse the droplets coming from your lungs. To do this you will be asked to wear the adapted face mask containing strips that capture droplets as you breathe out. You will be asked to do this for 30 minutes prior to and after receiving aerosol BCG. We think this could provide a simple way to detect tuberculosis bacteria and other lung infections in the future.

Depending on which group you are in, you will receive either intradermal BCG (together with aerosol saline) or an aerosol inhaled substance only. If you are in an aerosol only group, depending on which arm you are in you will be given either BCG or saline by aerosol inhalation, as indicated in the diagram above (Figure 1). Unless you are in Group 7 you will not know which of these two you have been given as they will look and taste the same.

The aerosol challenge (BCG or saline) 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. For those in the aerosol only groups, this will normally take place inside a specially adapted isolation tent. The intradermal BCG injection challenge is given as an injection just beneath the skin at the top of your arm.

After the BCG/saline challenge your observations will be checked and then you will be asked to wait in the out-patient area for one hour. Volunteers in group 7 will be asked to wear the specially adapted collection mask again for part of this time. After one hour, observations will be checked again. You will then be given a thermometer (to measure your temperature) and an e-diary 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. 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 the diagram above (Figure 1).

Follow up visits Day 2, Day 7, Day 14, Day 28, and 2 months:

On three of these visits you will come for a short check-up that will last around 30 minutes to ensure everything is fine, to check your symptoms, and have blood tests. On day 7, if you are in an aerosol only group we will also check your lung function again, so this visit will last around an hour. We may also need to check your lung function at other visits if needed, either due to previous results or any symptoms you might be having. On one of these visits you will also have a bronchoscopy (see below for details of that visit). For volunteers in group 7, we will ask you to wear the collection mask at your day 2, day 7, day 14 and day 28 visits.

Bronchoscopy visit:

Please note, during the COVID-19 pandemic you will be asked to attend 2 days prior to your planned bronchoscopy to have an additional test for COVID-19 infection. If the test is positive, your bronchoscopy will be postponed or cancelled and the relevant public health authorities will be informed (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 so you should plan to have the day off work. In the morning before the procedure, we will perform routine checks, take a blood sample, and go through any symptoms you have before starting. Volunteers in group 7 will be asked to wear the sample collection mask for 30 minutes during this time. A small plastic tube called a cannula will be inserted into your arm. The bronchoscopy will take place at the Oxford University Hospital NHS Foundation Trust, Oxford. Here, the respiratory consultant will discuss the procedure with you and ask you to sign a consent form. Your throat will be numbed with a local anaesthetic spray, which tastes bitter. If you wish, we can give you some medications via the cannula during the procedure to make you feel sleepy. 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 (this is a flexible telescope) will be passed through your mouth, down the back of your throat and into the windpipe. The lungs will be examined and digital images of your lungs and 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. A small pair of tweezers (called forceps) will also be passed down your airway on the end of a wire and a very small piece of tissue taken. This is called an endobronchial biopsy. We may also use other methods to collect samples, such as gently swabbing or brushing the airway. In total, the procedure 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 an hour. We will test your swallowing, remove the cannula, and check you are fine before we discharge you.

It is essential that somebody accompanies you home by car or taxi as you will not be allowed to travel by bus, to drive, or to depart alone if you have received any sedative medications. You should also not be alone overnight after your bronchoscopy, in case you feel unwell. For 24 hours after the bronchoscopy, if you received any sedation you should not drive, return to work, operate machinery, drink alcohol, sign legal documents or be responsible for small children.

If at the time of bronchoscopy you have already completed your first e-diary, because it is more than 14 days since the BCG challenge, (ie if you are in Group 3, 4, 5, 6 or 7) you will be asked to fill in a second 7 day e-diary to collect any symptoms following your bronchoscopy.

Follow up visits 3 months and 6 months:

There will be two further follow-up visits at 3 months and 6 months. We may need to repeat your lung function tests at these visits if indicated. Prior to or at your 3 month visit we will tell you if you are in Arm A (inhaled BCG) or if you are in Arm B (inhaled saline) if you were in an aerosol only group (with the exception of Group 7 who will already know they received BCG). For volunteers who received saline (Arm B) the 3 and 6-month visits will last around 30 minutes, during which time we will check your observations and take a blood sample.

For volunteers who received BCG (Arm A for inhaled groups 1-5, group 6 and group 7) these two visits may each last approximately 90 minutes as apart from checking your observations and taking a blood sample, 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 peak of the COVID-19 pandemic and if we restart we may require you to have an additional COVID-19 test prior to the procedure. Volunteers in group 7 will be asked to wear the collection mask during their 6 month visit.

Optional 12-month follow up visit (Group 6, Group 3 (BCG arm only) and Group 7)

After the last visit, study participation is complete. In total, most volunteers will spend about 24 weeks (6 months) enrolled in the study. Volunteers in group 6 and up to 10 volunteers in group 3 (BCG arm only) and group 7 will be asked if they would be available and willing to return for a follow up visit at 12 months. This visit is optional and you can still take part in the rest of the study without this visit. This optional visit will last around 30 minutes, in order to have blood tests looking to see how long some of the immune responses last following the BCG challenge.

What should I avoid during the study?

You should not donate blood during the study (6-month main study period only) 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 will decide 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, an intra-uterine device, or condoms) for the whole of the study (6-month main study period only). 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) or they exclusively engage in same sex intercourse. Even though no harmful effects of BCG vaccination on the foetus have been observed, there have not been studies to prove its safety. Pregnant women must not therefore take part in this study; neither should women who plan to become pregnant during the study. Women of child-bearing potential will be asked to have a pregnancy test before taking part, prior to receiving BCG and prior to bronchoscopy to exclude the possibility of pregnancy. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor. If you were to become pregnant, any baby born may need to be followed up.

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. During the course of the study we will need to take up to 66 ml of blood (approximately 4 tablespoons) at a single visit. The total amount we will take over the 6-month period of the study is 520ml, which is 50ml 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. Any side effects seen in our recently completed TB041 study were of short duration. Potential local side effects could include sore throat, 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. A doctor will be available throughout the BCG challenge and the clinic room is equipped with oxygen and medications to treat any other symptoms.

Intradermal injection with BCG

The most common side effects from intradermal injection are superficial discomfort at the injection site with swelling and redness that can last a few days. A small ulcer usually forms about a week later at the site of the injection. This usually heals over a few weeks to months and leaves a small flat scar. It is also possible to develop some swelling of glands in the armpit, but usually less than one centimetre across.

Uncommonly (happens to less than one in a hundred people) swelling of glands in the armpit of 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. Occasionally antibiotics may be required. Rare side effects (happens to less than one in a thousand people) include more severe inflammation of glands leading to abscesses.

As with a vaccination, following BCG challenge by either route, 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. Some of these side effects can mimic symptoms of COVID-19 disease. Detailed information about the steps we will take to deal with this can be found in “COVID-19 additional information” sheet.

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 07917 882967. 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 in a dedicated NHS bronchoscopy unit at the Oxford University Hospitals NHS Foundation Trust by a consultant respiratory physician, who will discuss the risks (described below) with you before the procedure.

The cannula 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 your oxygen levels and sometimes give you extra oxygen during the procedure to avoid this. As with all medicines, the local anaesthetic and sedatives can cause allergic reactions from mild to severe.

As a result of the sedative medication, it is very unlikely that you will remember the procedure itself. In fact, the majority of volunteers from a previous trial who provided feedback did not remember the procedure. The small volume of saline flushed into the lungs is safe and well tolerated. As we are taking a biopsy, a small amount of bleeding from the lung or airway will occur so your 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 may have a fever but this goes away without treatment. After any internal procedure like this, there is a risk of infection but this is minimised by taking fully sterile precautions throughout. 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 Consultant Radiologist and any abnormal findings will be appropriately followed up, with referral to appropriate specialists where required.

Lung function test

This is a very safe test, which sometimes causes a short period of lightheadedness 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 (BCG challenge volunteers only, not during peak of COVID-19 pandemic)

This is a simple and safe non-invasive procedure. The salty saline causes 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.

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, the inconvenience of having blood tests and procedures, and your travel expenses. The total amount compensated will be approximately £705-£795 depending on the exact number of visits, if you have longer visits to undertake lung function testing and collect sputum, whether any repeat or additional visits are necessary and whether you attend for an optional 12-month visit.

Study reimbursement will be made by bank transfer, usually within six to eight weeks of your completion of the 6 month main study period, so 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). Payment for the optional 12-month visit will be made separately after completion of this visit. 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 voluntary and you are free to withdraw at any time. 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. With your permission, we would like to store the samples already collected but if you did not want this, we would discard them. 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 arrangements in place to provide compensation for any harm arising from your participation in the study. NHS indemnity operates in respect of the clinical treatment that is provided. 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 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 should contact the Chief Investigator, Prof Helen McShane on 01865 617973 or helen.mcshane@ndm.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572221 or the head of CTRG via email: ctrig@admin.ox.ac.uk.

Would 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. It 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 and/or NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with 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. Some of the research being undertaken will also contribute to the fulfillment of a doctoral thesis. Study results will be published in a scientific journal but nothing that could identify you will be included in any report or publication.

We are required by law to share all COVID-19 test results and personal data (including your name, contact details, postcode) with Public Health England for referral to the NHS Test and Trace system.

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 safety blood tests on day 28 involve taking about 5 mL of blood to test for the levels of your blood cells as well as your kidney and liver function. The immunology blood tests 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 the BCG, and how it differs between the different groups. We will also do this analysis on the lung samples taken during bronchoscopy, and will look at lung, mask and sputum 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).

With your consent, some of your leftover samples will be stored and may be used for further studies concerning TB only. These will have ethical approval from an appropriate ethical committee. Samples will be stored indefinitely. Upon your request at any time, your remaining samples will be destroyed. Please note that if samples have already been used in research testing, they cannot be withdrawn and any resulting data will be retained. Your participation in this study will not be affected by your decision to allow or not to allow storage and future use of your leftover samples.

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 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, but no genetic tests concerning diseases or conditions other than TB will be done. 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 grants from The Wellcome Trust held by Prof Helen McShane. It 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: 18/SC/0307).

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: <http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx>.

During the COVID-19 pandemic, you will also be provided with a “COVID-19 additional information” sheet.

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 Prof 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 07917 882967: (24 hour emergency number). Alternatively, if your query is not urgent you can email vaccinetrials@ndm.ox.ac.uk.