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Group 8 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 or historically BCG-vaccinated, 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

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 other studies in our group, TB041 and TB044, 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.

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. 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 100 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 other studies (TB041 and TB044) and the earlier groups of this study (TB043) with no serious side effects. In our TB041 study, 31 people who had never received a BCG vaccine inhaled the BCG and completed 6 months of follow up with no safety concerns identified. Our TB044 study is ongoing and is the first study giving inhaled BCG to volunteers who have previously received a BCG vaccine, to determine the correct dose to use.

In the earlier groups (Groups 1-5 and 7) of this study (TB043), 63 volunteers who had never received a BCG vaccine inhaled the BCG. Follow up is ongoing but there have been no serious side effects or safety concerns so far. Group 8 of this study will give aerosol BCG to volunteers who have previously received the BCG vaccine. The main purpose of this study is to collect information about your body's immune response following aerosol BCG inhalation; however, we will also collect safety data about aerosol BCG challenge to supplement the information from our TB041 and TB044 studies. The dose of inhaled BCG we give to volunteers in Group 8 of this study will be determined by the results of our TB044 study.

Can I take part?

If you are aged between 18 and 50 years, live in or around Oxford, are in good health, and have previously received a BCG vaccination at least 12 months ago, 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 lung function tests) and be able to attend all of the follow up visits. You must agree to be tested for SARS-CoV-2 if required - 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. Those who are pregnant or who are trying to become pregnant should not take part in this study.

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, then we may need to notify results to the relevant public health authority (see below).

How is the study going to work?

Overall, this study will recruit 91 people into eight groups (Table 1). **We are currently recruiting volunteers for Group 8 only.** In Group 8, all volunteers will receive aerosol inhaled BCG (called a “challenge”) and undergo a bronchoscopy 14 days later (Figure 1).

	Group	(Randomised) Intervention	Sample size
No previous BCG vaccine	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 Fully enrolled	Arm 3A BCG: Aerosol inhaled BCG	10
		Arm 3B Control: Aerosol inhaled normal saline placebo	3
	Group 4: Bronchoscopy Day 28 post challenge Fully enrolled	Arm 4A BCG: Aerosol inhaled BCG	10
Arm 4B Control: Aerosol inhaled normal saline placebo		3	
Group 5: Bronchoscopy Day 56 post challenge Fully enrolled	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 Fully enrolled	Aerosol Inhaled BCG	10
Previous BCG vaccine	Group 8: Bronchoscopy Day 14 post aerosol challenge.	Aerosol Inhaled BCG	10

Table 1: Study Groups. Note we are currently recruiting into Group 8 only.

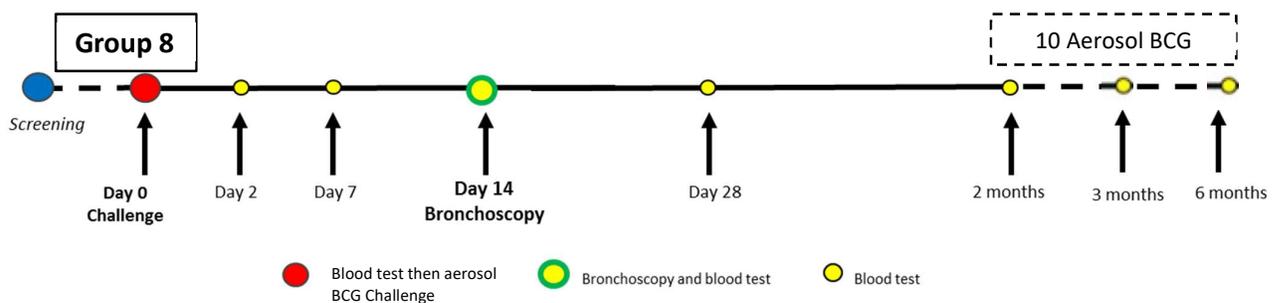


Figure 1: Trial Timeline for Group 8

Day 0 Challenge:

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 know in advance 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.

All volunteers in Group 8 will all inhale aerosol BCG. The aerosol BCG challenge 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 normally take place inside a specially adapted 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. 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 28, 2, 3 and 6 months:

On 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, we will also check your lung function again, so this visit will last up to 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.

Bronchoscopy visit D14:

In Group 8, local NHS guidelines regarding COVID testing prior to the bronchoscopy will be followed. At present this involves taking two lateral flow tests, one prior to the procedure and one on the day of the procedure. This may change in future and you will be provided with NHS information (and test kits if required) explaining what you need to do. The study team will also discuss this with you prior to the bronchoscopy. If the test is positive, your bronchoscopy may be postponed or cancelled. If this happens, we will discuss with you the options, which may include rescheduling the bronchoscopy, continuing the rest of the study without a bronchoscopy or withdrawal from the study.

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. 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 team 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 (termed 'light conscious sedation'). 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. 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 will be asked to fill in a second 7 day e-diary to collect any symptoms following your bronchoscopy.

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 will decide 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, an intra-uterine device, or condoms) for the whole of the study. Exceptions to this are allowed if you are truly abstinent from sex and this is in line with your preferred and usual lifestyle (periodic abstinence and withdrawal are not acceptable methods of contraception) or 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 people must not therefore take part in this study; neither should those who plan to become pregnant during the study. People 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. Anyone who finds that they have become pregnant while taking part in the study should immediately tell the 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

Volunteers in Group 8 are not required to undergo routine COVID testing as part of the study protocol, with the exception of any testing required by the NHS bronchoscopy site prior to the bronchoscopy.

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.

As with any 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 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 possible that you will not fully remember the procedure itself. The small volume of saline flushed into the lungs is safe and well tolerated. A small amount of bleeding from the lung or airway may 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 several days.

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.

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 up to £705. If any extra visits are necessary these will be additionally compensated.

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). 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 Research Governance, Ethics and Assurance Team (RGEA) office on 01865 616480 or the head of RGEA via email: ctrg@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 fulfilment 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 study COVID-19 PCR test results if applicable and personal data (including your name, contact details, postcode) with the UK Health Security Agency, while COVID-19 remains a notifiable disease.

What happens with my data?

The University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you 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 information from participants collected during the study initially for 5 years after the study has finished. Once the study has been completed, all documents would be archived in a secure facility. In addition, we will securely store the pseudo-anonymised research data and any research documents with personal information, such as consent forms, initially for 5 years after the end of the study. The need to store this information for longer, for example in relation to licensing of any vaccines, will be reviewed every 5 years. Files will be confidentially destroyed when storage is no longer required. For effective vaccines that may be licensed, secure storage of research data may be required for at least 15 years after the end of the study, subject to changes in clinical trials regulations. De-identified, archived data will be stored for 25 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 or destroyed. Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

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'.

Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information by contacting vaccinetrials@ndm.ox.ac.uk.

Site and Researcher

Oxford University Hospitals (OUH) will collect information from you for this research study in accordance with the University of Oxford's instructions. OUH and the University of Oxford will use your name, NHS number, and contact details to contact you about the research study, make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Your details and information collected from you may be shared between OUH and the University of Oxford in the course of this study. The only people in the University of Oxford who will have access to information that identifies you will be people who need to contact you regarding your participation in the trial or audit the data collection process. Individuals from the University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. OUH will keep identifiable information about you from this study in accordance with local NHS trust policies.

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 samples to see how much BCG can be found after challenge.

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>.

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.