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

Study Title: TB045: A clinical trial evaluating the safety of an aerosol BCG controlled human infection model in assessing the immunogenicity of historical BCG vaccination and vaccination with ID93/GLA-SE in healthy adult volunteers

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

Condition Studied	Research Study Length	Number of visits
		
Tuberculosis (TB)	Two to Six months	Seven to fourteen

What will the study involve?

- A screening visit (2-3 hours) to check you are healthy and can take part including a chest X-ray
- Vaccination with two doses of a novel TB vaccine (for some volunteers)
- Breathing in a weakened bacteria (BCG)
- Completing a symptom diary
- A bronchoscopy (looking into the airways with a small camera and takings samples)
- Up to 9 further visits with blood tests, and breathing tests to measure the function of your lungs

Could I be eligible to take part?

You must 

- Be aged 18-55 years old
- Be in good health
- Live in or around Oxford
- Know if you have, or have not had a BCG vaccine in the past

You must not 

- Be pregnant or breastfeeding
- Have any breathing problems e.g. asthma
- Be a current smoker, including vaping
- Have lived in a rural area of the tropics for more than 12 months

Why participate?

Information gained from this study may help in assessing how effective a new TB vaccine is.

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 side effects include short-lived headache, muscle pain, cough, sore throat, shortness of breath. These are described fully below.

There is absolutely no risk of contracting TB as a result of taking part in this study.

Dear Volunteer,

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

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

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

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

Contents

Part 1 – What Happens in This Study

1.1 What is the purpose of this study?

We are a tuberculosis (TB) vaccine research group working on developing vaccines that can be given either instead of or after BCG immunisation in the hope of providing greater protection against TB. TB is a disease caused by a bacteria (*Mycobacterium tuberculosis*). TB disease remains one of the top fifteen causes of death worldwide. BCG is the only vaccine currently licenced for use against TB, but it is not always protective.

The BCG vaccine works well against disease in childhood, but it is not good enough at protecting against disease in adulthood, which 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 vaccine alone.

Key Concept – What is BCG?

BCG stands for Baccilus Calmette-Guérin. It is a type of bacteria (baccilus = 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.

A new TB vaccine called ID93/GLA-SE has been developed and recently undergone clinical trials to show that it can be given safely to healthy people. The purpose of this study is to understand more about the body's immune response to this novel TB vaccine and provide some evidence about whether or not this vaccine is likely to work. It is important to understand this both in people who have been previously vaccinated with BCG and those who have never been vaccinated with BCG, so we are recruiting for volunteers that fit both descriptions.

To help understand more about the experimental vaccine this study uses a Controlled Human Infection approach or "Challenge". The purpose of this study is to see if a BCG Challenge can be done safely and whether the newly developed ID93/GLA-SE vaccine is able to prevent BCG "infection".

1.2 What is a 'Controlled Human Infection' (Challenge) Study?

It is difficult to develop new TB vaccines, as determining which ones will work well and which will not is not straightforward. In vaccine studies against other diseases, such as influenza and malaria, it is possible to experimentally infect volunteers in a controlled way with the disease in question to see if the vaccine being studied stops you getting infected. This is called a 'Controlled Human Infection' or "Challenge" study and is possible where the disease being studied is self-limiting or where safe, effective and short treatment regimens exist. Unfortunately, this is not the case with the bacteria which causes TB, which requires a minimum of 6 months of treatment with multiple medications. However, using a related but far less infectious bacteria is an alternative.

As such, we have developed a way of using the bacteria from the BCG vaccine in a Challenge study to test experimental TB vaccines. These bacteria will be introduced into the lungs of healthy volunteers by turning the BCG vaccine liquid into a very fine mist (aerosol) which can be breathed in (inhaled). We will use washings collected from the lung during a procedure called a bronchoscopy (see page 9) and blood tests to measure the mild BCG "infection" and the body's immune response to it.

What is an aerosol and how is it given?

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

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

Breathing in the aerosol of BCG in this study is not uncomfortable and takes about 5 minutes. During this procedure, you will be required to sit in a specially designed tent (See photo 1). This tent is designed to create negative pressure which minimises the exposure of BCG droplets to the environment during the procedure.

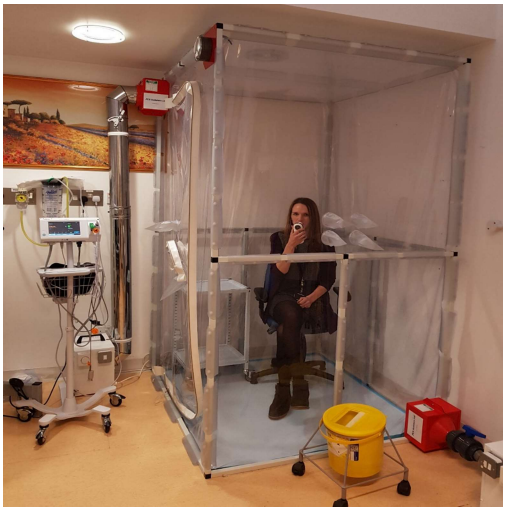

Photo 1. Volunteer inhaling aerosol BCG

1.3 Will everyone in this study get the experimental TB vaccine?

This study is split into different groups (see figure 1)- some groups will be given two doses of the novel TB vaccine (ID93/GLA-SE), while other groups will not receive any vaccines. There are no placebos ("dummy" doses) in this study. After we have received the results from your screening visit you will be randomly assigned into one of these groups (you will not be able to choose whether or not you have the novel TB vaccine).

Although not all volunteers in this study will have the novel vaccine, all volunteers will have an aerosol BCG Challenge. To understand how effective the new vaccine is at helping the body's immune system to "fight off" the BCG in the lungs, all volunteers will also have washings taken from their lungs in a procedure called a bronchoscopy. The bronchoscopy will take place 14 days after the BCG Challenge and is explained below.

We will then use the lung washings and the blood samples which we collect during the study to compare between the groups. This will help us understand how much the new vaccine helps in stopping the BCG infection

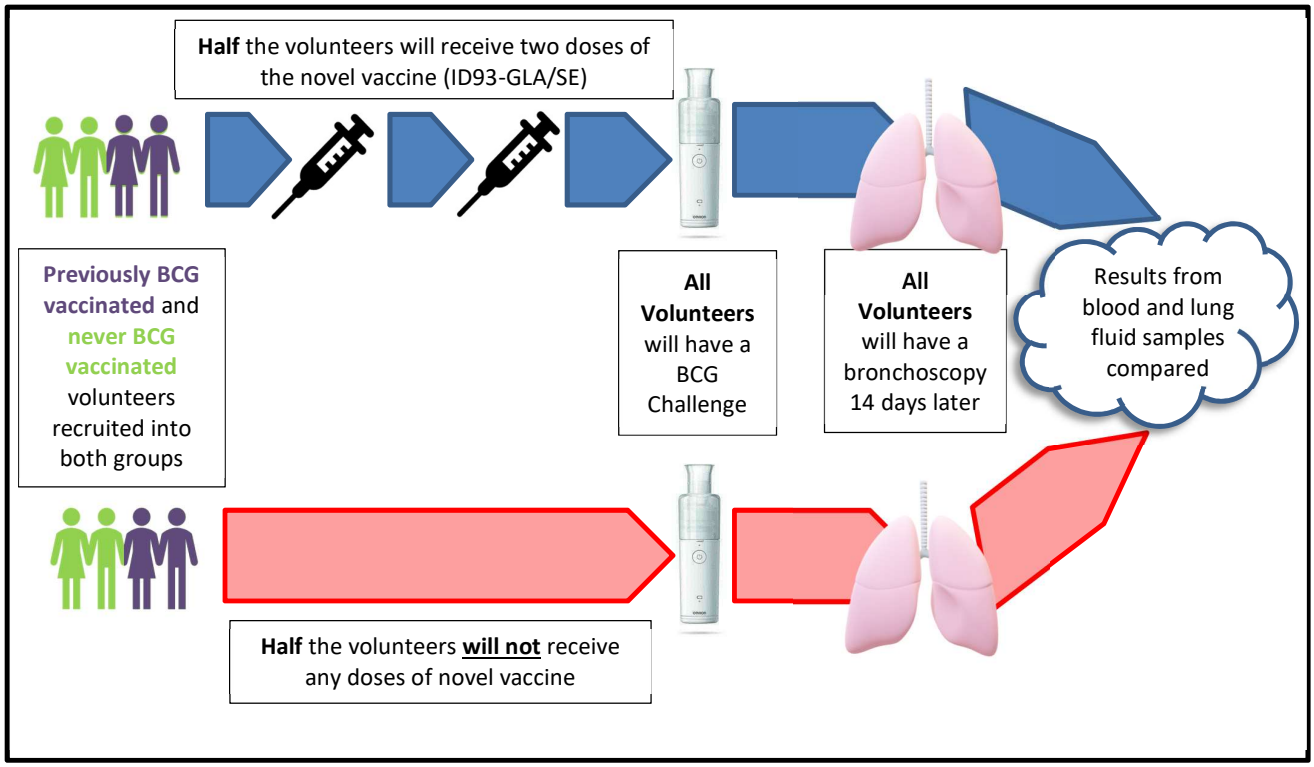

Figure 1. Diagram of the study plan – showing the main study procedures – vaccinations and aerosol BCG challenge

1.4 Can I take part?

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

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

- Be a healthy adult aged between 18 and 55 years with no significant findings in your medical history or identified during physical examination.
- Have EITHER:
    - received the BCG vaccine in the past, at least 12 months before enrolment in the study (with evidence; such as a visible scar or documentation in medical/occupational health records)

  OR
    - never received the BCG vaccine in the past and have no scar suggestive of previously having had BCG
- Live 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 (researchers) to discuss your medical history with your General Practitioner (GP) and/or to access your electronic medical records
- Allow the investigators to register you on The Over-volunteering Prevention System (TOPS), a confidential database set up to prevent people entering into multiple studies at the same time
- Refrain from blood donation during the course of the study
- Practice continuous effective contraception for the duration of the study (people of child bearing potential only)
- Be willing to be tested for evidence of SARS-CoV-2 infection and allow public health notification of the results if needed

- Be able and willing (in the investigator's opinion) to comply with all the study requirements including BCG Challenge, blood tests, lung function tests, and bronchoscopy and vaccination with the novel vaccine (ID93/GLA-SE)

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 a significant history of allergies or severe allergic reactions, including to vaccines or other medications including anaesthetics that are required during the study
- You have an allergy to the antibiotic Kanamycin or Kanamycin related antibiotics
- You have a significant history of heart problems, gut problems, liver, kidney, hormone gland, skin, bleeding problems or neurological diseases
- You have any significant problems with your immune system
- You have previously been diagnosed or treated for TB disease or latent TB infection, or any of these are found on your screening tests
- You have ever received an experimental TB vaccine or aerosol BCG
- You have hepatitis B, hepatitis C or HIV infection
- You are taking any tablet or inhaled steroid medication or other drugs working on your immune system, or have done so for more than 14 days in the past 6 months
- You have had immunoglobulins or any other blood products (such as blood transfusion) in the 3 months preceding your enrolment in this study
- You have a history of cancer (except basal cell carcinoma of the skin or carcinoma in situ of the cervix)
- 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 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 consecutive months in a rural area of a tropical climate (due to possible increased exposure to different types of bacteria that may affect the study results)
- You 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

1.5 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.

1.6 What will happen if I decide to take part?

If you decide you would like to take part in this study, you will need to attend a screening visit lasting two to three hours. You may also receive a pre-screening telephone call prior to booking or attending your screening visit. The screening visit, vaccinations and BCG Challenge visits and all follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM). The bronchoscopy will be performed at an NHS

bronchoscopy facility in the John Radcliffe Hospital site or in the EMCRF (Experimental Medicine Research Facility) on the Churchill Hospital site.

At the screening visit, you will be met by one of the investigators (researchers) 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 including looking for evidence of a previous BCG scar, heart, lungs, abdomen and glands. Your blood pressure, pulse, temperature and oxygen levels will be recorded. We will record your weight and height. You will also be asked to provide a urine sample to check for any problems and for people of child bearing potential a pregnancy test will be performed.

A number of blood tests will be carried out which include tests for anaemia, any blood clotting problems, to see how your liver and kidneys are functioning, to see if you have come into contact with TB without realising, and for HIV (the virus that leads to AIDS), Hepatitis B and Hepatitis C (viruses that affect the liver). In the event of you testing positive 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. Note, should your screening result for Hepatitis B or C be positive, the study team will arrange additional investigation. In the event that you are diagnosed with Acute Infective Hepatitis, this will be reported to the Health Protection Team (HPT) as a notifiable disease, required by law, without requirement for additional consent.

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. (see Photo 2)

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

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

1.7 When will you tell me which group I will be in?

If all your test results have been checked and there are no problems, we will randomly assign you a study group. We will contact you to let you know which group you have been assigned to and we will provide you with the dates for the study visits which you will need to attend. Randomly assigning you a study group helps make sure that basic characteristics of people in each group is similar. This means that we can be more confident that any difference which we get in the results are because of the novel vaccine rather than because there were differences in the volunteer's background.

1.8 What will happen at the different study visits?

All of the groups will be recruited at the same time, but the number of visits and time in the study is different for different groups. We plan to recruit 48 people into four groups (see Table 1). You will only enter one group. Figure 2 shows the number and timing of the visits for the different groups.

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

Group	Previously BCG Vaccinated	Total Study Length	Number of Visits	Number of novel TB Vaccine (ID93/GLA-SE) doses to be given	Number of Volunteers
A	Yes	6 months (168 days)	Up to 14	2 Doses total: Day 0 and Day 56	12
B	Yes	2 months (56 Days)	Up to 7	None	12
C	Never	6 months (168 days)	Up to 14	2 Doses total: Day 0 and Day 56	12
D	Never	2 months (56 Days)	Up to 7	None	12

Group A and C: Volunteers will receive two doses of ID93/GLA-SE 2 months apart, and then 2 months later receive a "Challenge" of aerosol BCG and 14 days later undergo a bronchoscopy

Group B and D: Volunteers will not be vaccinated but will receive a "Challenge" of aerosol BCG and 14 days later undergo a bronchoscopy

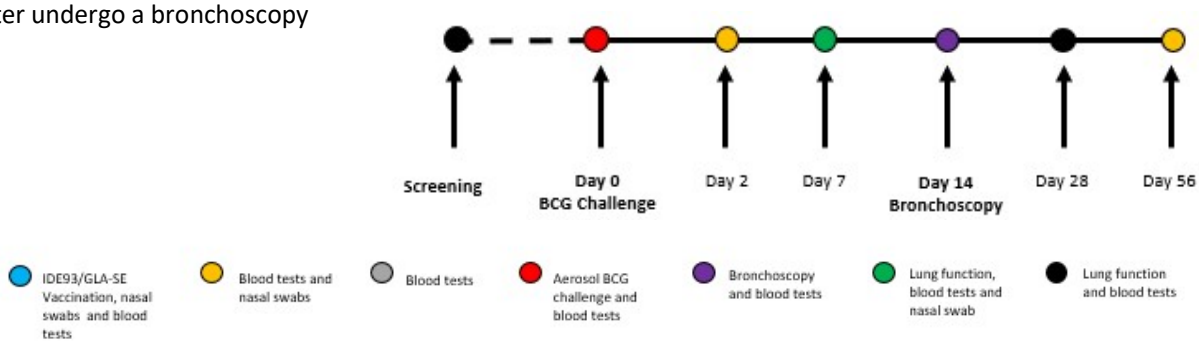

Figure 2. The timing of key visits for the different TB045 trial groups

Please note, you may be asked to take a lateral flow COVID-19 test prior to your planned Challenge. If the test is positive, you will not be enrolled at that time and enrolment will be postponed for at least 7 days.

ID93/GLA-SE vaccination visits (Group A and C only)

If you are in the groups A or C receiving the novel vaccine (ID93/GLA-SE), on the day of your vaccination 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 person of child bearing potential, a urinary pregnancy test will also be performed. You will then be given the vaccine into your arm.

After the vaccination your observations will be checked and then you will be asked to wait in our unit for one hour. After one hour, observations will be checked again and you will then be given a thermometer (to measure your temperature) and an electronic symptom diary (eDiary) account. You will be required to record thermometer readings for the next 7 days, 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).

There will be a second vaccination given approximately 2 months later where we will go through the same process again.

ID93/GLA-SE follow-up visits (Group A and C only)

These visits happen 14 days and 28 days after each vaccination and will last 30-45 minutes. In addition to a short check-up of any symptoms we will take blood tests and nose swabs.

Aerosol BCG Challenge (all groups)

You will be asked to visit in the morning on the day of the BCG "Challenge". If you are in groups B or D this is the day of your enrolment. You will be asked a few questions to check there have been no changes since screening. Your observations will be checked and blood samples taken. If you are a person of child bearing potential, a urinary pregnancy test will also be performed.

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

After the BCG Challenge your observations will be checked and then you will be asked to wait in our unit for 60 minutes. After this, observations will be checked again and your lung function may be measured. You will then be given a thermometer (to measure your temperature) and an eDiary account for you to record these readings and your symptoms over the next 21 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 one and a half to two hours.

Bronchoscopy visit (14 days after BCG Challenge)

On the day of your allocated bronchoscopy visit, you will not be able to eat or drink from midnight before the procedure. For this procedure, you will need to be with us for several hours and you should plan to have the day off from work. In the morning, before the procedure, we will perform routine checks and go through any symptoms you have. 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 people of childbearing potential.

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

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

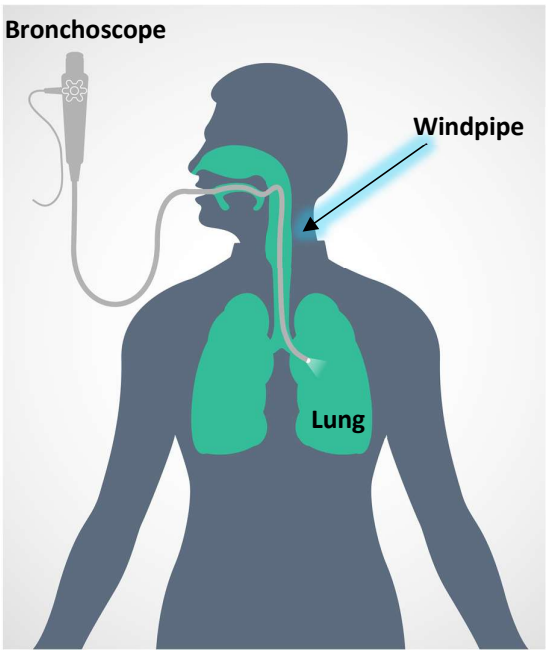

Figure 3. A diagram of bronchoscopy showing how the bronchoscopy camera is inserted into mouth and through the windpipe into the lung where the washings are taken.

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 your workplace, operate machinery, drink alcohol, sign legal documents or be responsible for small children.

Other follow up visits after the BCG Challenge

These visits will last 30-45 minutes. In addition to a short check-up and blood tests at each visit,your lung function tests will be completed 7 and 28 days after your BCG Challenge, and these may be repeated at other follow up visits if we think it is needed.

After the BCG Challenge, you will remain in study follow-up for approximately 2 months.

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

Participation in the study is entirely voluntary and you have the right to withdraw at any time. Additionally, volunteers may rarely be withdrawn from the study, or the study discontinued, at the discretion of the Investigator, sponsor or regulatory bodies. This may be due to:

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

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

1.10 What should I avoid during the study?

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

People of child bearing potential should use an effective contraceptive method (such as the oral contraceptive pill, a contraceptive hormonal implant or injection, an intra-uterine device, an occlusive cap with spermicide or condoms) for the whole of the study. Exceptions to this are allowed if the person of childbearing potential is truly abstinent from sex and this is in line with their preferred and usual lifestyle (periodic abstinence and withdrawal are not acceptable methods of contraception), they exclusively engage in same sex intercourse or if their sole partner has undergone a vasectomy. Even though no harmful effects of aerosol BCG on the foetus have been observed, there have not been studies to prove its safety. The novel vaccine (ID93/GLA-SE) has not been given to pregnant people and although we have no reason to believe that it poses a risk, there are no studies to prove this. Pregnant volunteers, those who are planning to become pregnant during the study and those who are breastfeeding must not take part in this study. Volunteers who are of childbearing potential will be asked to have a urinary pregnancy test at screening, prior to each ID93/GLA-SE vaccination, prior to receiving the BCG Challenge and prior to the bronchoscopy.

Any volunteer who becomes pregnant during the study should immediately tell their research doctor. If you were to become pregnant we would, with your consent, follow you up until the pregnancy outcome is clear. Any baby born may also need to be followed up. We would not routinely take blood from a pregnant volunteer unless there is clinical need.

1.11 Is the aerosol BCG Challenge and the novel vaccine (ID93/GLA-SE) safe?

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

The novel vaccine (ID93/GLA-SE) has been developed in collaboration with the University of Seattle, USA. It has been tested to find a safe dose and ensure that there were no significant side effects in seven trials in the USA and South Africa. There were no serious side effects seen in these studies, and the mild symptoms

experienced by some people are explained below. We will however continue to collect information from volunteers in this study about any symptoms that they experience after having the vaccination.

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

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

ID93/GLA-SE Vaccination

The novel vaccine (ID-93/GLA-SE) is a protein vaccine, this means it does not contain any live bacteria. However, like all vaccinations it is common to experience some mild symptoms after being given the vaccine. In the 7 studies which have been completed to date on humans, the most common symptoms which people have experienced are pain at the site of the vaccination, flu-like symptoms, headache and tiredness. These generally improved within 48 hours. There were no serious or life-threatening symptoms in any of these studies. Other common generalised symptoms expected with vaccination are low grade fever, nausea, reduced appetite and muscle and joint pains. At the site of the injection some people noticed swelling, redness, itching, bruising and swelling of local glands (lymph nodes).

Aerosol BCG Challenge

Inhalation is a safe route for giving medicines. All the side effects seen in our previous studies (TB041, TB043 and TB044) were non-serious and of short duration. Potential local side effects include a sore or tickly throat, shortness of breath, wheezing, chest pain, chest tightness, and a dry cough or cough with phlegm. Side effects could occur within the first few days of the aerosol BCG Challenge but can also occur 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 general symptoms such as headache, tiredness, muscle aches and pains, nausea, feverishness or a low-grade fever. If they occur, these symptoms usually resolve within 48 hours following BCG Challenge.

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

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 an experienced respiratory doctor. The specific risks of the procedure will be discussed with you beforehand by the respiratory team. These include post-procedure flu-like symptoms for 1-2 days, hypoxia (low oxygen levels), air leak (called a pneumothorax) requiring insertion of a special tube into the chest (less than 0.1%), low blood pressure, abnormal heart rhythm (less than 0.1%), and risk of death (less than 0.02%). These figures quoted are for all people undergoing bronchoscopy for any medical indication and it is likely that the risk for young, healthy volunteers is even lower. However, risk cannot be completely removed in any invasive procedure.

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

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. A small amount of bleeding from the airway may occur so your 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 the 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.

The cannula inserted before your bronchoscopy is similar to a blood test so can cause slight discomfort during the procedure, and minor bruising can occur. Very occasionally the cannula may need adjustments if placed incorrectly, or the administered medication may leak from the cannula into the surrounding tissue. However, cannulas are only placed by healthcare members who are experienced and will be monitored throughout the time they are inserted.

Chest X-ray

If you take part in this study you will have a chest X-ray. This will be in addition to those that you would have if you did not take part in the trial. This procedure uses ionising radiation to form images of your body and/or provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime, and the normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of cancer by about 0.0001%.
All chest x-rays will be reported by an NHS radiologist and any abnormal findings will be appropriately followed up, with referral to appropriate specialists where required, and with your permission.

Blood samples

Taking blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. Very rarely, blood taking can cause soft tissue infection to develop. At each visit during the course of the study, we will need to take up to a maximum of 73.5 ml of blood. However, at your screening visit, we will take around 20ml of blood. The total amount of blood we will take over the study will depend upon which group you are assigned to, and could be as high as 812.5ml. This total volume of blood is about the volume you could safely donate in 2 blood donations over a 6-month period. As we are taking this amount of blood for the study, you should not donate blood while you are participating in this study, or take part in any other studies where you give blood.

Lung function test

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

Nose or Throat Swabs

These are not painful but can be uncomfortable. Swabbing the back of the throat can cause individuals to cough or gag. Nose swabs can make your eyes water or rarely cause nose bleeding.

Allergic Reactions

As with any experimental procedures, medications, vaccines (including BCG and ID93 GLA/SE) or the products used to make them, there is a possibility of some completely unexpected side effects or allergic reactions. While extremely rare (<1/1000 people), serious allergic reactions including anaphylaxis may occur even if you have had the item before. 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 on 07990 431010. A qualified study doctor from the CCVTM is available at all times on this number.

1.13 What are the possible benefits 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.

1.14 Will my General Practitioner/family doctor (GP) be informed of my participation?

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

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.*

1.15 Will I be reimbursed for taking part?

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

- People in groups A and C will receive approximately **£1465**.
- People in groups B and D will receive approximately **£795.**

If you are required to have any repeat or extra visits then you will be compensated proportionately 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, you will receive a proportion of the total amount based upon the parts of the study you have completed.

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

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

Part 2 – How the Study is Conducted

2.1 What if new information becomes available?

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

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

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 or follow-up symptoms that you were having. With your permission, we would like to store the samples already collected but if you did not want this, we would discard them. Please note that if samples have already been used in research testing, they cannot be withdrawn and any resulting data will be retained. If you choose to withdraw from the study, your standard medical care will not be affected.

2.3 What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your 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 and procedures, undertaken as part of the study and if you needed to be admitted to hospital. At any time during the study, you will be entirely free to change your mind about taking part, and to withdraw from the study. This will not affect your subsequent medical care in any way. The 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 your X-rays or bronchoscopy. PALS is unable to provide information about this research study. If you wish to contact the PALS team please call 01865 235855 (Churchill Hospital), 01865 221473 (John Radcliffe Hospital), or by email at PALS@ouh.nhs.uk

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

2.4 What tests will be done on my samples?

The blood tests which we will perform at the screening visit have already been described in Part 1. At screening and at various points in the study we will take about 5ml of blood to test for the levels of your blood cells as well as your kidney and liver function. These are taken to monitor how different organs are responding.

The immunology blood tests (up to 62.5 ml of blood at each visit) that will be done throughout the study will look at your body's response. If you are in a group which receives the novel TB vaccine (groups A and C), we will look to see if the vaccine has triggered any response from the body's immune system. After the BCG Challenge we will look to see if there has been a response of the immune system to the BCG bacteria, and measure how it differs compared to the volunteers who didn't have the novel vaccine.

We will collect swabs from your nose on certain visits. This will allow us to measure changes in the immune responses of the nose which may be important in acting as the first line of defence in protecting people from TB infection.

We will use the samples from the bronchoscopy to attempt to grow the BCG which was given to you on the day of the BCG Challenge. We look for a difference in the amount of BCG that is present in these samples between groups that received the novel vaccine and those that did not, to give an indication of how well the novel TB vaccine protects people. Some samples may be shipped to collaborating organisations outside of the University of Oxford, such as in the US for analysis. Where samples are shipped to collaborators for analysis, labelling will be pseudonymised (your study ID number will be used such that the samples cannot be attributed to you, or linked to your personal data without the use of additional information) and collaborator teams will not have access to personal data.

Prior to BCG Challenge and bronchoscopy, tests may be taken to look for SARS-CoV-2 RNA (the genetic material of the virus that causes COVID-19 disease) or antigens (proteins) if felt to be relevant by the study team.

2.5 What will happen to leftover samples?

If you consent, your leftover samples may be stored indefinitely at the Oxford Vaccine Centre Biobank and may be used for further related research, including research into TB, 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.

2.6 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 BCG Challenge, vaccines or in protecting against TB. We will only look at specific areas of interest, not your whole set of genes. We will not perform analysis called whole genome sequencing on fresh or stored biospecimens. Samples will be tested in anonymised form; however, your DNA is unique to you so it can never be completely anonymous.

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

All information that is collected about you during the course of the study will be kept strictly confidential. Blood tests will be sent under a pseudonymised 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. Pseudonymised data, including safety data, may be shared with the funder and this will be outside of the UK and European Economic Area.

You have the option to consent to having your contact details stored by the Jenner Institute so that you can be made aware of future vaccine related research opportunities. These will be stored on a secure server, and will not be shared with any other institutions. You are free to ask us to remove these details from out database at any time.

2.8 What will happen to my data?

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

The University of Oxford will keep identifiable personal information about you for 5 years after the study has finished. We may store any research documents with some personal information, such as consent forms, securely at the University of Oxford for at least 25 years after the end of the study, as part of the research

record. However, such personal information will be limited only to the minimum necessary. The need to store study data will be reviewed every 5 years.

If you agree to your samples being used in future research, your consent form will be held securely until the samples have been used up. Files will be confidentially destroyed when storage is no longer required.
Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

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

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

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

2.9 Who is organising and funding the research?
This study is funded by 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.

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

Use of the novel vaccine (ID93/GLA-SE) used in this study has also been looked at by the Medicines and Healthcare products Regulatory Agency (MHRA). This agency is responsible for giving permission for experimental medicines and vaccines to be used in clinical trials. The use of this vaccine was reviewed and given a favourable opinion by _____ (ref xxxxx).

2.11 What will happen to the results of the research study?
The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until one or two years after the study is completed. A summary of published reports will be sent to any trial participants, if requested, for their information and interest. 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.

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

Volunteer Recruitment Coordinator
Centre for Clinical Vaccinology & Tropical Medicine

Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Telephone: 01865 611424
Email: vaccinetrials@ndm.ox.ac.uk

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