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Investigating a Vaccine Against Plague (PlaVac)

A phase I study to assess the safety and immunogenicity of a recombinant adenovirus-based vaccine against Plague

IMPORTANT: If you develop a fever or cough, shortness of breath or loss of sense of smell or taste or become unwell then you must contact the trial team on 01865 611400 for advice before attending any visit.

You are invited to take part in a clinical trial to test a vaccine against Plague. Plague is an extremely severe and highly contagious infectious disease which is re-emerging in some parts of the world. The clinical trial is being run by the Oxford Vaccine Group which is part of the University of Oxford.

Before you decide whether to take part, it is important for you to understand why the research is being done and what it would involve for you. Please take time to read the information carefully and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please contact the trial team (details below).

Thank you for taking the time to consider taking part in the trial.

Contact details:

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Contents

GENERAL OVERVIEW

Who are the Oxford Vaccine Group?

The Oxford Vaccine Group (OVG), which is part of the **University of Oxford**, is an independent research team of doctors, nurses and play assistants. We carry out research on topics related to infectious diseases and vaccines for babies, young children, teenagers and adults. In the past 5 years alone, around 7,000 participants in the Thames Valley area have taken part in our research studies.

Why have I been invited?

We are looking to recruit healthy male and female volunteers who are between 18 - 55 years of age and live in the Thames Valley or surrounding area. We use various ways to contact anyone who may be interested in this trial, including via the Electoral Roll or by requesting a data extract from NHS patient databases. In the case of NHS databases we will only request identification of persons on the basis of postcode and appropriate age range. This information is shared with CFH Docmail a UK mailing specialist (who have been assessed under the NHS Data Security and Protection Toolkit) solely for the purpose of arranging for the invitations to be sent.

What is Plague?

Plague is a disease caused by infection with *Yersinia pestis,* which is a type of bacteria. In humans, this infection can cause high fevers, swollen lymph nodes, shortness of breath, coughing up blood, bloodstream infection and, if left untreated, death. It is spread by the bite of an infected flea, handling an animal infected with Plague or from inhaling respiratory droplets from an infected person. There are 3 different forms of Plague infection; bubonic, pneumonic and septicaemic. Bubonic Plague is characterised by swollen and painful lymph nodes, near to where the bacteria entered through the skin. Pneumonic Plague is where the bacteria is breathed into the lungs and results in shortness of breath, fever and coughing up blood. If Pneumonic Plague is not treated with antibiotics within 24 hours there is almost 100% chance of death. Both Bubonic and Pneumonic Plague can develop into Septicaemic Plague, which is a life-threatening infection of the blood.

Since the 1990s, the number of human Plague cases has increased in 25 countries; from 2010 to 2015, there were 3248 cases of human Plague reported worldwide, including 584 deaths. It is found across the world, but the biggest burden is in very remote and poor parts of Africa and Asia. Plague can be treated effectively with antibiotics, if treated early, however this is often not possible in rural areas, where a vaccine would be much more effective. Currently, the only method for controlling Plague outbreaks is the reactive use of antibiotics. Therefore, what is needed is an effective vaccine to protect against this disease.

What is the purpose of the clinical trial?

In this clinical trial we are investigating a vaccine against Plague. Plague can be treated effectively with antibiotics if treated early. However, early treatment is often not possible in rural areas, therefore what is needed is an effective vaccine to protect against this disease. The University of Oxford have developed an intramuscular Plague vaccine. This clinical trial is being conducted to assess the safety of the vaccine and how well it stimulates the immune system to protect against Plague.

What vaccine is given in the clinical trial?

The vaccine we are testing in this research trial is called ChAdOx1 Plague.

Until now, this ChAdOx1 Plague vaccine has only been tested on laboratory mice and other animal species and this is the first time that the vaccine will be given to humans.

ChAdOx1 Plague is made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) from chimpanzees that has been genetically changed so that it is impossible for it to multiply in humans. To this virus we have added genes that make proteins from the Plague bacterium (*Yersinia pestis)* called F1 and V antigens, which play an essential role in the infection pathway of the Plague bacterium. By vaccinating with ChAdOx1 Plague, we are hoping to make the body recognise and develop an immune response to these Plague proteins that will help stop the Plague bacteria from entering human cells and therefore prevent infection. This vaccine does not contain plague bacterium and cannot therefore cause plague following vaccination.

Vaccines made from the ChAdOx1 virus have been given to more than 50,000 people to date, and have been shown to be safe and well tolerated, although they can cause temporary side effects which are explained below (see section What effects or risks can I expect from this clinical trial?)

We will give you an injection with the vaccine into the muscle at the top of the arm; this is the most commonly used route for vaccination. A number of participants will have a boost vaccine with the same dose – this could be either two or six months after the first dose.

Manufacture of vaccines and clinical trials are regulated and subject to approval by a government body called the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA have strict standards for manufacturing vaccines and subsequent testing, to ensure safety. We are conducting this trial with approval from the MHRA, having satisfied the necessary safety standards.

Who can take part in the clinical trial?

We are looking to recruit volunteers who are in good health and aged between 18 to 55 years. You would need to be willing and able to attend all the visits and agree to your GP being informed of your participation. We would confirm that you were able to take part by reviewing your medical history, either by using electronic records or by discussing with your GP.

You would be unable to participate in the clinical trial if you:

- Have any significant medical conditions (including significant psychiatric illness requiring hospitalisation), a history of alcohol or drug abuse, are pregnant or planning on becoming pregnant, or are breastfeeding you may not be able to participate.
- Weigh less than 50 kg
- Have any scheduled procedures requiring general anaesthesia during the period of the trial
- Have any impairment of your immune function
- Have had a severe allergic reaction to a vaccine
- Have donated blood within the last 3 (male) or 4 (female) months or plan on donating blood within the next year
- Have previous occurrence of disease caused by *Yersinia pestis* or received a vaccine against Plague
- Are currently in another interventional trial

We would also like to know if you are expecting to receive any other vaccines during the trial period as this may affect if you are able to participate in the trial.

If you are unsure whether or not you will be eligible for the trial, you can speak to a member of our team using the contact details at the end of this information booklet.

Do I have to take part?

No. We are looking for volunteers. Should you volunteer and later change your mind (for whatever reason) it is your right to do so, and you would not need to provide an explanation to the trial team or anyone else.

If you change your mind and withdraw during the trial, we would use the samples and data we have collected from you in our analysis of the research as detailed in this participant information sheet, up until the point you informed us that you wanted to withdraw.

Whatever you choose, it is important that you are happy with your decision and it is not the role of the trial team to decide for you. We would help present the details of the clinical trial and answer all your questions so you could make an informed decision.

Overview of clinical trial

This trial is being conducted to evaluate the safety of the vaccine, to understand how well it is tolerated by those who receive it, and to determine how well it stimulates the immune system to protect against Plague. We are aiming to recruit up to 45 participants

If enrolled, you will be allocated to one of three groups as described below, according to order of recruitment and based on your availability.

Since this is the first time this Plague vaccine is being given to people, throughout the trial we have an independent Data and Safety Monitoring Committee to decide if there are any concerns with the vaccine at any given dose or time. Recruitment to Group 2 and 3 will commence following a successful safety report from the first participants in Group 1. The dose of the vaccine will be changed if it is not well tolerated and if there are any concerns the monitoring committee will stop or pause the trial.

Group 1: This group will consist of up to 15 individuals who will receive a single injected dose of ChAdOx1 Plague vaccine

Group 2: This group will consist of up to 15 individuals, who will receive an injected dose of ChAdOx1 Plague vaccine followed by a boost of the same dose, 2 months later

Group 3: This group will consist of up to 15 individuals who will receive an injected dose of ChAdOx1 Plague vaccine, followed by a boost of the same dose, 6 months later

Overview of clinical trial visits

The trial would involve 11 visits for Group 1 and 14 visits for Groups 2 and 3. Visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at the Churchill Hospital site, Oxford.

For detailed information, please see the following tables.

Group 1 visit schedule

Group 1 participants would be asked to attend 11 visits. An initial screening visit, followed by one vaccination visit and nine follow-up visits. See below table for details of the visit timings.

Visit Name	Screening (V0)	V1	V2	V3	V4	V5	V6	V 10	V 11	V 15	V 16
Visit number for participant	1	2	3	4	5	6	7	8	9	10	11
Indicative Study Day		**1**	**2**	**7**	**14**	**28**	**56**	**84**	**182**	**210**	**250 - 365**
Day post last vaccine		0	1	7	14	28	56	84	182	210	250 - 365
Visit Window (days)		N/A	0	+/- 1	+/- 2	+/- 4	+/- 4	+/- 4	+/- 14	+/-14	0
Informed consent	x										
Biobank consent		x									
Confirmation of consent		x	x	x	x	x	x	x	x	x	x
Obtain 24 hr contact details		x									
Medical history (including demographics and medication)	x										
Interim medical history (including concurrent medication, AEs)		x	x	x	x	x	x	x	x	x	x
Physical examination	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x									
Urine sample	x										
Blood sample	x	x		x	x	x	x	x	x	x	x
Mucosal sample		x		x	x	x	x	x	x	x	x
Vaccination		x									
eDiary entries		x	x	x							
Intervention arm allocation		x									

Groups 2 visit schedule

Group 2 participants would be asked to attend 14 visits. An initial screening visit, two vaccination visits (second vaccine at two months after the first) and eleven follow-up visits. See below table for details of the visit timings.

Visit Name	Screening (V0)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V15	V16
Visit number for participant	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Indicative Study Day		**1**	**2**	**7**	**14**	**28**	**56**	**57**	**63**	**70**	**84**	**182**	**210**	**250 - 365**
Day post last vaccine		0	1	7	14	28	56	1	7	14	28	126	154	194 - 309
Visit Window (days)		N/A	0	+/- 1	+ 7	+/- 4	+/- 4	0	+/- 1	+7	+/- 4	+/- 14	+/-14	0
Informed consent	x													
Biobank consent		x												

Confirmation of consent		x	x	x	x	x	x	x	x	x	x	x	x	x
Vaccination			x					x						
eDiary entries		x	x	x			x	x	x					
Interim medical history (including concurrent medication, AEs)		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x													
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x					x							
Urine sample	x													
Blood sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mucosal sample		x	x	x	x	x	x	x	x	x	x	x	x	x

Group 3 visit schedule

Group 3 participants would be asked to attend 14 visits. An initial screening visit, two vaccination visits (second vaccine at six months after the first) and eleven follow-up visits. See below table for details of the visit timings.

Visit Name	Screening (V0)	V1	V2	V3	V4	V5	V6	V 10	V 11	V 12	V 13	V 14	V 15	V 16
Visit number for participant	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Indicative Study Day		1	2	7	14	28	56	84	182	183	189	196	210	250 - 365
Day post last vaccine		0	1	7	14	28	56	84	0	1	7	14	28	194 - 309
Visit Window (days)		N/A	0	+/- 1	+ 7	+/- 4	+/- 4	+/- 4	+/- 14	0	+/- 1	+7	+/- 4	0
Informed consent	x													
Biobank consent		x												
Confirmation of consent		x	x	x	x	x	x	x	x	x	x	x	x	x
Obtain 24 hr contact details		x												
Medical history (including demographics and medication)	x													
Interim medical history (including concurrent medication, AEs)		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x													
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x							x					
Urine sample	x													
Blood sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mucosal sample		x	x	x	x	x	x	x	x	x	x	x	x	x
Vaccination		x							x					
eDiary entries		x	x	x					x	x	x			
Intervention arm allocation		x												

CLINICAL TRIAL PROCEDURES

Recruitment

If you are interested in taking part in the trial, please complete the website screening form on our website https://trials.ovg.ox.ac.uk/trials/plague . This has three parts and should take about ten minutes to complete. The first contains some short questions to see if you are suitable to be screened by our clinical team. If, based on your responses, you are found to be not suitable to volunteer for the study, no data is stored about you, and you would not be invited to take part in the trial.

If your responses indicate that you may be suitable to volunteer for the study, the second part of the website form will then ask for your consent to collect your personal details and medical information. This allows us to record your contact details and things about you like your age and whether you have any medical conditions or take any medication. If there are no reasons why you could not take part identified on the online questionnaire, a member of the Oxford Vaccine Group will contact you by telephone to discuss the trial, your suitability, and answer any questions you may have. Following this, if you are interested and seem suitable for the trial then we would arrange for you to come to our clinic at CCVTM for an in-person screening visit. We would also ask for your consent to contact your GP surgery to obtain any relevant medical and immunisation history that may affect your participation in the trial. If you complete the telephone screening and/or online screening only, and do not progress to in-person screening, your data will not be kept beyond the end of the trial.

Screening visit

The purpose of screening is to assess whether you are able to participate in the trial.

The screening visit takes about 90 minutes. You will first be asked to watch a presentation about the study, and then have an opportunity for you to ask any further questions you might have about the trial and what is involved. You would be allowed as much time as you feel necessary before making any decision on whether to take part. If you wished to proceed, we would ask you to sign an informed consent form. Only once this is signed would we then start any trial procedures.

We would ask you questions about your health, vaccination history, undertake a physical examination and take a urine sample and a blood sample to ensure you are healthy. We would also perform an ECG – this involves attaching sticky pads for a few minutes to your chest to take a recording of the electrical activity of the heart, and is not painful.

Blood would be screened for general health (to check your blood count, kidney and liver function), HIV, hepatitis B and C. For all females, we would perform a pregnancy test on your urine sample.

It may be necessary to repeat a blood or urine test to be sure you are healthy before you can receive the vaccine. The trial team would also ask about your availability for planned visit dates.

During your screening you would be asked to provide your National Insurance number (or passport number if you do not have a National Insurance number). This would be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. The Trial Over-volunteering Prevention Service (TOPS) database is to ensure safety of all our participants in this trial and therefore if you are unwilling to have your information submitted on TOPS you would not be able to take part in our trial. More information can be found at http://www.hra.nhs.uk/about-the-hra/our-committees/the-over-volunteering-prevention-system/.

If the trial team found any reason why you could not take part in the trial this would be discussed with you.

Once the trial team have confirmed your suitability for the trial, depending on your availability we would inform you which group you will be allocated to and arrange a date for your first visit. Your participation in this trial is at the researchers' discretion.

Additionally, you will be invited to take part in the Oxford Vaccine Centre Biobank if eligible. BioBank is a separate study storing samples for vaccine and infectious diseases research, and optional to all participants of trials conducted by Oxford Vaccine Centre therefore separate consent is sought for this.

Is coming to screening a commitment to taking part?

No. It is an opportunity to meet with the trial staff and ask questions. You do not need to make a decision there and then.

TRIAL VISITS:

Vaccination visits:

Vaccination visits (see tables 1 and 2) take about 90 minutes and are held at the CCVTM. The clinical team will ensure that you are still happy to continue with the trial and will ask about any changes in your medical history since your last visit. The clinical team will also:

- Review your blood sample results from your previous visit
- Measure and record your oral temperature, pulse and blood pressure
- Perform urinary pregnancy test (for females)
- Take a blood sample
- Collect a mucosal sample (an absorptive strip placed inside your nose)
- Administer vaccine by injection in the top of your arm.
- You will be required to stay at the clinic for at least 60 minutes after the vaccination, so that you can be observed. Your temperature, blood pressure and heart rate will be checked again to make sure you are well before you leave the clinic.
- Set up the electronic diary access and provide training on how to fill this in for the 7 days after the vaccination.
- Schedule your next visit

What happens at the other visits?

Follow up visits (see tables 1 and 2), take about 30 minutes, and are held at the CCVTM. The clinical team will ensure that you are still happy to continue with the trial and will ask about any changes in your medical history since your last visit. The clinical team will also:

- Review your symptoms as recorded in your electronic diary (e-diary)
- Measure your temperature, pulse and blood pressure
- Take a blood sample
- Collect a mucosal sample (an absorptive strip placed inside your nose)
- Schedule your next visit

We would ask each participant to attend every visit, complete the e-diary, and keep in contact with the team, who are there for your safety

Diaries

Following vaccination, you will have access to an e-diary system, which is required to be completed online. You will be given unique log-in details associated with your trial number and receive an email with a link to the diary. Training for this will be given at the first visit and a paper copy of the diary will be provided to allow for completion in the event of inability to access the online version for whatever reason.

You will be asked to record your temperature once a day (a thermometer will be provided), and record any symptoms that you experience for 7 days after the vaccination. You will be asked to record any new medications taken during the trial, any change to your health, and any medical or health professional consultations, throughout the whole period of the trial. The diaries will be reviewed by the trial team at each visit.

Sampling

The following samples would be examined to study your body's immune response to the trial vaccine.

Blood, Urine and Mucosal Samples

We would take blood and urine samples as part of the screening visit, to help us assess your general health (and urine pregnancy test for females at screening and before vaccination).

Blood and mucosal samples would also be taken at each trial visit (according to Tables 1 and 2), in order for us to monitor your immune response and for safety reasons.

Blood samples:

A maximum of 645mls of blood will be taken over the trial. As a comparison, if you were to give blood to the National Transfusion Service a woman would be able to give a maximum of 1350ml per year, and men 1800ml per year. For this reason, participants will be asked not to donate any blood while participating in the trial. Up to 67.5ml of blood could be taken at each visit for Groups 1 – 3.

Some blood would be used to look at the pattern of genes being actively used by your body in response to the trial vaccine. The response to infection and to vaccines is in part genetically controlled, so knowing the pattern of genes that are being used may help us to understand how individuals respond to vaccination with ChAdOx1 Plague. For this reason, it is necessary for us to record your ethnicity as this information influences how we interpret your genetic tests.

Mucosal samples:

A mucosal sample will be taken from the nose at each visit indicated on Tables 1 and 2. This consists of placing a soft, absorptive strip on the inside of your nose, for 60 seconds, which will soak up some lining fluid. Before the strip is placed in your nose, a trained clinical investigator will examine your nasal cavity, to ensure it is safe to insert it.

What will happen to any samples that I give?

Samples will be de-identified. They will be labelled with your trial number and initials, but no other identifying details.

The blood and mucosal samples collected during this trial would be transported to either the Oxford University Hospitals NHS Foundation Trust laboratories or University of Oxford research laboratories for analysis. Those analysed in the Oxford University Hospitals NHS Foundation Trust will either be discarded once analysed, or where bacteria have been grown, these will be transferred to University of Oxford research laboratories for storage and further analysis.

OTHER INFORMATION

What side effects or risks can I expect from this trial?

You may have side effects while on this trial; these are outlined below. We will observe everyone in the trial for any side effects, particularly in the first seven days after receiving the vaccine with an e-diary that you will fill in. Side effects may be mild or serious. Most side-effects will stop shortly after receiving the vaccine. In rare cases, side effects can be serious or prolonged, although no serious concerns have been raised in human trials for other similar virus-based vaccines. It is important to notify the trial team if you are at all worried about your symptoms.

You may take medicines after you have received a vaccination to help lessen side effects; for example, if you have a fever. Any medication you have taken during the trial should be recorded in your diary. If you have a severe reaction, we may give you medicines to assist you, such as adrenaline.

Vaccination

In general, the known risks following vaccination are minor and brief (lasting a few days). As with any vaccination, the following events could occur:

- Pain, redness or swelling of your arm around the spot where the vaccine was injected
- General: fatigue, headache, fever, gastrointestinal symptoms such as nausea (feeling sick), vomiting, diarrhoea or abdominal pain

It would be expected that any fever following vaccination would be short lived and would occur within 48 hours of receiving the vaccine. If a fever persisted it would be important to contact the study team and follow current government guidance for suspected Covid-19.

As with all injected vaccines, unexpected, severe allergic reactions may very rarely occur. An allergic reaction can be recognised by itchy skin rash, swelling of the face, difficulties in breathing and swallowing or by a sudden drop in blood pressure. If such reactions occur, they usually start very soon after vaccination. That is why it is important that you stay at the trial site for at least 60 minutes after vaccination, where all medical equipment and personnel are available to treat an allergic reaction. Reactions in the nervous system are also extremely rare but can cause an illness called Guillain-Barré syndrome. This is a condition in which people can develop severe weakness and can be fatal. These adverse events have not previously been seen following administration of similar vaccines using ChAdOx1 as a viral vector.

ChAdOx1 Plague vaccine

Adenovirus vaccines have previously been trialled in human volunteers, protecting against different diseases. These were not associated with serious side effects. As it is the first time that the trial vaccine (ChAdOx1 Plague) will be tested in humans there might be side effects that we don't yet know about. If any new side effects are identified, from this trial or from animal studies, we will tell you.

The ChAdOx1 part of the vaccine (the "viral vector" or "backbone") is the same as has been used in a recently developed COVID-19 vaccine (ChAdOx1 nCoV-19 - commonly known as the Oxford/AstraZeneca vaccine or Vaxzevria). In the Spring of 2021, some countries that were using this vaccine for their national COVID-19 immunisation programmes temporarily paused the use of the vaccine due to concerns that rare blood clotting conditions could be associated with the vaccine. Following these reports, a review has been undertaken by the MHRA (Medicines and Healthcare products Regulatory Agency) and the EMA (European Medicines Agency). The reports were of a very rare type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST), and also of clots in some other organs together, with low levels of platelets (thrombocytopenia). Up to and including 31 March 2021 there have been 79 UK reports of these blood clots and unfortunately 19 people died. By 31 March 2021 20.2 million doses of the ChAdOx1 nCoV-19 vaccine had been given in the UK. This means the overall risk of these blood clots is extremely rare, approximately 4 people in a million who receive the vaccine.

After investigation, the UK Medicines Healthcare Regulatory Agency concluded, based on the data currently available to them, they could not say that there was a definite link between the vaccine and the rare clotting events. The MHRA statement on this can be found here: https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots.

The European Medicines Agency concluded that unusual blood clots with low blood platelets should be listed as very rare side effects of this vaccine.

Both agencies concluded that there wasn't enough evidence at present to say what the risk factors (e.g. age, gender, or other medical conditions) might be for having one of these rare clotting problems.

We don't yet know whether these rare clotting problems might be related to the vaccine vector virus (ChAdOx1), or to the SARS-CoV-2 part of the vaccine (the spike protein). The ChAdOx1 vector has been used in other clinical trials since 2012 (influenza, tuberculosis, prostate cancer, malaria, meningitis B, chikungunya, Zika and HIV vaccine trials). These rare blood clotting problems have not been seen in participants in these trial, however the number of people in this trials has been relatively small. These events remain extremely rare (in the UK it is estimated to affect 4 in a million people who receive a vaccine dose), and all medical regulators are collecting and analysing further data on them. We don't know whether these rare clotting problems could be related to the ChAdOx1 part of the vaccine, we would advise you to be particularly alert to the following symptoms in the first 28 days after you have a trial vaccine:

- Sudden severe headache that does not improve with usual pain killers or is getting worse
- An unusual headache which seems worse when lying down or bending over, or may be accompanied by blurred vision, nausea and vomiting, difficulty with speech, weakness, drowsiness or seizures
- New and unexplained pinprick bruising or bleeding
- Shortness of breath, chest pain, leg swelling or persistent abdominal pain

You will be provided with a 24h study mobile number. If you experience any of the above events or become in any way concerned you can use this to contact one of the study doctors at any time. We will ask you to record these symptoms in the E-Diary too

If any new information, or any other new safety concern, arose during the trial in relation to ChAdOx1, this would be reviewed, and you would be kept fully updated.

Blood sampling

This trial involves several blood tests. Taking blood samples may sometimes result in bruising to the area and some people can feel faint. If you were feeling faint, our staff would ask you to stay at the clinic until you felt well again. Participants' blood samples will be monitored closely throughout the trial as there is a small risk of anaemia and blood sampling will be reduced if needed.

Mucosal sampling

Validated synthetic absorptive matrix (SAM) strips are used to sample fluid from your nostril. Due to the sensitivity of the inside of the nose, insertion of the SAM strip may cause involuntary head movement e.g. sneezing.

Safety

At different times during the trial, a group of experts will look at the side effects and the results of blood tests to decide if it is safe to vaccinate more people. The group of medical experts can also meet at any moment, if needed, to discuss the safety of the trial.

You will receive a card with trial contact information. Keep this card with you at all times during the trial. Show this card to the medical staff if you need emergency care during the trial. The medical staff can then contact your trial doctor or nurse if needed to ask about the vaccine you received.

You would have telephone access to a trial doctor 24 hours a day until the end of the trial. It would be very important that you stay closely in touch with the trial team and let us know promptly if you become unwell in any way.

We would ask you to provide contact details of a person who can act as a 24 hour contact in the case of an emergency or needing to contact you urgently and provide contact details of any doctors treating you. We may contact these people if we are not able to contact you in the two weeks following vaccination and will hold their details for the duration of the trial (up to one year).

COVID-19 guidelines

The clinic will be set up to follow strict COVID-19 guidelines, including social distancing rules. Every participant will be asked to wear a face covering. The clinical researcher that reviews you will be wearing appropriate personal protective equipment. Please DO NOT attend the clinic if you have any symptoms of COVID-19, have tested positive for COVID-19 or are in quarantine – you can let the trial team know and we can re-arrange your visit as appropriate.

Pregnancy and contraception

You should not take part in this trial if you are pregnant or breastfeeding.

It is currently unknown whether the vaccine being tested is safe during pregnancy. For this reason, it is important that women use adequate contraception during the trial period, for at least 3 months after your final vaccination. Women who are not of childbearing potential (i.e. postmenopausal or

permanently sterile due to surgery such as a hysterectomy) will not be required to use contraception. This will be discussed with you at the screening visit. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the trial, although we will ask to follow you up for safety reasons.

Male participants with female partners are not required to use barrier methods for the purposes of contraception, as the risks of vaccine excretion are negligible.

What are the benefits of taking part?

There is no direct benefit to you from taking part in the trial. Information from this trial will provide valuable data on how effective this vaccine is. The data from this trial will be used to support further trials in Africa, Asia and the Americas, to work towards developing a safe and effective vaccine for use in countries, predominantly developing nations, to help prevent Plague infection and outbreaks.

Reimbursement

Each participant is compensated for their time and for the inconvenience based on the following figures:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per visit
- Time required for visits: £20 per visit

Additional reimbursement for unscheduled visits at £45 per visit will be provided up to maximum of £135 (the equivalent of three unscheduled visits). This will not be given unless an unscheduled visit occurs.

Each participant can therefore receive £495– £630 depending on the Group you are allocated to. Payments will be made in instalments after V0, V5, V8 and V16.

Payments will be made via internet bank transfer. Participants will be asked to provide banking details including account name, sort code and account number. All details will be stored confidentially and retained by the Oxford Vaccine Group while the participant is actively involved in the trial. These details will be retained for 7 years as per the University of Oxford policy.

If you choose to leave the trial early or were withdrawn from the trial you would be reimbursed according to the length of your participation based on these figures.

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

Yes. In order to enrol into this trial, you would be required to sign a form, documenting that you consent for us to contact your GP. This is to inform him/her that you would be entering the trial, and to ensure there are no medical reasons that would prevent you from taking part in this trial. We will also require access to your healthcare records and vaccination history. There may also be instances where GPs will be contacted to follow up incidental findings that may be of clinical significance, such as high blood pressure or indications of depression.

What if we find something abnormal?

If abnormal results or undiagnosed conditions are found during the course of the trial these will be discussed with you and, if you agree, your GP will be informed. Any newly diagnosed conditions will be looked after within the NHS.

What if I am offered/due to receive a COVID-19 vaccine from the national immunisation programme during the trial?

We are aware of the importance of people being able to take up COVID-19 vaccines when they are offered them. Participation in this trial will not affect your ability to receive COVID-19 vaccinations from the national immunisation programme. If you have concerns about this, please contact us to discuss further.

Would my taking part in this trial be kept confidential?

Yes. All information that is collected about you during the course of the research would be coded with a trial number and kept strictly confidential. Any information about you that leaves the clinic would have your name and address removed so that you could not be recognised, with the exception of your own GP.

Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations. In addition, the following groups may inspect the trial records whilst maintaining confidentiality:

- Monitors who check that the trial is being conducted to a high standard, including the Data and Safety Monitoring Committee (DSMC), an independent panel of experts responsible for trial safety.
- The Clinical Trials and Research Governance Office (CTRG), University of Oxford, who are responsible for ensuring the appropriate conduct of the trial on behalf of the research Sponsor (the University of Oxford).

Anonymised data and samples would be sent to other researchers working with us on this research project, including researchers outside the UK.

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 data controller and is responsible for looking after your information and using it properly.

We will be using information from you and your medical records in order to undertake this trial and will use the minimum personally identifiable information possible. We will keep identifiable information about you such as contact details for a minimum of 5 years after the trial has finished. The need to store this information for longer in relation to licensing of the vaccine will be subject to ongoing review.

Paper notes will be held by the Oxford Vaccine Group in a locked cabinet. Once the trial has been completed, all documents, including personally identifiable data, would be archived in a secure facility, for a minimum of 5 years. Storage of this data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required. If you complete online or telephone

screening, and do not progress to in-person screening, your data will only be stored until the end of the trial.

If you have agreed that samples can be retained for future research then your personally identifiable information will be kept with restricted access solely for the purposes of sample management for a minimum of five years after the last sample has been either used or disposed of in order to meet regulatory requirements. Samples will be provided for future research only in a form that does not identifies you. We store research data securely at the University of Oxford indefinitely following removal of identifiable information.

The trial team will use your name and contact details, to contact you about the clinical trial, and make sure that relevant information about the trial is recorded for your care, in relation to your health during the trial and to oversee the quality of the trial. At the completion of the trial, unless you consent otherwise (e.g. if you request to be informed of other trials), your personal details will not be used to contact you other than exceptional circumstances concerning your safety.

If you consent to take part in another trial carried out by the Oxford Vaccine Centre, we will retain a copy of your consent form until such time as your details are removed from our database but will keep the consent form and your details separate. Personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

Your bank details will be stored for 7 years in line with university financial 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. Professor Andrew J Pollard, or his successor, as Director of the Oxford Vaccine Group will have the responsibility for custody of the data. Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights

If you withdraw from the trial, 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 Oxford Vaccine Group on 01865 611400 or email info@ovg.ox.ac.uk.

Will any genetic tests be done?

Analysis of gene expression may be performed using peripheral blood. This analysis may highlight differences in gene expression caused by vaccination. In addition, DNA samples obtained from peripheral blood will contribute to a Biobank of samples from multiple different Oxford Vaccine Group studies. These DNA samples will be used to analyse the genetic factors influencing vaccine responses (immunogenicity and reactogenicity). DNA extraction and storage will only occur with the specific consent of participants, and DNA will not be analysed for any other purpose than to assess factors influencing vaccine responses.

What will happen at the end of the clinical trial?

The results of the research will be published in a scientific medical journal; this can potentially take a few years. All OVG publications will appear on the OVG website and you will receive a letter or email

containing these results. Your individual results would not be identifiable, nor would you be identified in any report or publication. The results of the research will also potentially be used for future academic research within the Oxford Vaccine Group.

Once the last laboratory test is performed in the trial, all samples will be destroyed, unless you have consented for them to be transferred to the Biobank.

Is there anything else I should know?

If you have private medical insurance, you are advised to contact your insurance company before participating in this trial. The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

Where can I get advice on whether to take part?

We are happy to answer any questions you might have and contacting us does not commit you to taking part in the trial. For independent advice you can contact **INVOLVE** (www.invo.org.uk) which is a government funded national advisory group supporting those considering involvement in NHS, public health and social care research. Please feel free to discuss this trial before deciding whether or not to participate.

What if I wish to complain?

If you wish to complain about any aspect of the way you have been approached or treated or how your information is handled during the course of this trial during the course of this trial, you should contact Professor Andrew Pollard, Director of the Oxford Vaccine Group, (Tel: 01865 611400, Email: info@ovg.ox.ac.uk). You can also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480 or the head of CTRG, email ctrg@admin.ox.ac.uk.

At any time during the trial you would be entirely free to change your mind about taking part, and to withdraw from the trial. This would not affect your subsequent medical care in any way.

Who has reviewed and approved this trial?

The study has been reviewed by the trial sponsor (the University of Oxford) and has been approved by an independent research ethics committee (South Central - Berkshire B)

Who is organising and funding the trial?

The trial is funded by Innovate UK. Innovate UK is part of UK Research and Innovation (UKRI) which is the national funding agency investing in science and research in the UK.

In summary, what would happen if I decide to take part in the trial?

- We would ring you to check that it is appropriate to include you in the research.

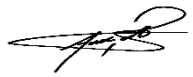
- You would then attend a screening visit at the CCVTM where you will have opportunity to discuss the trial further.
- If you decide to take part in the trial you would sign a consent form.
- You would have a physical examination, blood test and urine test (and a pregnancy test for women). These are to assess your eligibility for the trial.
- You would be allocated to an appropriate trial group.
- Following satisfactory screening results you would be enrolled into the trial, and your 1st appointment would be arranged.
- Your visits would be booked according to which group you are allocated to (see tables 1 and 2).
- You would be vaccinated with the trial vaccine. (if allocated to group 2 or 3 you would have an additional booster vaccine, 2 or 6 months after the first vaccination).
- You would have blood and mucosal samples taken.
- You would be seen twice in the week after vaccination and asked to fill in an e-diary.
- We would continue to see you for clinic visits up to 12 months after the start of the clinical trial (see table 1-3).

What do I do now?

Thank you for considering taking part in this trial. You do not need to make a final decision straight away. If you decide you would like to take part or wish to discuss any element of the trial further, then please contact us by either:

- telephone 01865 611400
- website https://trials.ovg.ox.ac.uk/trials/plague
- email info@ovg.ox.ac.uk

Yours sincerely,



Prof Andrew J Pollard
Professor of Paediatric Infection & Immunity
Honorary Consultant Paediatrician

If you would like to change your mailing preferences on the electoral roll, you can contact the mailing preference service on;
Email: mps@dma.org.uk or Tel: 02072 913310