PARTICIPANT INFORMATION SHEET: COV002

Investigating a Vaccine Against COVID-19

"A phase 2/3 study to assess the efficacy and safety of a recombinant adenovirus-based vaccine against Coronavirus Disease (COVID-19)"

Updated information about unblinding can be found on p8.

Updated information about side effects can be found on p12.

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 study team on phasetwocov@sgul.ac.uk for advice before attending any visit.

If you have received any COVID-19 vaccine(s) outside of the study and have not already informed your local trial team please register these details at this link:

https://is.gd/covid_vacc_info

Participation could really make a difference during a public health emergency.

We would like to invite you to take part in our COVID-19 vaccine study. Before you make a decision, it is important you take the time to understand why we are doing this research and what it would involve. Please read the following information carefully and consider discussing it with friends and relatives.

What is the purpose of this research study?

The purpose of this study is to test how well a new vaccine works against COVID-19.

A new virus causing respiratory disease emerged in Wuhan, China in December 2019 and has since rapidly spread to many other countries around the world, despite unprecedented containment efforts. The virus is part of the Coronavirus family which may cause respiratory infections ranging from the common cold to more severe diseases. This recently discovered coronavirus causes COVID-19.

Common symptoms of COVID-19 include fever, tiredness, and dry cough. Whilst about 80% of infected people have no or mild symptoms and will recover from the disease without needing special treatment, 1 in every 6 people who gets COVID-19 becomes seriously ill. Older people and those with underlying medical problems are more likely to develop serious illness. Thousands of deaths have been reported so far.

The WHO declared the COVID-19 epidemic a Public Health Emergency of International Concern on 30th January 2020 and a pandemic on 11th March 2020. This means that the epidemic is expected to spread to all countries of the world and infect 50-80% of people.

There are no currently licensed vaccines or specific treatments for COVID-19. Vaccines are the most cost effective way of controlling outbreaks and the international community have stepped-up their efforts towards developing one against COVID-19.

This study will enable us to assess how well people across a broad range of ages may be protected from COVID-19 with this new vaccine called ChAdOx1 nCoV-19. It will also give us valuable information on safety aspects of the vaccine and how well participants' immune systems respond to immunisation with the vaccine.

Summary of the study

In total this study will enrol up to 12, 390 adults and children across the UK.

- Adult participants will be randomised to receive one or two doses of either the *ChAdOx1 nCoV-19* or a licensed vaccine (MenACWY) that will be used as a 'control' for comparison
- Participants in some groups will be invited to receive a second (booster) dose of the vaccine
- Between 6 and 12 blood tests will be taken over the course of a year to check if there are any problems and to look at immune responses to the vaccine
- For some participants there will be a diary to complete for up to 28 days following vaccination
- There is a weekly questionnaire that monitors your and members of your households exposure to COVID-19
- In order to monitor for exposure to COVID-19 in those who do not develop symptoms we will perform weekly nasal swabs or saliva collection
- The study will take a year to complete (from the time the final dose of vaccine is given)

What is the vaccine we are testing?

The vaccine we are testing in this research study is called *ChAdOx1 nCoV-19*.

ChAdOx1 nCoV-19 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 grow in humans. To this virus we have added genes that make proteins from the COVID-19 virus (SARS-CoV-2) called Spike glycoprotein (S), which play an essential role in the infection pathway of the SARS-CoV-2 virus. By vaccinating with ChAdOx1 nCoV-19, we are hoping to make the body recognise and develop an immune response to the Spike protein that will help stop the SARS-CoV-2 virus from entering human cells and therefore prevent infection. Vaccines made from the ChAdOx1 virus have been given to more than 320 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 *Are there any risks from taking part in the trial?*).

The vaccine ChAdOx1 nCoV-19 was first given to 500 healthy adults in Oxford in April 2020 as part of a separate safety trial (COV001). Including in this current trial (COV002), the vaccine has now been given to over 5000 people in total. The most up to date recruitment figures will be provided at the first visit.

We are not sure what dose of vaccine is most likely to be protective against COVID-19 disease. Vaccine doses are measured using standard scientific test methods. The vaccine received by

the first approx. 1500 participants in the current COV002 trial was based on a dose measured using one type of scientific test (dose 1 in visit schedules below). Participants enrolled in Groups 4c, 6a, 6b, 8 and 10 will have a dose measured using a different type of scientific test (dose 2 in visit schedules below) which will give a higher dose of vaccine similar to the dose used in our earlier COV001 trial.

We are interested in evaluating both doses in the trial so that we can provide the data needed to inform policymakers on how to use the vaccine, if the vaccine is shown to work. This may help us understand which dose is the most effective.

Although during a pandemic it would be preferable to give a single dose of vaccine, data from the first COVID-19 vaccine trial suggests that 2 doses of vaccine stimulates the immune system more than a single dose. However, we don't know how much of an immune response is needed for protection. Participants in Groups 4 and 6 will be offered an optional booster vaccine at least 4 weeks after their first vaccination. We are now inviting participants in groups 1, 2 and 5a, who have not already received two doses of vaccine to have an optional booster dose.

Participants will receive the same booster vaccine type as they received for their first vaccine. Therefore participants who received the ChAdOx1 nCoV-19 vaccine will receive a dose of booster ChAdOx1 nCoV-19 that will be similar to the dose used in the earlier COV001 trial. Participants who received MenACWY as their initial vaccine will receive a MenACWY booster dose which is the same as their first dose. All participants will remain blinded to which vaccine they receive at the point of booster vaccination. Participants who choose to receive a booster dose will need to stay in the study and have further visits for up to 15 months in total.

We don't know which dose, if any, will provide protection. Although Group 1, 2, 4 and 5 received a lower dose, this does not mean that it will be better or worse than the higher dose, and we will study the immune response carefully to identify any differences.

A group of up to 60 volunteers who previously received a vaccine containing ChAdOx1 in studies, will be invited to take part in group 11. Additionally, a group of up to 60 volunteers that are living with HIV, will be invited to take part in group 12 (this is only possible in some sites). We would specifically like to investigate the immune response to the ChAdOx1 nCoV-19 vaccine in those individuals. These individuals will receive two doses of ChAdOx1 nCoV-19 vaccine, 4 – 6 weeks apart and will not be blinded.

What is the control (comparison) vaccine, MenACWY?

In this study we will be using a licensed vaccine against group A, C, W and Y meningococcus (MenACWY) as an 'active control' vaccine, to help us understand participants' response to ChAdOx1 nCoV-19. MenACWY has been given routinely to teenagers in the UK since 2015, and protects against one of the most common causes of meningitis and sepsis. This vaccine is also given as a travel vaccine for high risk countries. We will be using one of the two licensed versions of MenACWY, either Nimenrix or Menveo. Volunteers who have had these vaccines previously can still take part in this study.

Given we don't expect MenACWY to offer any protection against COVID-19, by comparing COVID-19 disease rates, immune responses and post-vaccination symptoms between

participants receiving ChAdOx1 nCoV-19 and MenACWY we will get a better understanding of how well ChAdOx1 nCoV-19 is working.

Do I have to take part?

No. 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 allow an extra visit for a follow up appointment for safety reasons.

Can I take part?

Adults that are aged 70 years and over are able to take part in **group 2, 8 and 10 however,** we have completed enrolment into groups 2, and 8. In order to be enrolled in the study;

- you must be willing to allow the investigators to discuss your medical history with your General Practitioner (GP)
- you agree to refrain from blood donation for 3 months after the last study vaccination

You cannot take part in this study if you:

- are taking part in a COVID-19 drug trial
- are taking part in a serological study where you are informed if there is evidence of SARS-CoV-2 in your blood
- have any vaccine in the 30 days before or after this study vaccine. The exception to this is the seasonal influenza vaccine and pneumococcal vaccine. If you are offered these by your GP or your place of work, we ask that you have these at least 7 days before or after you receive the study vaccine.
- have previously had other similar vaccines that might impact on understanding your results such as adenovirus vectored vaccines or coronavirus vaccines
- have received immunoglobulins or blood products in the 3 months before having the study vaccine
- have immunosuppression or immunodeficiency
- have a history of angioedema
- have a history of anaphylaxis
- have a current diagnosis or are having treatment for cancer
- have a history of serious psychiatric condition likely to affect participation in the study
- have a bleeding disorder

- continuously take anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
- have suspected or known current alcohol or drug dependency
- have severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness
- have a history of laboratory confirmed COVID-19 or a blood test shows that you have had contact with the COVID-19 virus (With the exception of groups 5d, 9, 10 and 11)

You cannot take part in group 4, 6, or 10 if;

- you have a history of allergic disease or a reaction that could be made worse by paracetamol

If you were to develop symptoms of COVID-19, we will ask you to attend for a visit. If you would rely on public transport to attend this visit, this may put other people at risk, so we would not be able to enrol you in the study.

If you are unclear whether you are eligible to be involved in the study you can contact the study team who will be able to advise you.

What will happen if I decide to take part?

If you decide you would like to take part in this trial there is a short online questionnaire to complete to check that you are able to take part.

There will be a screening visit before the vaccination day. So that we can limit the amount of time you spend face to face with a member of research staff we will conduct some of the visit with you over the phone. At the end of the online questionnaire you will be asked if you agree that a researcher can contact you by phone to ask questions about your current health and discuss details of your medical history in order to assess that you are eligible and if enrolled used as baseline health information. If you are eligible you will be invited to attend the second part of the visit.

Screening Visit – *1.5 hours (Listen to a consent presentation, ask any questions, sign a consent form, ID check, medical history, physical examination if required, temperature check, blood test)*

We will ask you to watch a video presentation of the information about the study to ensure you understand what to expect by taking part, the risks involved and what side-effects you might expect to experience. Then you will have opportunity to ask any questions of a member of the research team before signing a consent form, if you decide you would like to take part.

You can of course expect to receive full and comprehensive answers to any questions you may have.

You will be asked to agree to allow the research team to contact your own Doctor (GP) to make sure there are no medical reasons why you should not participate.

Having signed the appropriate forms, a doctor will ask questions about your current health and discuss details of your medical history, may perform a physical examination which could involve listening to your heart and lungs with a stethoscope, examining your abdomen as well as feeling for lymph nodes around your neck and in your armpits. Your height, weight and temperature will be recorded and if necessary your blood pressure and pulse may be recorded.

A blood sample may be taken to check if you have had contact with the COVID-19 virus. If results indicate you have, you will not be able to continue with the study. It is important to note that this is a research test that has not been validated for diagnostic purposes, so results cannot be used to provide certainty of prior infection nor of protection from future infection.

If you are in groups 2 or 8 additional blood tests will be also be carried out which include tests for anaemia, tests to see how your liver and kidneys are functioning and tests to see if you have been exposed to HIV (the virus that leads to AIDS), Hepatitis B or Hepatitis C (viruses which affect the liver). In the event of you testing positive to any of these infections, we would inform you of the result and, with your permission, offer referral for medical review, confirmation of the result, and treatment if necessary.

Sometimes minor abnormalities can be found with the blood tests. In this situation you may be asked to return for a repeat blood test so that it can be checked again. If the test results are still abnormal you may not be able to participate and we will ask your permission to contact your GP or a specialist doctor, whichever is the most appropriate, to ensure the abnormality will be followed up.

Once all your test results have been checked and no problems have been highlighted, you will be contacted to arrange a date to start the trial.

Vaccination Visits - *1hour (vital signs if necessary, blood test, receive vaccine, up to 30 minutes observation in clinic after the vaccine)*

If you qualify to be in the trial, we will ask you to attend on the vaccination day (Day 0). We will ask you a few questions to check there have been no new problems since screening. We will check your temperature and we will take blood samples. You will be randomly allocated to receive ChAdOx1 nCoV-19 or MenACWY.

We will give you an injection with ChAdOx1 nCoV-19 or MenACWY into your arm and we may cover the vaccine site with a dressing. In line with routine guidance, there is no longer a need to observe you after you have received the vaccination. If you feel ok, you can leave straight away. This whole process will be repeated again at the time of the booster vaccination day (Day 28 for Group 10 participants).

Overall, the vaccination visit will take about an hour.

Groups 2 and 8: As well as being allocated to receive either the ChAdOx1 nCoV-19 or MenACWY vaccine you will also be randomly allocated to receive either one or two doses. Group 10: You will be randomly allocated to receive 2 doses of either the ChAdOx1 nCoV-19 or MenACWY vaccine.

Electronic Symptom Diary "e-diary" – *Completed at home by participant*

Group 2, 8 and 10: We will give you a thermometer, tape measure and an E-diary account to record all your symptoms and your temperature every day for 7 days after vaccination.

Groups 2 and 8: After these 7 days we will ask you to record if you feel unwell or take any medications over the next 3 weeks. The research staff will monitor the E-Diary and may phone you to ask for more information. You will also be asked to record in the diary any serious medical illnesses or hospital visits you may have over the course of the study.

Paracetamol – *Group 10 only*

If you are in group 10 we will ask you to take paracetamol for 24 hours after the vaccination. Paracetamol can reduce fever and pain after vaccination. If you have been asked to complete a diary there will be space to record the time you took the paracetamol.

Weekly survey

We will send you a survey each week by email or text to enquire about COVID-19 symptoms of you and your household contacts for the duration of the study. If you work in a clinical area you will not be asked to complete this survey.

Follow-up visits – *30 minutes (vital signs, blood tests, and check for side effects or new health problems)*

Following vaccination, we will ask you to attend a series of short follow-up visits to ensure everything is fine, to check your symptoms, the injection site and to have blood tests done.

Weekly COVID-19 surveillance – *2 minutes plus time for posting*

In order to monitor for exposure to COVID-19 in those who do not develop symptoms we will ask you to collect weekly throat/nasal swabs or saliva samples. These samples will be processed as part of the ongoing community testing programme conducted by the Department of Health and Social Care (DHSC). You will be given instructions about how to collect these samples yourself and how to send them to the laboratory for testing. For further information on how the DHSC will handle data from your weekly swabs, please see https://www.test-for-coronavirus.service.gov.uk/register-kit

If the results of your swab indicate that you have been exposed to COVID-19 or if you develop symptoms of COVID-19 disease, we may ask your permission to collect a stool sample. You would receive instructions for how to collect the sample, how to use the packaging provided and how to arrange a courier to collect the sample.

Note: due to the high number of planned volunteers in this study, visits may take longer than the estimates given here

During the course of the trial you may be asked to attend for an extra visit, for example, if a blood test needs to be repeated.

We may ask to photograph your vaccination site. You will not be identifiable in these photographs, as only the vaccination site and your unique trial number will be visible. These photographs may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

Early unblinding for administration of COVID-19 vaccines

The UK government is now beginning a national roll out of an approved COVID-19 vaccine. The vaccine will be rolled out according to the government prioritisation plan, so it may be some time before participants receive an invitation for vaccination. Before having this approved vaccine, you would need to find out which vaccine you were given as part of the study (unblind). It will only be possible to unblind when the approved vaccine is being rolled out in your area AND you are in an eligible group of people.

Before you are given the approved vaccine your site may ask you to come for an extra visit to collect a blood sample and a swab. You will also be asked to complete an online form with details of the vaccines you were given and the dates you had them and continue to attend your remaining visits as scheduled and send your weekly swabs.

If you were in a group that received a single dose of the study vaccine, the national guidance is for you to either

- receive another dose of the study vaccine when available
- a single dose of the approved vaccine (although there is no risk or benefit information following vaccination with mixed vaccines).

Record of vaccinations

When you have been unblinded from the study, we will send you and your GP a letter containing the type of vaccine you received, batch number and date of administration. We may also provide you with a small card with this same information that can be carried with you. We do not know yet what the government guidance or requirements will be with regards documentation of vaccines for travel purposes, but will provide updates when this becomes clearer.

Unblinding of all participants

The main analysis of the study objectives looking at how effective the ChAdOx1 nCoV-19 vaccine is at preventing COVID-19 disease has been completed and this shows that the vaccine is 100% effective at preventing severe COVID-19 disease in the trials. The number of new infections in the UK has now fallen, and due to a significant number of participants already being unblinded as part of the national vaccine rollout we have decided to unblind all participants in the trial.

Once you are unblinded if you:

- <u>Received one dose of the ChAdOx1 nCoV-19 vaccine:</u>
  We will offer you a second dose of vaccine to complete your immunisation course. If you prefer to wait to receive a vaccine in the national rollout via the NHS then you may alternatively do that.

- Received the control vaccine, MenACWY:
  We will invite you over the coming weeks to receive two doses of ChAdOx1 nCoV-19 in the approved 4 to 12 weeks schedule. We may also take a blood sample before your first dose of vaccine. If you prefer to wait to receive a vaccine in the national rollout via the NHS then you may alternatively do that. Participants that are under 30 years of age, in line with recent UK guidance, will not be offered doses of ChAdOx1 nCoV-19 in the study.
- Received two or more doses of the ChAdOx1 nCoV-19 vaccine:
  You should consider yourself fully immunised. If you received your two doses of ChAdOx1 nCoV-19 vaccine more than 12 weeks apart you should still consider yourself fully immunised and we do not recommend that you receive a further vaccination dose. The current national UK expert recommendation guidance, which is based on knowledge of the immune response from other vaccines, is that in cases of a delay in receiving second vaccine doses, the first dose should not be repeated. This guidance is available at https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a (Note: This has been produced by Public Health England but has been adopted by all constituent UK countries). Additionally, we have recently published an analysis that indicates that a long interval between doses may actually provide an even greater level of protection against mild COVID-19 than shorter intervals. There is currently no evidence or recommendation that a third dose or "seasonal booster vaccine" would be necessary or beneficial to individuals for longer term protection, although our research group is studying this currently.

"I have been unblinded – what happens now?"

There are still a lot of important questions that your continued participant in the trial can help us answer such as determining long term immune responses, monitoring for exposure to COVID-19 in those who do not develop symptoms and continued monitoring for safety. We are particularly interested in the minority of cases where vaccinated individuals still go on to develop COVID-19 and whether this can be predicted in the future by doing blood tests. For the reasons above we are asking all participants to continue to attend for their remaining follow up visits, such as the 1 year time point visit, even after they have been unblinded. It is also important that you continue to contact the study team should you develop symptoms of COVID-19.

"I have received a COVID-19 vaccine outside of the study – what happens now?"

For the above reasons we are also asking participants that have received COVID-19 vaccines outside of the study to remain in the study and complete their remaining follow up visits. If you have received a COVID-19 vaccine outside of the study and have not already informed your trial team, please enter the vaccine details in the link below. **This will greatly help our analysis of the data from the study.**

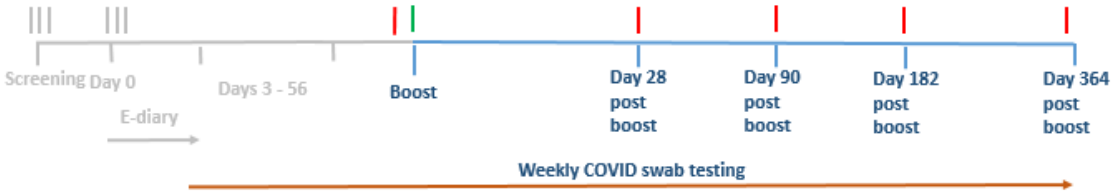
https://is.gd/covid_vacc_info

Visit schedules

The picture below represents the visit schedule for participants in group 2 being invited to receive a booster vaccination:

Consent | Vaccination – dose 2
Blood test

Ages 70 + years: Group 2 booster

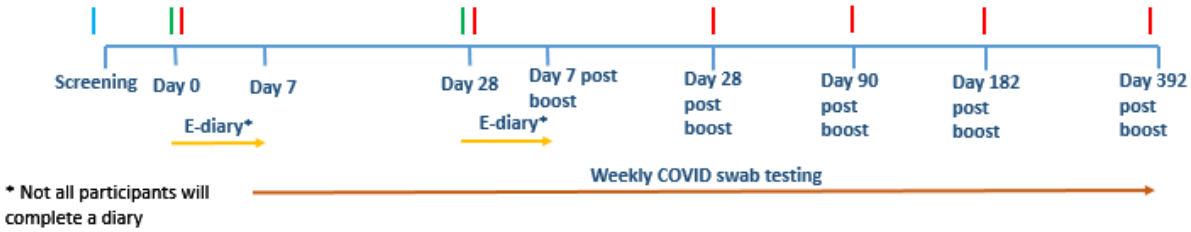


Group 10

The picture below represents the visit schedule for participants being invited to take part in group 10:

Age 70+ years: Group 10 two dose

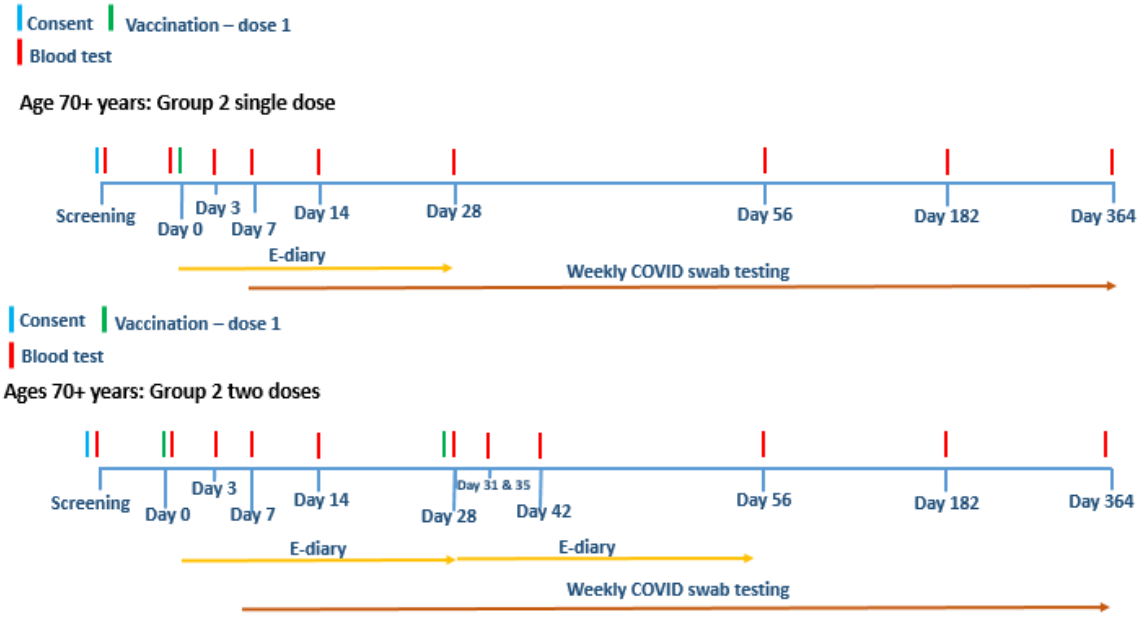
Consent | Vaccination – dose 2
Blood test



* Not all participants will complete a diary

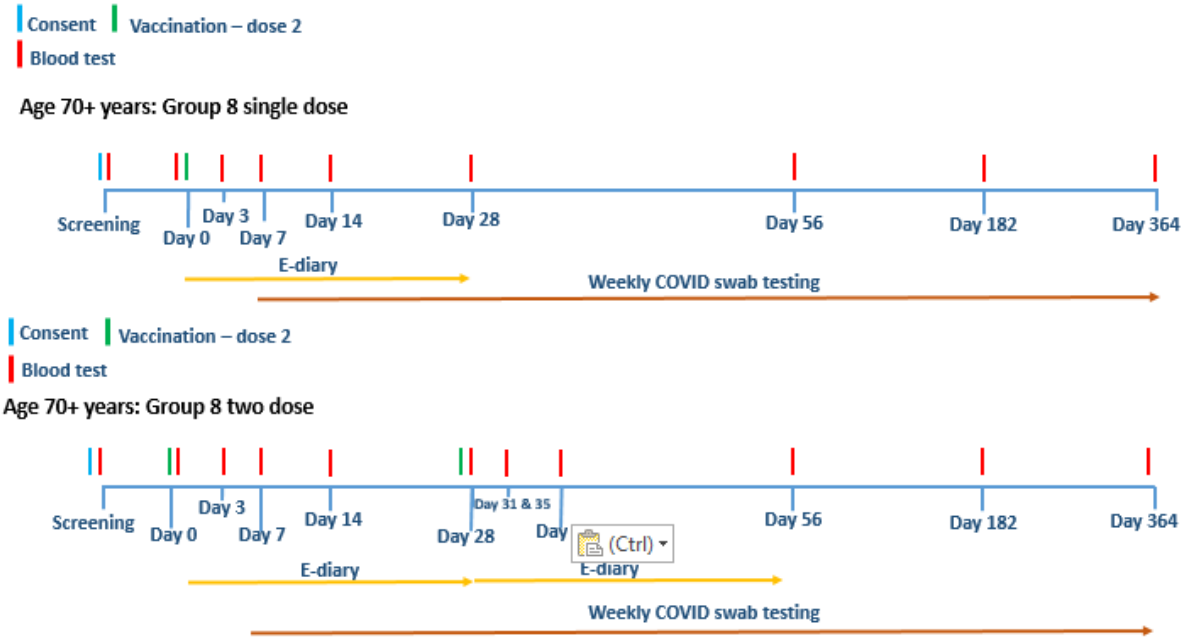
Group 2:

The pictures below represents the visit schedule for participants that have already had a vaccination in group 2:



Group 8:

The pictures below represents the visit schedule for participants that have already had a vaccination in group 8:



Considerations before taking part in this study

Blood Donation: Under current UK regulations, participants will not be able to donate blood during the course of the study.

Private Insurance: If you have private medical or travel insurance you are advised to contact your insurance company before participating in this trial, as involvement may affect the cover provided.

What should I avoid during the trial?

You should not donate blood during the trial or take part in other studies that involve blood sampling or the administration of drugs or vaccines, including trials testing other interventions for COVID-19. If during the trial you require any vaccinations for health, travel, or occupational reasons, you should inform the Investigators beforehand. We will discuss with you the most appropriate time to receive them.

Are there any risks from taking part in the trial?

The risks and side effects of the proposed vaccinations and trial procedures are detailed here:

1. *Blood samples*

Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. During the course of the trial we will need to take between 5 (approximately 1 teaspoon) and 60ml of blood (approximately 4 tablespoons) at a single visit. The total amount we will take over the period of the trial (if you do not develop symptoms of COVID-19) will depend on your group;

Groups 2 and 8: Single dose = around 388-540 ml, Two doses = around 250-655 ml

Group 4 and 6: 255-508 ml

Group 10: around 300-453 ml

If abnormal results or undiagnosed conditions are found during the course of the study these will be discussed with you and, if you agree, your GP (or a hospital specialist, if more appropriate) will be informed. Any newly diagnosed conditions will be looked after within the NHS. Participants will not be informed of the results of their levels of immunity against the COVID-19 virus.

2. *Vaccination Side Effects: ChAdOx1 nCoV-19 and MenACWY*

It is likely that you will experience some symptoms at the vaccination site as well as general symptoms due to vaccination. It is important to remember ChAdOx1 nCoV-19 is in the early stage of development and the amount of safety data available are limited. For this reason, there is a chance you could experience a side effect that is more severe than what is described below, or that has not been seen before.

Other ChAdOx1 viral vector vaccines have previously been administered in many other clinical trials. We can predict from past experience what the symptoms should be like with this new vaccine. We expect that symptoms will be mild in strength most of the time, although symptoms may also be moderate or severe. All symptoms should resolve completely within a few days. The chimpanzee adenovirus has been weakened so that it cannot grow in human cells. The SARS-CoV-2 protein it carries cannot cause COVID-19 disease. The MenACWY vaccines are licensed vaccines, meaning they have been approved for use in the general population. They have been given to many hundreds of thousands of people, with no safety concerns.

a) *Local Reactions at vaccination site*

Following vaccination with either the *ChAdOx1 nCoV-19* or MenACWY vaccine you may experience some discomfort at the injection site as the vaccination is given. This usually gets better within 5 minutes. Later, you might experience pain resulting in some difficulty moving

your arm, but this should resolve within a few days. In addition to pain, you may experience redness, swelling, itchiness or warmth at the injection site.

b) General reactions

During the first 24-48 hours after vaccination, you may experience flu-like symptoms such as muscle aches, joint aches, feverishness, chills, headache, nausea, tiredness and/or feeling generally unwell. These symptoms should usually resolve within a few days and can be experienced whichever vaccine you are given

c) Serious Reactions

With any vaccination there is a risk of rare serious adverse events, such as an allergic reaction. These may be related to the immune system or to the nervous system. Severe allergic reactions to vaccines (anaphylaxis) are rare, but can be fatal. In case of this unlikely event, medication for treating allergic reactions is available and the investigators are appropriately trained in the management of anaphylaxis. Reactions in the nervous system are also extremely rare, but can cause an illness called Guillain-Barré syndrome, 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. In the current trial we have undertaken safety reviews when volunteers in the trials of ChAdOx1 nCoV-19 developed unexplained neurological symptoms including changed sensation or limb weakness, and have paused the study while a safety review took place. After independent review, these illnesses were either considered unlikely to be associated with the vaccine or there was insufficient evidence to say for certain that the illnesses were or were not related to the vaccine. In our trial for each of these cases, after considering the information, the independent reviewers recommended that vaccinations should continue. Close monitoring of the affected individuals and other participants will be continued. Almost 200 million doses have now been administered worldwide and these neurological illnesses have not been identified as a side effect.

With any new medicine or vaccine there is always a possibility of an unexpected side effect.

Following reports of blood clots with lowered platelets a review has been undertaken by the MHRA (Medicines and Healthcare products Regulatory Agency) and the EMA (European Medicines Agency). The reports were into a very rare type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST), and in some other organs together with low levels of platelets (thrombocytopenia) that might be associated with vaccination with ChAdOx1 nCoV-19. 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.

More investigations are needed, but as a precaution the JCVI (Joint Committee on Vaccination and Immunisation), that advises the UK government on vaccination policy, have recommended that those under 30 years old who have not yet had a first dose of the ChAdOx1 nCoV-19 vaccine, have an alternative COVID-19 vaccine. This decision was made by looking at the risk of clots following vaccination versus the benefits of receiving protection from COVID-19 disease. Severe COVID-19 disease is much less common in young adults.

To remain in line with this guidance, participants in the study who are under 30 years and were randomised to the control group will not be offered a first dose of the study vaccine as had previously been planned. Instead they should wait until they receive an invitation for vaccination via the NHS roll out. For those over 30 years of age, ChAdOx1 nCoV-19 vaccine will be offered after unblinding as a study procedure, also in line with JCVI guidance.

The JCVI recommended that second doses of the ChAdOx1 nCoV-19 vaccine should continue, as there were no reports of clots associated with the second dose. So participants who have received a single dose of vaccine, can continue to attend for an Extra Visit B following unblinding.

Updated, 7th May 2021: The latest guidance from the JCVI extends the above and advises a preference for adults aged 30 to 39 without underlying health conditions to receive an alternative to ChAdOx1 nCoV 19.

The full reports released by MHRA and JCVI can be found at the following links:

https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement-7-may-2021/use-of-the-astrazeneca-covid-19-azd1222-vaccine-updated-jcvi-statement-7-may-2021

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

Additional side effects to be alert for in the 28 days following vaccination are;

- 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.

Theoretical Concerns – could immunisation with ChAdOx1 nCoV-19 make COVID-19 disease worse?

In the past, experimental vaccines were developed by different research groups against the SARS virus, which is in the same family as the COVID-19 virus and also infects the lungs. In some cases, animals that received certain types of experimental SARS vaccines appeared to develop *more severe* lung inflammation when they were later infected with SARS compared with unvaccinated animals. There has also been one report of this increased disease associated inflammation being seen in a mouse study for a vaccine against MERS-CoV (another related virus) but this has not been observed in any other reported animal studies.

These problems were not seen in animal studies with ChAdOx1-MersCoV vaccine, which is very similar to the vaccine being used in this study, when the animals were exposed to the wild virus Studies of the ChAdOx1 nCoV-19 vaccine in animals are currently ongoing but: *we do not yet know whether this could also be a side effect of exposure to the pandemic COVID-19 virus in this COVID-19 vaccine study, whether this effect could occur in humans or whether this might lead to more severe COVID-19 disease in some cases.*

What are the advantages of taking part?

You will not necessarily gain any direct benefit from the trial, but the information gained from the study might help to develop an effective vaccine against COVID-19. If in the future you become exposed to COVID-19, ***you should not assume that the vaccine you received in this study will give you any protection against COVID-19***. Participants who receive MenACWY will reduce their risk of meningitis and sepsis caused by group A, C, W or Y meningococcus.

What should you do if you believe you may have developed COVID-19 during the study?

If you believe that you may have COVID-19 while enrolled in the study then you must immediately inform the study team on phasetwocov@sgul.ac.uk. Do not attend the clinical trial site unless you have been informed to by the study team. If you are at all unsure please contact the study team.

When calling to inform the study team that you may have COVID-19 we will either ask you to arrange for a COVID-19 test locally or attend a visit at the study site. At the visit we will use a nose and/or throat swab to collect a sample and check if you have the virus or not. We will also be taking a blood sample at this stage for immunology monitoring. Around a week following a positive swab result, you will receive a telephone or video call to review your health. You may be asked to attend for a visit if the study team feel an in person review is necessary.

If you are unwell and unable to contact the study team directly then contact the NHS 111 service or phone 999 if you are severely unwell.

If you have a positive swab performed outside the study or diagnosed as having COVID-19 disease while in the study then you must contact the study team and should not attend the clinical trial site until the trial team have informed you it is safe to do so. We would also contact you regularly to check your health.

If you are admitted to hospital during the study then you should inform the medical or nursing staff that you are taking part in this trial. We will provide a contact card for you to give to these staff which will have a link to a website for them to fill in details about your admission.

It is important that you understand that if you do become seriously unwell and need to be admitted to hospital, the standard referral routes within the NHS will be used. Participants will be treated the same way as the general population in this context of the COVID-19 pandemic. We are unable to offer extra medical support outside what is available within the NHS for the general public.

Will I be paid for taking part in this trial?

If you are in group 4, 6, or 10 you will not receive any compensation for your time, travel or inconvenience of procedures.

If you are in group 2 or group 8, once enrolled you will be compensated for your time, the inconvenience of having blood tests and procedures, and your travel expenses. The total amount compensated will be approximately between £390-555

Trial reimbursement will be made by bank transfer within six weeks of your completion of the trial, so please bring your bank details with you to your screening visit (no cash payments can be made). Should you decide to withdraw from the trial before it is completed, payment will be *pro rata* (you will receive a proportion of the total amount).

What if new information becomes available?

Sometimes during the course of a trial, new information relevant to the trial becomes available. If this happens, we will tell you about it and discuss whether you want to, or should, continue in the study. If you decide to continue to take part, you will be asked to sign an updated consent form. On receiving new information, we may consider it to be in your best interests to withdraw you from the study. Your participation in this study may also be stopped at any time by the study doctor or the Sponsor for other reasons.

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

If, at any time after agreeing to participate, you change your mind about being involved with this study you are free to withdraw without giving a reason. If you withdraw we would not usually perform any more research procedures, although occasionally we might need to offer you a follow up visit for safety purposes, for example to check the injection site or a blood result. Your decision will not result in any penalty. Unless you state otherwise, any blood taken whilst you have been in the study will continue to be stored and used for research as detailed above. You are free to request that your blood samples are destroyed at any time during or after the study. If you choose to withdraw from the trial, your standard medical care will not be affected.

What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and make every effort to ensure your safety and well-being. The University of Oxford, as the research Sponsor, has arrangements in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

In the event of harm being suffered, while the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. NHS indemnity operates in respect of the clinical treatment which may be provided if you needed to be admitted to hospital.

Complaints statement

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the research investigators who will do their best to address your concerns by sending us an email to phasetwocov@sgul.ac.uk. Alternatively you may 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

Would my taking part in this trial be kept confidential?

All information that is collected about you during the course of the research will be coded with a study number and kept confidential. The information is available to the trial team, authorised collaborators, ethical review committees, St George's University Hospitals NHS Foundation Trust, government regulatory agencies and the Sponsor (University of Oxford), who can ask to access the trial data. Responsible independent monitors may be given access to data for monitoring and/or audit of the trial to ensure we are complying with regulations. They are bound by the same confidentiality rules. The electronic diary is sent to you by email to complete online. Your email address will be stored on a secure University of Oxford server, access to the diary system is password controlled and only study site staff and sponsor IT management can view the email address.

Samples collected using home swab kits may be processed at laboratories within and outside the UK, as determined by the community testing programme. These processing laboratories receive only the swab and barcode label; your personally-identifiable information is not shared with these laboratories. The laboratories provide a test result for the barcode to an NHS database (NPEx (National Pathology Exchange)) and this result is recombined with your personally-identifiable information by NHS Digital.

NHS Digital provide your results along with personally-identifiable information to the Sponsor (University of Oxford) who will match this with personal data including identifying contact information sent to them by your hospital/clinicin order to centralise the processing of weekly surveillance results..

If you have a positive swab result for COVID-19 during the course of the study then the Public Health Authority will be notified as COVID-19 is a "notifiable disease" and this is legal requirement in the UK. This may mean your personal information (test results, name, contact details) from your health records will be shared with Public Health either by the processing lab or the study site. You may also be contacted by the NHS Test and Trace service.

If you consent to collect a stool sample when required; the stool sample (in an anonymised form) will be collected from you by a courier and processed in a laboratory by International Health Management Associates (IHMA), an accredited central laboratory. The sample will then be shipped for analysis by Astra Zeneca in a laboratory in the US. You would need to provide your name and address to the courier company.

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 or restricted access office at the St George's University Hospitals NHS Foundation Trust or at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), University of Oxford. Trial results will be published in a scientific journal but nothing that could identify you will be included in any report or publication.

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 study 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 study has finished. The need to store this information for longer in relation to licensing of the vaccine will be subject to ongoing review. De-identified research data will be stored indefinitely. 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 identify you. We store research data securely at the University of Oxford indefinitely following removal of identifiable information. If you agree to your details being held to be contacted regarding future research, 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.

The study team will use your name and contact details, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, in relation to your health during the study and to oversee the quality of the study.

If you are diagnosed with COVID-19 during the course of the study your personal information (test results, name, contact details) from your health records will be shared with Public Health either by the processing lab or the study site. You may also be contacted by the NHS Test and Trace service.

At the completion of the study, 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 study carried out by the St George's University Hospitals NHS Foundation Trust, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

Group 2 and 8: 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. Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights

Involvement of the General Practitioner (GP)/Family doctor (GP)

In order to enrol into this study, you will be required to sign a form documenting that you consent for us to contact your GP. This is to inform them that you are interested in being involved in the study, and to check there are no medical reasons that they are aware of that would make your participation inadvisable. Your GP may be asked to share information about your medical history and give access to any other medical records as required. The researchers will not enrol you in the trial if your GP has relevant concerns about your eligibility

or safety. We will write to your GP to let them know about your enrolment and study completion status, so they can update your medical records accordingly.

If you have up to date copies of your medical records or GP summary records please bring these to your screening visit.

What will happen to any samples I give?

If you consent, some of your leftover blood samples can be stored and used for future infectious disease or vaccine-related research. This is optional; your participation in this study will not be affected by your decision whether to allow storage and future use of your leftover samples. Upon your request at any time, your remaining blood samples will be destroyed.

To avoid repeat testing, if you are not enrolled into this study and you apply to enter another study conducted by the St George's University Hospitals NHS Foundation Trust based in Tooting, the results from your screening visit blood tests may be used to determine whether you are eligible for the trial you applied for.

Your study visit samples will be analysed in the site laboratories, Oxford University research laboratories or other specialist laboratories. Other tests to look at the response of your body to the vaccine or to COVID-19 will be done with collaborating laboratories in the UK and in other countries, including the United States. Any samples or data sent to them would not include information that identifies you.

Your weekly swab tests for COVID-19 will be performed in partnership with the Department of Health and Social Care national community testing programme.

Will any genetic tests be done?

We may 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 look at the expression of certain genes which relate specifically to the immune response to COVID-19, but no genetic tests concerning diseases or conditions other than COVID-19 and other vaccine related responses.

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 1 or 2 years after the study is completed. If you contact the researchers in the future, you can obtain a copy of the results. You will not be identified in any report or publication.

The de-identified data from this study will be shared with the collaborating partners who are organising and funding this research work. 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. Data from this study may be used as part of a student post-graduate degree, for example a MD or PhD.

Taking part in future vaccine-related research

With your consent, we would like to keep your contact details after your participation in this study is complete, so we may inform you of opportunities to participate in future vaccine-

related research. This is entirely optional and your participation in this study will not be affected by your decision to allow or not allow storage of your contact details beyond your participation in this trial.

Your details will be stored electronically on a secure server and only authorised individuals at the St George's University Hospitals NHS Foundation Trust will have access to it. We will not, under any circumstances, share your contact details with any third party institutions without your permission. Being contacted does not oblige you to agree to take part in future research and you can ask us to have your contact details removed from our database at any time.

Who is sponsoring, organising and funding the research?

The study is organised and sponsored by the University of Oxford. The study is funded through financial support to the University of Oxford from the National Institute for Health Research (NIHR), which is a UK government funded research agency. Funding for analysis of some exploratory objectives has been received from AstraZeneca. Neither your GP nor the researchers are paid for recruiting you into this study.

Who has reviewed the study?

This study has been reviewed by the NHS Research Ethics Service (RES) – South Central – Berkshire and has been given a favourable ethical opinion. The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates the use of all medicines in the UK, has reviewed the study design and has granted permission to use this unlicensed vaccine in this clinical study.

Further information and contact details

If you have to relocate during the course of the study and would like to continue taking part, it may be possible if there is a study site nearby that are able to perform the remainder of your study visits. If this were the case we may transfer copies of your research notes including consent forms. The responsibility for your continued care in the study would be transferred to the new study site.

We hope this information sheet has answered all of your questions. If you would like further information about participating in research please visit the following website: http://www.nhs.uk/conditions/Clinical-trials/Pages/Introduction.aspx. For independent advice about participating in this trial you may wish to contact your GP. If you would like to speak to one of our team members to discuss any aspect of this trial or **if you are interested in taking part in the study, please contact us**:

Vaccine Institute
Room 0.123 Ground floor Jenner Wing
St Georges University of London
Cranmer Terrace
Tooting
London
SW17 0RE
E-mail: phasetwocov@sgul.ac.uk