PARTICIPANT INFORMATION SHEET: COV001

A study to assess a new COVID-19 vaccine in healthy adults

"A phase I/II study to determine efficacy, safety and immunogenicity of the candidate COVID-19 vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers"

Updated information about unblinding can be found on p9.

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 <<contact details>> 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:

<<external vaccine registration website URL>>

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.

The trial will involve up to 1112 volunteers. We will randomly sort up to 1102 volunteers so that half will be given the COVID-19 vaccine and half will receive a control. You won't know whether you received the COVID-19 vaccine or not until the trial is completed (unless you are one of 10 volunteers recruited into group 3).

What is the purpose of this research study?

The purpose of this study is to test a new vaccine against COVID-19 in healthy volunteers.

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 coronavirus disease 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 to 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 if healthy people can 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 its ability to generate good immune responses against the virus. We will do this by randomly allocating participants to receive the vaccine or a control injection in addition to doing blood tests and collecting information about any symptoms that occur after vaccination.

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?*)

We will give you an injection with either the ChAdOx1 nCoV-19 or a licensed vaccine (MenACWY) that will be used as a 'control' for comparison into the muscle around the shoulder region; this is the most commonly used route for vaccination. At the start of the trial we will also recruit a separate small group of 10 volunteers that will receive 2 doses of ChAdOx1 nCoV-19 4 weeks apart.

Until now, this 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.

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. Due to the urgent need for a vaccine against COVID-19, with agreement from the MHRA, some of the tests usually required for a newly manufactured vaccine have been modified, in order to make the vaccine available more quickly for assessment in this clinical trial. It is not anticipated that this will have an impact on the safety of the vaccine.

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 return to the clinic for a follow up appointment for safety reasons.

Can I take part?

In order to be involved in the study you must:

- Be a healthy adult aged between 18 and 55 years.
- Be able and willing (in the Investigator's opinion) to comply with all study requirements. You must be able to attend study visits and not rely on public transport or taxis
- Allow the Investigators to discuss your medical history with your GP.
- Practise continuous effective contraception for at least 3 months after your last vaccination (women of childbearing potential only).
- Refrain from blood donation for 3 months after the last study vaccine.

You cannot participate in this study if:

- You have participated in another research study involving vaccines, medications or frequent blood samples or received any vaccines in the last 30 days. The exception to this is the licensed seasonal influenza vaccine and the licensed 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.
- You are planning to participate in another study at the same time as this study.
- You have previously received an investigational vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccine, any other Coronavirus vaccines)
- You have had antibody infusions and/or any blood products (such as a blood transfusion) in the 3 months preceding your involvement in this trial.
- You have any bleeding disorders
- You have problems with your immune system.
- You are pregnant, breast feeding or intend to become pregnant during the study.
- You have a history of a severe allergic reaction.
- You have a history of cancer.
- You have a history of a serious psychiatric condition that may affect participation in the study.
- You have any other serious long-term illnesses requiring hospital follow-up.
- You have a chronic respiratory condition, including asthma
- You have any of high blood pressure, diabetes, chronic kidney, liver, heart or neurological disease
- You are seriously overweight (BMI ≥40 Kg/m^2) or underweight (BMI ≤18 Kg/m^2)
- You drink on average more than 42 units of alcohol a week (a pint of beer is 2 - 3 units, a small glass of wine (125mL) one unit and a shot of spirits (25mL) one unit).
- You have injected recreational drugs at any time in the last 5 years
- You have hepatitis B, hepatitis C or HIV infection.
- You were diagnosed with confirmed COVID-19 at any point
- You have a new onset of a fever and a cough or shortness of breath or new onset of loss of sense of smell or taste since February 2020*****
- You live in the same household as any vulnerable groups at risk of severe COVID-19 disease
- You are likely to have been previously exposed to COVID-19 (e.g. frontline healthcare worker seeing COVID-19 patients, had to self-isolate for any reason, had contact with a confirmed COVID-19 case)*****

*****For frontline healthcare workers a screening test may be performed to distinguish possible prior exposure to COVID-19. The result of this test may allow inclusion. See more information below.

Mild conditions that are well-controlled would not automatically exclude you from participating. 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.

You must be able to comply with all of the trial requirements and be able to attend all of the follow up visits. Access to a car or other means of private transport is a requirement. You will not be able to take part in this study if you rely on public transport or taxis to attend the visits.

How is the trial going to work?

The main focus of this study is to find out if this vaccine is going to work against COVID-19, if it won't cause unacceptable side effects and if it induces good immune responses. The dose used in this trial was chosen based on previous experiences with other ChAdOx1 based vaccines.

You will be allocated to one of the study groups described below. ***IMPORTANT: <u>You will not know which group you were allocated to or which treatment you received until the study is finished,</u>*** unless you are in Group 3. This is very important for the research group in order to minimise bias when interpreting the results. We will enrol participants in Groups 1 and 3 first, and then start recruiting into Group 2.

You may receive either:

a) 1 dose of the COVID-19 vaccine
b) 1 dose of the control vaccine
c) 2 doses of the COVID-19 vaccine (10 people only)

The first 2 people will receive the vaccine or control. We will review them within 48 hours before we proceed with vaccinations in 6 more volunteers in the same group. They will also be reviewed within 48 hours before we vaccinate the remaining volunteers.

Booster dose

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.

Groups 2c, 2d and 2e were added to compare different booster doses. Group 2c received the same dose at booster as the first dose and group 2d received half the dose at booster. Group 2e received a MenACWY booster dose which is the same as their first dose. Participants were randomly assigned to group 2c or 2d. We are now inviting all participants in groups 2 and 4 to have a further (booster) vaccine. 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 booster dose of ChAdOx1 nCoV-19. 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.

Previous vaccinations per group:

Group (max numbers)		**Week 0**	**Week 4**	**Week 8**	**Booster**
1 **(88 volunteers)**	a/b	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR**	-	-	-

		MenACWY Vaccine			
2 **(up to 412 volunteers)**	a/b	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine	-	-	-
	c	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose)		ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose)	-
	d	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose)		ChAdOx1 nCoV-19 $2.5x10^{10}$vp	-
	e	MenACWY Vaccine		MenACWY Vaccine	-
	f/g	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine	-	-	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine
3 **(10 volunteers)**	a	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose)	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose)	-	-
4 **(up to 602 volunteers)**	a/b	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine	-	-	-
	c/d	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine	-	-	ChAdOx1 nCoV-19 Vaccine ($5x10^{10}$ vp dose) **OR** MenACWY Vaccine

vp = viral particles

Late Vaccination

To help reduce the possibilities of further waves of COVID-19 disease, booster vaccines may be needed in the future. To understand the effect of a delayed vaccination on the immune system and to inform decisions about boosters, individual participants, that have not yet been unblinded or received a COVID-19 vaccine outside of the study or at an Extra Visit B, will be invited to receive one or two doses of the ChAdOx1 nCov-19 vaccine.

Where participants have already had two doses of ChAdOx1 nCov-19 in the study, the late vaccination visit will involve them receiving a ***third*** dose of the ChAdOx1 nCoV-19 vaccine. For the participants who previously had two doses of MenACWY in the trial, the late vaccination visit will be their ***first*** dose of ChAdOx1 nCov-19. As we are (mostly) inviting participants that are still blinded for these visits, the majority will not actually know whether they are receiving their *first* or *third* dose of ChAdOx1 nCov-19 vaccine at the late vaccination visit, although they will be informed of this just over one week later as described below. (Note: A small number of already-unblinded participants will also be invited, from groups 2c and 3, who will already know this is their third dose.)

Around one week after the 'late vaccination' visit, the participants in the late vaccination sub-groups will be unblinded and told which vaccines they have already received in the study. The participants who previously only received the MenACWY vaccine(s) in the study will also receive an additional dose of the ChAdOx1 nCov-19 vaccine 12 weeks after the initial dose given at the "late vaccination visit". This will be their second ChAdOx1 nCoV-19 vaccine and fourth vaccine overall in the study (2xMenACWY vaccines followed up with 2xChAdOx1 nCoV-19 vaccines). As most participants do not know which vaccines they received previously, they must be prepared to attend 4 or 5 visits over the next 6 months when accepting the invitation for vaccination.

Some vaccines provide better immune responses in females than in males. To investigate this further, female participants will be questioned about their menstrual cycle prior to receiving their vaccination.
An outline of the new groups is below, for the full table of procedures see tables on p19.

Late Vaccination visits:

Group 1c (for participants previously in Group 1a):

	No. of previous study vaccines	Late Vaccination (LV) *Approx. 9 months post 1st vaccine dose*	Visit 2 14 days after LV	Visit 3 28 days after LV	Visit 4 6 months after LV
Vaccine	1	X			
Blood tests		X	X	X	X

Group 1d (for participants previously in Group 1b):

	No. of previous study vaccines	Late Vaccination (LV) *Approx. 9 months post 1st MenACWY vaccine*	Visit 2 14 days after LV	Visit 3 28 days after LV	Visit 4 3 months after LV	Visit 4 6 months after LV
Vaccine	1	X			X	
Blood tests		X	X	X		X

Group 5a (for participants previously in two-dose ChAdOx1 nCoV-19 Groups: 2c, 2f and 4c) and 3b:

	No. of previous study vaccines	Late Vaccination (LV) *Approx. 9 months post 1st vaccine dose*	Visit 2 14 days after LV	Visit 3 28 days after LV	Visit 4 6 months after LV
Vaccine	2	X			
Blood tests		X	X	X	X

Group 5b (for participants previously in two-dose MenACWY Groups: 2e, 2g and 4d):

	No. of previous study vaccines	Late Vaccination (LV) *Approx. 9 months post 1st MenACWY vaccine dose*	Visit 2 14 days after LV	Visit 3 28 days after LV	Visit 4 3 months after LV	Visit 5 6 months after LV
Vaccine	2	X			X	
Blood tests		X	X	X		X

All participants accepting the invitation for late boost will be asked to complete a diary for 7 days after each vaccination to record any side effects of vaccination. After this period we ask participants to inform the study team of any serious health problems or if admitted to a hospital.

If you developed COVID-19 symptoms and have had a positive PCR test since the first vaccination, you can only receive a booster dose after a minimum 4 weeks interval from your PCR positive test, provided your symptoms have significantly improved. The decision to proceed with booster vaccinations in those cases will be at clinical discretion of the investigators. For participants who are asymptomatic and have a positive PCR test (e.g. done outside the study), a minimum of 2 weeks from PCR positivity will be required before boosting.

What will happen if I decide to take part?

(See the final page of this document for the schedule of trial visits)

Screening Visit – *2 hours (Review participant information sheet with an investigator, consent form, ID check, discuss medical history, physical examination if required, vital signs measured, blood test and urine sample)*

If you decide you would like to take part in this trial, you will need to attend a screening visit before the vaccination day. This should last for about two hours. The screening visit, the vaccination and all of the post-vaccination follow-up visits will take place at <<trial site>>.

At the screening visit you will be met by one of the Investigators who will go through this information sheet with you to ensure you understand what to expect by taking part, the risks involved and what side-effects you might expect to experience. You can of course expect to receive full and comprehensive answers to any questions you may have.

Once you are happy that you understand what the trial involves, and the Investigator is happy that you have understood everything, you will be asked to sign a consent form. You will be asked to agree to allow the Investigators to contact your own Doctor (GP) to make sure there are no medical reasons

why you should not participate. You will also be asked to agree to being registered on the TOPS (The Over-Volunteering Prevention System) database which is set up to prevent people entering into multiple studies or trials at the same time.

Having signed the appropriate forms, the Investigator will go through a few questions for administrative purposes and detailed questions related to your health. After this you will be asked about your health and past medical problems in detail. This will be followed by a physical examination which will involve a doctor 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 blood pressure, pulse and temperature will also be recorded.

A number of blood tests will 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. You will also be asked to provide a urine sample at this visit to check for glucose (to exclude diabetes), protein and blood (which can indicate kidney disease). Women will also have a urine pregnancy test performed.

A test to check for pre-existing antibodies against SARS-CoV-2 may be done at the screening visit, to identify those who might have already had the infection and exclude them from the study. Test availability is limited and it will not be available for all study participants. We will prioritise testing in those who have higher chances of being exposed to COVID-19, such as frontline healthcare workers for example, but cannot guarantee that all of those in the priority group will get tested. 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.

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 - *1 hour (vital signs if necessary, blood test, urine pregnancy test, receive 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 blood pressure, pulse and temperature (observations) and we will take blood samples. All women will have a urinary pregnancy test before each vaccination.

We will give you an injection with the vaccine or control 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.

Booster vaccinations

If you decide to have a booster dose of the vaccine, we will ask you some brief questions about your health, before giving the vaccine into your arm and may coverwith 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.

After receiving the booster, there will be four additional follow up visits as outlined in the tables at the end of this information sheet.

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

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. 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 or contact you using a smartphone or computer app to ask for more information.

You will also be asked to fill out a household COVID-19 exposure questionnaire for the duration of the study.

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 follow up visits, depending which group you are allocated to (lasting approx. 30 minutes), as detailed in the tables at the end of this document.

For groups 1 and 3 you will need to attend short visits at 3 and 7 days after each vaccine to ensure everything is fine, to check your symptoms, the injection site and to have blood tests done. We will also give you a phone/video call on the day after your vaccination to ask about any serious reactions..

We will check your observations, take a blood sample, and review your completed E-diary. You will also be asked to attend an extra visit 1 year after your vaccination to give us further useful data about the vaccine. 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. You will be compensated for the time and inconvenience of any extra visits. After the last visit, your participation in the trial will be complete.

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.

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

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. If you decide to have the approved COVID-19 vaccine, this will not be part of this study and would be administered by the NHS, however we would still ask you to continue to attend your remaining visits as scheduled.

Before you are given the approved vaccine your site may ask you to come for an extra visit to collect a blood sample. You will also be asked to complete an online form with details of the vaccines you were given and the dates you had them.

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
- receive 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:

- Received one dose of the ChAdOx1 nCoV-19 vaccine:
  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.
- 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 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.**
<<external vaccine registration website URL>>

Length of research

If you decide to take part in this study, you will be involved in the trial for approximately 6 months and will be asked if you are willing to attend an extra visit at 1 year after your first vaccination. If you decide to have a booster dose of vaccine, the length of your involvement in the study would be increased to 12 – 15 months. (Note: this does not apply to vaccines received as part of the trial unblinding process)

Considerations before taking part in this study

Blood Donation: Under current UK regulations, participants will not be able to donate blood for 3 months after the last dose of vaccine is administered.

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.

Contraception: 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. post-menopausal 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 study, 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. Participants that have been unblinded and are due to receive doses of ChAdOx1 nCoV-19 vaccine either as part of the national rollout, as an Extra Visit if they received a single dose of vaccine in the study or if they were a control, will be advised that they do not need to continue to use effective contraception within the trial. This is in line with national guidance.

What should I avoid during the trial?

You should not donate blood for 3 months after the last vaccine has been administered 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 up to 60ml of blood (approximately 4 tablespoons) at a single visit. The total amount we will take over the period of the trial will depend on your group (Group 1 = up to 506.5ml, group 2 = up to 400ml, group 3 = up to 621.5ml, group 4 = up to 182.5ml, Group 5 = up to an additional 252.5ml). The volume of blood taken at each visit ranges from 5ml to approximately 60ml.

The following blood tests will be performed:

- Tests for Hepatitis B, Hepatitis C and HIV are done at the screening visit.
- HLA typing, a test of a component of the body's immune system may be done at the first vaccination visit (groups 1 and 3 only).
- Tests of red and white blood cells, liver and kidney function are done at the screening visit and most of the other visits (including the vaccination day), in order to check the vaccines are safe.
- Tests of the immune responses to vaccines are done at most of the visits.

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.

2. Vaccination Side Effects

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 these are vaccines 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.

Although the vaccine is being tested for the first time, 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.

a) Local Reactions at vaccination site

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.

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 kept in the clinic room 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. 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. 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.

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

[INSERT LINKS]

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.

<u>Theoretical Concerns – could this vaccine make COVID-19 disease worse?</u>

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 about reactions to MenACWY?

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. After immunisation with MenACWY participants may experience the local and general reactions described above for ChAdOx1 nCoV-19, and as with any vaccine there is a small risk of a significant allergic reaction.

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 <<contact details>>. 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 the study team we will either ask you to arrange for a COVID-19 test locally or attend a visit at the study site. At this 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.. For further information on how the DHSC will handle data from your swab, please see INSERT GOVERNMENT LINK. You may be asked to attend for a visit if the study team feel an in person review is necessary. We may also 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.

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 are 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.

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?

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 **£<<XXX>>** depending on the exact number of visits and whether any repeat or additional visits are necessary.

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 INSERT SITE EMAIL. 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, Oxford University Hospitals NHS 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. Any information about you that leaves the hospital/clinic will have your name and address removed so that you cannot be

recognised from it. However, with your permission, we may share a copy of your consent form with the independent monitor.

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/clinic in order to centralise the processing of weekly surveillance results.

If you have a positive swab result 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 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 in a restricted access office at the INSERT SITE NAME. 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. 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. 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 INSERT SITE NAME, 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. 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.

Prevention of 'Over Volunteering'

Volunteers participating in this study must not be concurrently receiving investigational medications or vaccines in another study at the same time. In order to check this, you will be asked to provide your National Insurance or Passport number. This will be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. More information can be found at *www.tops.org.uk*. Your national insurance or passport number is also required to allow processing of compensation payments.

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 INSERT SITE NAME based at the INSERT LOCATION, 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 blood tests will be analysed in the site (hospital) laboratories and Oxford University research laboratories. Other blood tests to look at the response of your body to the vaccine will be done with collaborating laboratories in the UK and in other countries. Any samples or data sent to them would not include information that identifies you.

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 INSERT SITE NAME 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 primarily funded through financial support to the University of Oxford from United Kingdom Research and Innovation (UKRI) which is a UK government funded research agency. 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**:

<<Insert Site recruitment contact details (address, email, phone)>>

Trial Visit Schedule

Late Vaccinations:

GROUPS 1c, 3b and 5a (Late Vaccination participants that received ChAdOx1 nCoV-19 earlier in the trial)

	Late Vaccination (LV) ***Approx. 10 months post 1st vaccine dose***	**Around 8 days after LV** *Remote by email or phone*	**Visit 2** **14 days after LV**	**Visit 3** **28 days after LV**	**Visit 4** **6 months after LV**	**COVID-19 Testing** *At study site or other testing facility*	**COVID-19 PCR positive** **+7 days** *If required*	**COVID-19 Follow-up** *If required*
Vaccination	X							
Blood Tests	X		X	X	X	X	X	
Menstrual cycle questions	(X) females							
Urine Test	(X) females							
Unblinding		X						
Nose/Throat Swab						X	X	
Phone/Video call							X	x

GROUPS 1d and 5b (Late Vaccination participants that received MenACWY earlier in the trial)

	Late Vaccination (LV) ***Approx. 10 months post 1st vaccine dose***	**Around 8 days after LV** *Remote by email or phone*	**Visit 2** **14 days after LV**	**Visit 3** **28 days after LV**	**Visit 4** **3 months after LV**	**Visit 5** **6 months after LV**	**COVID-19 Testing** *At study site or other testing facility*	**COVID-19 PCR positive** **+7 days** *If required*	**COVID-19 Follow-up** *If required*
Vaccination	X				X				
Blood Tests	X		X	X		X	X	X	
Menstrual cycle questions	(X) females				(X) females				
Urine Test	(X) females				(X) females				
Unblinding		X							
Nose/Throat Swab							X	X	
Phone/Video call								X	X

Original groups:

GROUPS 1a and 1b: 1 Screening visit, 1 Vaccination visit, 7 follow up visits

	Screening	**Day 0** **VACCINATION**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 56**	**Day 182**	**Day 364**	**COVID-19 Testing** *At study site or other*		**COVID-19 PCR positive** **+7 days** *If required*	**COVID-19 Follow-up** *If required*	**Extra Visit for Booster** *If required*	**Extra Visit(s) for unblinding** *If required*

										testing facility					
Vaccination		X													X	(X)
Blood Tests	X	X		X	X	X	X	X	X	X	X		X		X	X
Urine Test	X	(X) females														
Nose/Throat Swab											X		X			
Phone/Video call			x										X	x		

GROUPs 2a, 2b and 4: 1 Screening visit, 1 Vaccination visit, 3 follow up visits

	Screening	**Day 0** **VACCINATION**	**Day** **28**	**Day** **182**	**Day** **364**	**COVID-19 Testing** *At study site or other testing facility*		**COVID-19 PCR positive** **+7 days** *If required*	**COVID-19** **Follow-up** *If required*	**Extra Visit for Booster vaccine** *If required*	**Extra Visit(s) for unblinding** *If required*
Vaccination		X								X	(X)
Blood Tests	X	X	X	X	X	X		X		X	X
Urine Test	X	(X) females									
Nose/Throat Swab						X		X			
Phone/Video Call								X	x		

GROUPs 2c, 2d and 2e: 1 Screening visit, 2 Vaccination visits, 4 follow up visits

	Screening	**Day 0 VACCINATION**	**Day 28**	**Day 56**	**Day 70**	**Day 84**	**Day 182**	**Day 364**	**COVID-19 Testing** *At study site or other testing facility*		**COVID-19 PCR positive +7 days** *If required*	**COVID-19 Follow-up** *If required*	**Extra Visit(s) for unblinding**
Vaccination		X		x									(X)
Blood Tests	X	X	X	x	x	x	X	X	X		X		X
Urine Test	X	(X) females		(X) females									
Nose/Throat Swab									X		X		
Phone/Video Call												x	

GROUPs 2f, 2g, 4c, 4d (Booster): 1 Screening visit, 2 Vaccination visits, 5 follow up visits

	Screening	**Day 0 VACCINATION**	**Day 28**	**At least 4 weeks post first vaccination**	**Day 28 post boost**	**Day 90 post boost**	**Day 182 post boost**	**Day 364 Post boost**	**COVID-19 Testing** *At study site or other testing facility*		**COVID-19 PCR positive +7 days** *If required*	**COVID-19 Follow-up** *If required*	**Extra Visit(s) for unblinding**
Vaccination		X		x									(X)
Blood Tests	X	X	X	x	x	x	X	X	X		X		X

Urine Test	X	(X) females		(X) females									
Nose/Throat Swab									X		X		
Phone/Video Call												x	

GROUP 3a: 1 Screening visit, 2 Vaccination visits, 9 follow up visits

	Screening	**Day 0 VACCINATION**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 31**	**Day 35**	**Day 42**	**Day 56**	**Day 182**	**Day 364**	**COVID-19 Testing** *At study site or other testing facility*		**COVID-19 PCR positive +7 days** *If required*	**COVID-19 Follow-up** *If required*	**Extra Visit(s) for unblinding**
Vaccination		X					X											(X)
Blood Tests	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X
Urine Test	X	(X) females					(X) females											
Nose/Throat Swab														X		X		
Phone/Video Call			x														x	