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PARTICIPANT INFORMATION SHEET

LEGACY02: Examining lymph node cells to assess how age affects immune responses

You are invited to take part in a study to test how lymph nodes respond to immunisation against Crimean Congo Haemorrhagic Fever (CCHF) virus and how this changes with age.

This is a trial investigating the effect of Crimean Congo Haemorrhagic Fever ("CCHF") vaccine on the immune system. This is a novel vaccine which is in a phase 1 clinical trial at the University of Oxford and has limited safety data on its use. Participants will not be exposed to the virus and there will be no risk of contracting CCHF.

The study is being run by the Oxford Vaccine Group, which is part of the University of Oxford.

Before you decide on whether to participate in this study, it is important that you take the time to understand why the research is being done and what it would involve. Please read this information sheet carefully. If you have any further questions about the study, please do not hesitate to contact us (contact details are below and at the end of the leaflet).

If you are interested in taking part in this study, please complete the online pre-screening questionnaire at: https://www.ovg.ox.ac.uk/studies/legacy02

If you have further questions about the study that you would like to discuss with our team, please contact us at:

Email: info@ovg.ox.ac.uk

Tel: 01865 611400

Summary

Who can take part?	Adults in good health 1. Aged 18 to 45 years 2. Aged 65 years and above
Study injections	Two doses of ChAdOx2 CCHF, 12 weeks apart, given as an injection in the arm.
Procedure	Lymph node cell sampling using fine needle aspiration (FNA) of both armpits on three occasions 1. Before first study injection And then 2. 7 days after the first study injection Followed by 3. A third FNA 12 weeks after the second FNA (7 days after the second injection)
Study Aims	To investigate how age affects immune responses in lymph nodes to a new immunisation. To compare responses in older people with those in younger people.
Chief Investigator	Dr Katrina Pollock

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Principal Investigator	Dr Katrina Pollock
Study Site	Oxford Vaccine Group, University of Oxford, Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Headington, Oxford, OX3 7LE
What happens in the study?	1. Volunteers will attend a screening visit, to decide their eligibility to take part, and to obtain their consent. 2. At the next visit, the first (baseline) FNA sampling will be conducted. 3. The first study injection and the second injection will be given 12 weeks apart. 4. Any armpit or lymph node symptoms after the injections will be recorded in an electronic diary for 7 days. 5. All participants will have fine needle aspiration (FNA) sampling. All participants will be followed up for 6 months. Participants will attend a total of 9 study visits (1 screening, 2 injections, 3 FNA and 3 follow up visits). All visits will include a blood test. The safety of participants will be closely monitored throughout the study.
Reimbursement	Screening visit: £110 Study Injections () visit: £110 FNA visits: £150 per visit Follow up visit: £90 per visit Diary card: £30 per diary Total reimbursement (9 visits): £1110
Risks of participation	After **FNA**, there may be some discomfort, bruising or bleeding. Very rarely infection may occur. These risks are described below page 3. After **study injection,** short-lived symptoms may occur, such as fever and discomfort of the arm. The study injection has been made using similar technology to the Oxford-AstraZeneca Covid vaccine, which has been associated with rare disorders including abnormal blood clotting. A full discussion of risks, including potential rare but serious reactions, can be found on page 10.
Benefits of participation	By participating in this study, you will not directly receive any personal health benefit from the study or its procedures. However, you will be helping us to understand how immune responses to immunisation change with ageing.

What is the purpose of this study?

As we age, our immune system also changes and we respond less well to immunisation. Older people are often severely affected by diseases which can cause pandemics. It is important to understand how age changes the immune system. By understanding these changes, we can design vaccines which are suited to people of different ages.

We are researching how lymph nodes respond to immunisation and how this changes as we age. Lymph nodes are small bean shaped organs present all over the body. After an immunisation is given in the arm, the lymph nodes in the armpit swell in response. Inside the lymph nodes are cells that make antibody in response. Antibodies protect us from infection after we have been immunised.

Cells from lymph nodes can be sampled using a small needle. This is called **fine needle aspiration (FNA)** and it is a well-established test in the clinic; in research it enables direct testing of immune cells.

This information will help researchers design future vaccines, and decide how they are given to different populations, for example older people, to offer the best protection against disease.

This study will test how age affects the immune responses of cells in lymph nodes. To stimulate the lymph nodes, we will use an injection into the arm and compare differences between older and younger adults. The study will use a new immunisation (which we will call the study injection) called ChAdOx2 CCHF. This is designed to produce an immune response against a disease called **Crimean Congo Haemorrhagic Fever (CCHF)**.

Crimean Congo Haemorrhagic Fever does not occur in the UK, and so this study will test how lymph nodes respond to a completely new type of immunisation in people who have not had the infection. Understanding this is very important for research against pandemics which are caused by new infections.

What is fine needle aspiration (FNA)?

Fine needle aspiration (FNA) involves taking cells and fluid from a lymph node (gland).

You will have an examination to feel for lymph nodes (glands) in your armpit. An ultrasound scan will look closely for your lymph glands. Once a suitable gland has been identified, the area will be cleaned and numbed using local anaesthetic. Using the ultrasound scan for guidance, a needle will be used to collect a small amount of fluid and cells from the gland. You should not feel any pain but may feel some pressure. This procedure will then be repeated on your other armpit. The whole visit can take up to 90 minutes, but the FNA procedure itself takes only a few minutes.

FNA is commonly performed in outpatient clinics to help diagnosis in patients with different health conditions, for example for lumps or swollen glands. It will be performed by a doctor trained in the technique.

FNA is a safe and well-tolerated procedure but, as with any medical intervention, it carries some risks:

• Pain: The FNA should not be any more uncomfortable than a blood test. Any tenderness afterwards will resolve. You can take a simple painkiller like paracetamol if you need it; avoid taking aspirin, as this may increase the risk of bruising.

• Bleeding: The needle used is fine but bleeding under the skin may sometimes occur after the FNA. It usually stops quickly by itself. Any bruising will fade within 2 weeks.

• The risk of bleeding is higher if you are taking any medications that make your blood thinner such as warfarin, aspirin or clopidogrel. If you regularly take any of these medications, you will not be able to participate in the study. If you take any aspirin or blood thinning medication in the 7 days before the FNA procedure, please let us know.

• Infection after FNA is rare. If you get redness, pain and/or tenderness in the days afterwards you may need antibiotic treatment.

If the practitioner is not able to collect enough sample, they may decide to repeat the FNA with your permission.

What is the study injection?

ChAdOx2 CCHF consists of a weakened version of a virus called a *chimpanzee adenovirus.* Chimpanzee adenoviruses are naturally occurring viruses that are completely unrelated to the CCHF virus. The

natural, unmodified versions of chimpanzee adenoviruses can cause mild cold/flu-like symptoms in chimpanzees.

The weakened version of a chimpanzee adenovirus was developed using genetic engineering. This modified version of the virus is completely unable to reproduce inside the human body. This means it cannot copy itself in humans and it cannot cause infections or be spread from person to person. This modified virus is called **ChAdOx2**, which stands for 'Chimpanzee Adenovirus Oxford 2'.

A gene from the CCHF virus was inserted into the weakened chimpanzee virus. This gene provides the instructions for two important components of the CCHF virus (glycoproteins). These coat the surface of the CCHF virus and enable it to invade cells and cause infection.

You cannot catch CCHF from the study injection. The genetic code for CCHF glycoproteins is the only component of CCHF virus in the injection. The virus itself is not used to manufacture ChAdOx2 CCHF, so there is no chance of being exposed to CCHF virus at any point during this study.

This ChAdOx2 technology is similar to that used to make the Oxford/AstraZeneca COVID-19 vaccine (which used another modified chimpanzee adenovirus, ChAdOx1).

As part of its manufacture, ChAdOx2 is grown in a laboratory using modified cells that were originally derived from a sample of human tissue. These cells are called HEK 293 (human embryonic kidney 293) cells. More information on the use of human-derived cell lines in the manufacture of vaccine is available at https://vaccineknowledge.ox.ac.uk/vaccine-ingredients#Human-Cell-Lines.

The dose we will give is $5x10^{10}$ viral particles per injection. This is based on experience with similar vaccines, and is equivalent to the approved dose that is used for the Oxford/AstraZeneca COVID-19 vaccine. It is anticipated that this dose will be sufficient to produce a satisfactory immune response whilst being well tolerated.

What other studies are testing ChAdOx2 CCHF?

ChAdOx2 CCHF is being developed as a vaccine at The University of Oxford and uses similar technology to the Oxford/AstraZeneca COVID-19 vaccine. The first clinical trial of ChAdOx2 CCHF vaccine to test safety and immune response started recruiting in August 2023 and is well underway. Forty-six participants up to 55 years are receiving two doses of ChAdOx2 CCHF 12 weeks apart and being followed up to monitor their response to the vaccine. The clinical trial is registered by the ISRCTN registry and is available to view online with this registration number, ISRCTN 12351734.

What is Crimean-Congo haemorrhagic fever?

Crimean-Congo haemorrhagic fever (CCHF) is caused by a virus and can result in severe illness and death. Cases occur in many parts of the world, including southern Europe, the Middle East, Africa and south-west Asia. The World Health Organisation estimates that 3 billion people live in areas at risk, and the CCHF virus infects up to 15,000 people per year, causing 500 deaths. The virus is transmitted by ticks, which can live on many domestic and wild animals, including cattle, sheep and goats. Humans usually become infected after a tick bite, although the virus can also be caught from close contact with infected animals or humans. In some people infection causes no symptoms, but in others it can cause very serious illness with impaired blood clotting, which can lead to severe bleeding. There are currently no specific, effective treatments and there is no approved vaccine.

Previous experience with ChAdOx-based vaccines

Although ChAdOx2 CCHF is still in early development, as are some other vaccines based on ChAdOx2, there is now a lot of experience in humans with ChAdOx1-based vaccines. and we have data from a phase 1 trial using the sameChadOx2 vaccine.

Experience with the study injection

The University of Oxford is running a Phase 1 trial of the ChAdOx2 CCHF vaccine. From the initial safety data, the vaccine reactions have been as expected, and have been mild in nature in 99% of cases. They include common vaccine reactions at the site of injection like pain or general reactions like fatigue, muscle pain, headache or feeling generally unwell. Less commonly volunteers experienced joint pain, feverishness or fever, nausea (feeling sick), chills (feeling cold), warmth at the injection site or itching. These mild symptoms got better by themselves.

Experience with the Oxford/AstraZeneca COVID-19 vaccine

The Oxford/AstraZeneca COVID-19 vaccine is made using ChAdOx1 virus technology. This has been shown to be safe for the vast majority of individuals and highly effective at protecting against severe COVID-19. However, following administration of the vaccine to millions of people, a very rare but serious side-effect of blood clots in combination with low platelets has been associated with the vaccine. Further details of this are included in this information sheet (see page 10, *Are there any risks from the ChAdOx2 CCHF injection?*).

Experience with other ChAdOx1 vaccines

Trials have been carried out of ChAdOx1 based vaccines against many other diseases such as flu, malaria, meningitis B, TB, HIV and Zika virus. Over 500 individuals have received these other ChAdOx1 vaccines (not including the Oxford/AstraZeneca COVID-19 vaccine). The other ChAdOx1 vaccines were shown to be safe during these trials and they were also found to create strong immune responses against the viruses, bacteria or parasites being targeted.

Study visits

Please see page 5 for a summary image of the visits.

Visit	**What to expect**
Screening visit	1. Discussion of study 2. Sign consent form 3. Identity check 4. Review of medical history 5. Physical examination, including "vital signs" (temperature, pulse, blood pressure) 6. Blood test (and urine pregnancy test, if appropriate)
Study injections (immunisation) visits	1. Vital signs (temperature, pulse, blood pressure) 2. Blood test (and urine pregnancy test, if appropriate) 3. Ultrasound scan of both armpits 4. Administer injections by IM injection into non-dominant deltoid muscle 5. Set up eDiary after study injections
FNAs	1. Vital signs (temperature, pulse, blood pressure)

	2. Fine needle aspiration (FNA) and ultrasound scan of both armpits 3. Blood test
Follow up visits	1. Blood test 2. Review for serious medical events

What happens in the study?

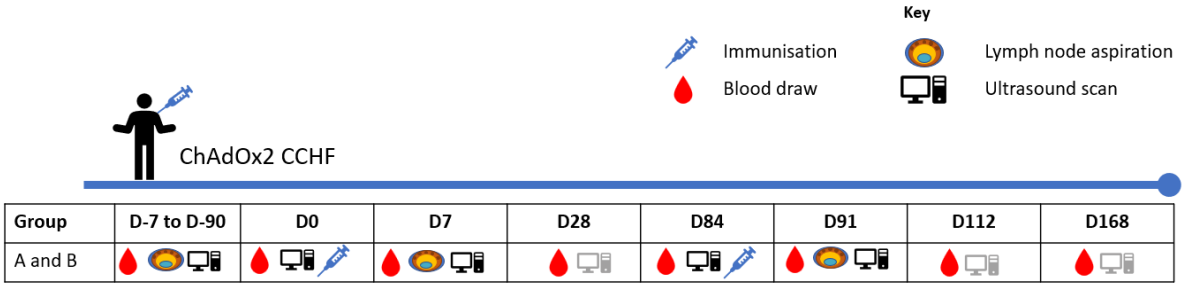
1. Recruitment and eligibility screening

We wish to recruit up to 16 people to take part in this study at Oxford Vaccine Group. Participants must be in good health and aged either between 18 and 45 years or 65 years and above. Volunteers will be asked to complete an initial online questionnaire, followed by a phone call from the study team, to assess whether they are eligible to take part. After this, volunteers will be invited to attend a screening visit which will include a medical assessment. Those who are eligible will then be invited to attend the first (baseline) FNA followed by the first injection visit.

2. Allocation to a study group

Participants will be healthy adults in two age groups allocated based on the age of the participant; Group A (18-45 years) and Group B (≥65 years)

3. Study Visits



Group	D-7 to D-90	D0	D7	D28	D84	D91	D112	D168
A and B								

Ultrasound scans in grey are dependent on site staff capacity and may not be required

All participants in the study will be given two doses of ChAdOx2 CCHF, 12 weeks apart.

Lymph node samples will be taken from both armpits. Inside the lymph nodes are cells that make antibody responses to vaccines, and it is this response that we want to measure.

Participants will attend a total of 9 study visits (1 screening, 2 study injection visits, 3 FNA visits and 3 follow up visits).

All participants will be followed up for 6 months after the first study injection.

All follow up visits will include a blood test, to assess the immune response. In addition to visits, participants will be asked to complete a short diary for 7 days after each study injection.

How long would I be in the study?

If you are eligible to take part, we will enrol you into the study for 6-9 months starting from your first FNA visit. You can, if you decide to (for whatever reason), withdraw from the study at any time (see What happens if I do not wish to carry on with the study? Page 11).

Can I take part? To take part in the study, all the following **must apply** to you**:**

You must

Be aged EITHER between **18 to 45 years** OR **65 years or over** at the time of your screening visit
Be **in good health** without a history of serious ongoing medical conditions
Be able and willing to **comply with all study requirements** including attending all follow up visits
Be willing to **allow your past medical and vaccination history to be checked by the study team** (either by allowing us to discuss your medical history with your GP, or by giving us a medical history summary)
Be willing to **register with TOPS** (The Over-volunteering Protection System)
Agree to **refrain from blood or blood product donation** during the study
Tell us about any **vaccinations** you may have received recently or expect to receive soon
Contraception
(If applicable) For *participants who could potentially become pregnant***:** Use **contraception** for the duration of the study *and* have a **negative pregnancy test** at the screening visit and study injections (immunisations) visits
Have previously received a vaccine that uses a viral vector for example the Oxford AstraZeneca COVID-19 vaccine, Johnson & Johnson (Janssen) vaccine, Some Ebola vaccines, or other viral vector vaccines in development or in clinical trials such as Zika virus, Influenza, Respiratory syncytial virus (RSV), HIV, Malaria)

You must NOT have

Current and Past Medical Problems
A **serious or unstable long-term illness** *e.g.*, a condition that requires hospital or specialist follow-up.
A **body mass index (BMI) above 35** (The NHS provides a BMI calculator at: https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/)
A history of **Crimean-Congo haemorrhagic fever** infection
A history of a **blood transfusion** or **Immunoglobulin infusions** within 3 months of the study
Regular **anticoagulant** (blood-thinning) **medication** (*e.g.* warfarin, edoxaban)
A history of a **severe allergic reaction to a vaccine or to local anaesthetic, including hypersensitivity**
A history of **angioedema**

A history of **cancer that is not fully resolved (potential participants who have had chemotherapy will be reviewed on a case by case basis for eligibility in this study)**
A **serious ongoing mental health condition** if this may affect your participation in the study
A history of either a **major blood clot**, **blood clotting disorder**, or **bleeding disorder**
A history of **thrombosis with thrombocytopenia syndrome** (TTS, also known as VITT)
A history of **capillary leak syndrome**
An intake of more than **14 units of alcohol per week** on average (The NHS recommends the following calculator: https://alcoholchange.org.uk/alcohol-facts/interactive-tools/unit-calculator)
Previously **injected recreational drugs** (within the last 5 years)
A history of **hepatitis B**, **hepatitis C** or **HIV infection**
Other Vaccines
You should try not to receive **flu or COVID-19 vaccines within 14 days** (before or after) each study immunisation. This extends to **30 days for any other vaccine**.
Other Clinical studies
You must NOT participate in **another clinical study** that involves receiving a drug or vaccine in the 12 weeks before the study starts and for the duration of the study
(If applicable) Pregnancy/Breast Feeding During the Study
You must NOT be pregnant or breastfeeding during the study

If you are unclear whether you might be eligible to be involved in the study, you can contact the study team (details at the end of this information sheet).

Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep (it will be sent electronically but you can request a paper copy) and you will be asked to sign a consent form.

What will happen if I decide to take part?

Online pre-screening questionnaire

If you decide that you would like to take part in this study, then you will need to complete a short set of online questions that cover some of the key criteria for participation in the study. If the study is right for you at this point, we will contact you to provide further instructions on the next steps. In addition, we will ask you to provide consent for the study team to access your medical records via the electronic patient records or through your GP. This consent is only to allow access to your medical records, and not the consent for enrolment into the study. If you choose to participate in the study, a separate consent will be taken at the screening visit.

Pre-screening phone-call

If you express an interest in taking part, and if the study is right for you from the pre-screening questionnaire, a member of the study team will contact you by telephone to discuss the study and answer any questions you may have. We would also ask you a few more detailed questions to assess

your eligibility. If you remain interested, and if the study is right for you, we will arrange for you to come to our clinic for a screening visit. **This visit may take up to 15 minutes.**

Screening visit

This may take place up to 3 months before the first study visit. This, and all other study visits, will take place at the Oxford Vaccine Group, University of Oxford.

At the screening visit, you will meet with study staff, who will discuss this information sheet with you and would provide an opportunity for you to ask any questions you might have about the study and what's involved. You may take as much time as you feel necessary before making any decision on whether to take part. If you then decide to take part, and the study team considers that you have understood the information, you will be asked to sign the study consent form.

This will be followed by a physical examination, which will include the doctor listening to your heart and lungs with a stethoscope and examining your abdomen. Your vital signs (blood pressure, pulse, and temperature), weight and height will be measured. A blood sample will be taken (approximately 10 mL equivalent to 2 teaspoons). If applicable, a urine sample may also be taken to perform a pregnancy test. **This visit will take about 90 minutes.**

Study injection visits

If you qualify to be in the study after the screening visit eligibility checks, we will arrange for you to attend the first FNA visit. After this you will attend the first study injection visit. We will check there have been no new problems since your screening visit. Your blood pressure, pulse, and temperature (vital signs) will be checked, and a blood sample taken (approximately 50ml or just over 3 tablespoons). If appropriate, you will have a urinary pregnancy test before study injections. You will have an ultrasound examination of both armpits.

You will then be given a single dose of ChAdOx2 CCHF into your upper arm. The second injection visit (12 weeks after the first) will follow the same steps. **Overall, these visits will each take about 120 minutes.**

Electronic symptom diary 'eDiary' *(to be completed at home)*

During the study injection) visits you will be given access to an online symptom eDiary. This will be set up using your personal e-mail address. We will ask you to record if you have any symptoms of pain, swelling and/or tenderness you may experience in your armpits in the 7 days following study injections (. If you forget to fill in the diary, you will receive automatic reminders; you may also be contacted by a member of the study team. The diaries will be checked for completion at your day 7 and day 91 visits respectively.

FNA visits

You will attend three FNA visits. The first (baseline) FNA visit will be conducted after your screening visit. The other two FNA visits will be conducted 7 days after each injection visit. **These visits will take about 90 minutes**. Each FNA will collect a very small amount of cells and fluid, in the needles used to take them. We will ask about any recent serious medical problems. You will have a blood test (approximately 45ml or 3 tablespoons) and you will have an ultrasound examination and FNA of both armpits.

Follow up visits

After study injections, you will attend the clinic for several follow up visits, as shown in the diagram above. **These visits will take about 30-45 minutes**. The visits are for us to check if you are experiencing

any problems after the study injections and review your injection and FNA sites. At each visit you will have a blood test (approximately 50 mL).

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

What other medical matters are relevant to the study?

Other vaccinations or medications during the study

If during the study you require any vaccinations for health, travel, or occupational reasons, you should inform the study team beforehand. We ask you not to receive any other vaccines within 30 days (before and after) of receiving each study vaccine, EXCEPT for flu and COVID-19 vaccines (apart from the Oxford-AstraZeneca COVID-19 vaccine), which can be given 14 days or more before or after a study injection.

If you are prescribed any new medications during the study, please inform the study team.

Private insurance

If you have private medical insurance or travel insurance, participation in a study will often not affect your cover for any conditions unrelated to the study; however, to be certain, you must tell your insurer you are planning to participate.

Contraception

There are no data on the use of this study injection in pregnancy or whilst breast feeding. It is therefore a requirement of participation that volunteers who could become pregnant must use contraception (exceptions to this are below).

Female participants where any of the following apply will not be required to use contraception:

1. Post-menopausal
2. Surgical sterilisation
3. Complete abstinence from sex with a male partner

Acceptable contraception methods include:

1. Oral, injected or implanted hormonal contraceptives that prevent ovulation
2. Intrauterine device (IUD)
3. Intrauterine system (IUS)
4. Sole sexual partner is a vasectomised male

Note that barrier methods of contraception are not sufficiently reliable.

Male participants in the study are not required to use barrier methods (condoms) for the purposes of contraception. There is no evidence that the vaccine can be shed into semen.

Pregnancy

If you were to become pregnant during the study, you should tell us immediately. With your consent, we would continue to follow you up for safety reasons and we would follow up the baby for three months after birth.

What should I avoid during the study?

Blood donation

Under current UK regulations, participants must refrain from blood donation during their involvement in the study. However, you will be able to restart blood donation once the last study visit has been completed.

Taking part in other clinical studies

You should not take part in other clinical study in which drugs or vaccines are administered, or which involve repeated blood sampling, whilst participating in this study as this may affect the results of this study and also for your safety.

Are there any risks from the ChAdOx2 CCHF injection?

We can predict, from experience with other ChAdOx vaccines, what the symptoms are likely to be with this new study injection. We will monitor safety throughout the study and if you experience any unusual side effects, you should tell us about them.

You may experience some mild tenderness or discomfort at the injection site. Other less common, but possible, symptoms around the injection site might include redness, swelling, itchiness or a feeling of warmth. You may experience flu-like symptoms such as muscle aches, joint aches, feverishness, chills, headache, nausea, tiredness and feeling generally unwell.

Based on previous experience with a ChAdOx vaccine, the Oxford AstraZeneca COVID-19 vaccine, we would expect these symptoms to be mild and to resolve within a few days in most people.

Percentage of participants reporting side effects in trials of the Oxford/AstraZeneca COVID-19 vaccine	
Vaccine site reactions	**General reactions**
Vaccination site tenderness (68%)	Fatigue (53%)
Vaccination arm pain (58%)	Headaches (53%)
	Feeling generally unwell (44%)
	Muscle aches (44%)
	Feeling feverish (34%)
	Joint pains (27%)
	Nausea (22%)
	Fever 38°C and over (8%)

Percentage of participants reporting side effects after one dose in the Phase 1 trial of the ChAdOx2 CCHF study injection*	
Vaccine site reactions	**General reactions**
Vaccination arm pain (63%)	Fatigue (57%)
	Headaches (48%)
	Feeling generally unwell (35%)
	Muscle aches (57%)
	Feeling feverish (15%)
	Joint pains (24%)
	Nausea (15%)
	Fever 38°C and over (7%)

*These data are from an initial analysis of the Phase 1 clinical trial, CCHF01, REC [23/LO/0420] EudraCT Number 2022-003889-20).

Serious rare blood clot disorder with similar vaccines

The Oxford/AstraZeneca COVID-19 vaccine has been associated with a very rare but serious blood clot condition that can lead to death or serious long-term disability. The condition consists of unusual types of blood clots together with low levels of platelets in the blood. It is called thrombosis with thrombocytopenia syndrome (TTS), it is also called vaccine induced immune thrombocytopaenia and thrombosis (VITT).

This condition is not predictable, although it appears slightly less common in older people, and is typically reported after the first dose of vaccine, within three weeks. It has been reported in 1 in approximately 100,000 doses of AZD1222 vaccination in the UK (The Lancet Global Health).

Very low levels of blood platelets (immune thrombocytopenia) that can be associated with serious bleeding (including internal bleeding) have also been very rarely reported, usually within the first four weeks following vaccination with the Oxford/AstraZeneca COVID-19 vaccine.

We do not know whether these rare reactions may also occur with other ChAdOx vaccines, such as the ChAdOx2 CCHF injection used in this study.

We advise you to seek urgent medical advice from the study team if you experience any of the following in the first 28 days after each of your study injections:

- Sudden severe headache that does not improve with usual painkillers or is getting worse
- An unusual headache that 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 24-hour study mobile number. If you experience any of the above events or become in any way concerned, you can use this to contact the study doctors at any time.

Capillary leak syndrome

Cases of capillary leak syndrome (CLS) following vaccination with the Oxford/AstraZeneca COVID-19 vaccine are extremely rare (less than one case per million doses). Some affected patients had a previous diagnosis of CLS. CLS is a serious, potentially fatal condition causing fluid leakage from small blood vessels (capillaries) resulting in rapid swelling of the arms and legs, sudden weight gain and feeling faint (low blood pressure). Seek immediate medical attention from the study team if you develop these symptoms following vaccination.

Other serious vaccine reactions

With any vaccination there is a risk of rare serious adverse events. A severe allergic reaction to injection (anaphylaxis) is extremely rare but can be fatal. In case of this unlikely event, medication for treating allergic reactions is kept in the clinic room and the study team are appropriately trained in the management of anaphylaxis. Nervous system reactions are also extremely rare but have been reported with vaccinations in the past. A rare neurological illness called Guillain-Barré syndrome (GBS) has previously been associated with a flu vaccine used in the USA during a swine flu outbreak in 1976. This is a condition in which people can develop severe weakness; it can be fatal. Cases of GBS have been reported after COVID-19 vaccinations and GBS is possibly a very rare side effect of the Oxford/AstraZeneca COVID-19 vaccine (about 10 cases per million doses of vaccine).

Unknown/unexpected side effects

With any new medicine or vaccine that is in early development, there is always a possibility of an unpredicted or unexpected side effect occurring. This could include something severe. If you experience concerning or unexpected symptoms, you should phone the 24-hour study contact number and speak to a study doctor.

Potential interaction with similar vaccines

When people are injected with ChAdOx2 CCHF they should make the intended immune response against CCHF viral glycoproteins. However, they may also make an immune response against the ChAdOx part of the vaccine. Some scientists believe that having a strong immune response against ChAdOx might interfere with future doses adenovirus-based vaccines (*e.g.* the Janssen COVID-19 vaccine), although these are not currently in widespread use in the UK. **This means that it is possible that receiving the study vaccine may reduce the effectiveness of similar vaccines that you may be given in future.**

Are there any other potential risks from taking part in the study?

Fine needle aspiration (FNA) sampling

FNA sampling is described on page 3, *What is fine needle aspiration (FNA)?* It may cause pain, bruising and bleeding. Rarely, it may cause infection.

Blood samples

Blood sampling may cause slight pain and occasionally bruising. Occasionally, people feel light-headed, nauseous or faint. At most visits we will take about 50ml of blood, which should be well tolerated by healthy adults. The **total** amount of blood we will take from each participant over the whole study period is approximately 300 ml. For comparison, a **single** donation to the NHS blood bank would be approximately 470ml.

What if we find something unexpected?

Since we carry out several medical tests throughout the study, we may possibly detect previously unknown health issues (*e.g.,* high blood pressure, abnormal blood results). If abnormal results or undiagnosed conditions were to be found during the study, these would be discussed with you and, if you agreed, your GP would be informed. We would refer any newly diagnosed conditions to your GP.

Sometimes incidental medical findings require your GP to carry out further investigations, such as blood tests, scans or referral to specialists.

What are the advantages of taking part?

You will not gain any direct personal benefit from the study as you are unlikely to be at immediate risk from CCHF virus. You should not assume you have gained protection from future CCHF virus infection by receiving the study injections.

Will my taking part in this study be kept confidential?

All information collected about you during the research study will be coded with a study number and kept strictly confidential. Any information about you that leaves the clinic will have your name and address removed so that you cannot be recognised, except for your signed consent form and letters sent to your own GP. To enrol into this study, you are required to consent for us to contact your GP.

We will write to your GP to inform them when you enrol in the study and when you complete it, so they can update your medical records accordingly. Your GP may also be asked to share information about your medical history and give access to any other medical records as required to ensure there are no medical reasons that would prevent you from taking part. We would only notify your GP of the results of any medical tests with your permission.

Responsible members of the University of Oxford and Oxford University Hospitals NHS Foundation Trust, may also be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. No one else will be told that you are involved in the study.

Will I be paid for participating in this study?

Study participants will be reimbursed for their time and inconvenience. The reimbursement provided are considered to be reasonable amounts to cover the costs of participating in this research. There should not be any consequences for tax or benefit purposes.

Reimbursement for all participants will be based on the following figures:

1. Screening visit: £110
2. Study injections visits: £110 x 2 = £220
3. FNA visits: £150 x 3 = £450
4. Follow up visits: £90 x 3 = £270
5. Full completion of the Diary card: £30 x 2 = £60

The sum reimbursed is based on the number of visits you attend. If you choose to withdraw part-way through the study, we will calculate your reimbursement based on the visits you have attended. The reimbursement for a volunteer who completes all the study visits is £1110

Payments are made directly by bank transfer in instalments during the study. For this reason, we require participants to provide their bank details at the screening. Bank details are kept confidential.

Personal information such as your name, bank details and national insurance number may be shared with the University finance team to process or verify your reimbursement payments. Financial auditors may also audit the records where this information is held. All confidential data will be stored according to the UK General Data Protection Regulation (see below).

If we ask you to attend any additional (unscheduled) visit, you will be reimbursed for this at the rate appropriate for the type of visit.

What if new information becomes available?

Sometimes during a study, new information relevant to the study becomes available (such as results from this or other studies). If this were to happen, we would tell you about it and discuss whether you would want to, or should, continue in the study. If you decided to continue to take part, you would 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.

If any new information or safety concerns were to arise during the study in relation to ChAdOx2, this would be reviewed, and you would be kept updated.

What happens if I don't want to carry on with the study?

At any time during the study, you are entirely free to change your mind about taking part, and to withdraw from the study. This would not result in any penalty, nor will your legal rights be affected; however, you will only be reimbursed for the study visits you have attended. Unless you state otherwise, any blood taken whilst you have been in the study would continue to be stored and used for research, as detailed below. You may request that your blood samples are destroyed at any time during or after the study. For safety, if you withdraw, we may still ask to follow up any medical problems you might have experienced whilst in the study.

Once you have given informed consent but lose capacity to consent during the course of the study, you will be withdrawn from the study. Any identifiable data or tissue already collected with consent will be retained and used in the study. However, if you or your guardian requests that the data already collected should not to be utilised, in this instance, we would withdraw all collected samples from analysis (except those that have already been utilised). No further data or tissue will be collected or any other research procedures carried out.

In exceptional circumstances, your participation in the study might also be stopped early by the study doctor or the sponsor of the study.

What will happen to any samples I give during the study?

Your samples will be assigned a code and will only be identifiable by this code number. The lymph node samples and blood samples collected during this study will be analysed in the Oxford Vaccine Group and University of Oxford research laboratories. We may also send de-identified samples to other researchers working with us on this research project. This may include researchers in other countries, including outside of the European Union. All samples you provide will be tested in a de-identified form However, as your DNA is unique, samples can never be completely anonymous.

If you choose to take part in this study, we will also ask for your separate permission to store your samples that remain after the study is over (including cells and DNA), in a collection of samples called the Oxford Vaccine Centre Biobank. Details of this will be provided in a separate booklet after you are enrolled into this study, and you are free to decline the Biobank and continue to take part in this study

if you wish. If you consent to your samples being stored as part of the Biobank, a copy of your informed consent form for the Biobank (which contains your personal information) will be kept, in the same way as your consent form for the study. If you do not wish for your samples to be stored in the Biobank, they will be destroyed 12 months after the end of the study.

The following tests will be performed on your blood samples:

- Blood tests for blood cell counts and liver and kidney function.
- Blood tests for Hepatitis B, Hepatitis C and HIV (at the screening visit). A reactive test may mean you are ineligible for this study as the vaccine is new and has not been tested in this setting.
- A blood test for glucose (at the screening visit).
- A blood test for HLA typing, a genetic test of components of the body's immune system.
- Tests of immune responses following study injections looking at your antibodies and immune cells.
- If you opt in, samples in this study will be stored in the Oxford Vaccine Centre Biobank and may be used in future vaccine research studies.
- If you opt in, samples taken in this study may be used for research involving the creation of specific antibodies called 'monoclonal antibodies.'

Detailed immunological tests will be performed on your lymph node samples. These may include RNA and DNA sequencing analyses, which show which proteins the cells are making and indicate the activity of the cell's genes.

The medical practitioners in the study team are legally obliged to report a case of acute infectious hepatitis to the UK Health Security Agency. This may involve a referral to your GP or specialist for further testing if a blood test for hepatitis B or C is reactive.

Will any genetic tests be done?

We will do genetic tests on your blood and lymph node samples to look at the patterns of genes that regulate your own individual immune response. This will help us to work out which aspects of the immune response to vaccines are due to genetic differences between individuals. We will also try to identify and study the genes that appear to be important in your immune response to the study injections (. Other genetic tests may be done if you consent to your samples being stored in the Biobank (as described in more detail in the Biobank leaflet). You will not receive the results of any genetic tests performed.

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 a Sponsor has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

NHS indemnity operates in respect of the clinical treatment which may be provided.

Complaint statement

If you wish to complain about any aspect of the way in which you have been approached or treated or how your information is handled, during this study, you should contact the research investigators on 01865 611400, info@ovg.ox.ac.uk. Alternatively, you may contact the sponsor organisation of this

study (University of Oxford) at the Research Governance, Ethics and Assurance (RGEA) team office on 01865 616480 or email rgea.complaints@admin.ox.ac.uk.

What will happen to my data?

United Kingdom 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, based in the United Kingdom is the Sponsor for this study and 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 to undertake this study.

We will use the minimum amount of personally identifiable information. The Oxford Vaccine Group will use your name, NHS number, home address, and contact details to contact you about the research study, for example, to inform you about your upcoming study visits, and to oversee the quality of the study. The University of Oxford Data management and IT Team will be able to view your email address, which is necessary for the eDiary to function.

A photocopy of your ID (driver's licence, passport, or national ID card) and either your national insurance or passport number for TOPS database registration (see below) and payment processing will be taken at the screening visit. We will securely retain copies until the end of the study. Your bank details will be stored for a minimum of 7 years in line with the University of Oxford's financial policy.

At the completion of the study, unless you consent otherwise (*e.g.,* if you request to be informed of other studies), your personal details will be destroyed. If you agree to future contact (e.g., to be informed of other studies) your details (e.g., name, NHS number, home address, and contact details) will be held separately from the study data and you can request at any time to have your details removed. De-identified research data will be stored for at least 99 years.

If you only complete online screening (i.e., before you give informed consent) your data will only be kept to the end of the study.

Data will be collected and held by the Oxford Vaccine Group. It will be accessible to staff at the Oxford Vaccine Group, responsible staff from the University of Oxford who may monitor/audit the data collection process, and inspectors from ethics. The database servers are held by the sponsor.

UK 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 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. The University's data protection officer can be contacted by email at data.protection@admin.ox.ac.uk

You can find out more about how we use your information by contacting info@ovg.ox.ac.uk.

TOPS database registration

Volunteers participating in this study must not be enrolled in another study that involves receiving investigational medications or vaccines at the same time. 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 studies. More information can be found at *www.tops.org.uk*.

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 can take approximately 2 years after the study is completed. Your individual results would not be identifiable, nor would you be identified in any report or publication. A reference to the publication(s) will be available on the Oxford Vaccine Group website and other study site websites as appropriate. If you contact the researchers in the future, you can obtain a copy of the results.

The de-identified research 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 or licence vaccines in the future or make profits in other ways. You would 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.

Who is sponsoring, organising and funding the research?

The study is organised and sponsored by the University of Oxford. The study is funded by the UK Research and Innovation, Medical Research Council

Who has reviewed the study?

This research has been checked by an independent group, the Research Ethics Committee, who protect participants' interests. This study has been reviewed and approved by London - Central Research Ethics Committee.

The Oxford Vaccine Centre Patient Public Involvement (PPI) group have reviewed the main participant-facing documents associated with this study (participant information sheet, informed consent form and advertising materials). Further information and contact details

We hope this information sheet has given you enough information to decide whether to volunteer for this study. If you would like further information about participating in research, please visit the following website: http://www.nhs.uk/conditions/Clinical-trials/Pages/Introduction.aspx

For independent advice about participating in this study, you may wish to contact your GP.

If you are interested in taking part in this study, then please complete the online pre-screening questionnaire at: https://www.ovg.ox.ac.uk/studies/legacy02

If you have further questions about the study that you would like to discuss with our team, please contact us at:

Email: info@ovg.ox.ac.uk

Tel: 01865 611400

Thank you for your interest in taking part in this study.