From:
Professor Helen McShane
Chief Investigator, COV-CHIM02
University of Oxford

Covid19-challenge@paediatrics.ox.ac.uk

REC ref.-24/LO/0404

A SARS-CoV-2 challenge study in vaccinated healthy adults using the Omicron BA.5 subvariant (COV-CHIM02)

Introduction

Thank you for showing an interest in this research study. Before you decide to participate, it is important you take the time to understand why the research is being done and what it would involve.

First, we want to introduce the study and key facts. Then we will go through the study in more detail. Please ask us any questions and there will be time for you to discuss this with friends, relatives and your General Practitioner (GP) if you wish.

And remember, it is entirely your choice whether you participate in this study or not.

Our study aims to develop a safe human infection model with SARS-CoV-2 (the virus that causes Covid-19) in healthy volunteers who have previously been vaccinated against SARS CoV-2 AND, either have been infected with SARS-CoV-2 and have evidence of this, or have developed antibodies against SARS-CoV-2. This human infection model will involve giving volunteers Covid-19 in a controlled way to learn more about the disease. Most people who have been vaccinated against SARS-CoV-2 will make antibodies against SARS-CoV-2. If you decide to take part in this study, we will do a blood test to see what level of antibodies you have before you take part. Information from this study will enable future research that may help us understand what kind of immune response stops people from being infected with Covid-19 and the impact of the virus on the immune system. This may eventually help with the development of better Covid-19 vaccines and treatments, and development of a test that tells people if they are protected from the virus.

You will be compensated approximately £4,935 for your time, travel and inconvenience.

Could I be eligible to take part?

✔ You must

- Be aged 18-40 years old
- Be in excellent health
- Be willing to travel to Oxford
- Have been vaccinated against Covid-19 and have evidence of this, AND either:
  1) Have evidence of previous Covid-19 infection(s)
  2) OR have developed antibodies against Covid-19 (we will do a blood test for this at your first visit)

✖ You must not

- Be pregnant or breastfeeding
- Have any significant medical conditions
- Be a current smoker, including vaping

<u>If you decide to join our study:</u>

1. You will be given SARS-CoV-2 (the study virus) with its risks:
   a. You could get Covid-19 infection.
   b. You could develop long COVID.

2. You will need to isolate in our quarantine unit for at least 14-17 days and will not be able to receive any visitors. The only in-person contact will be with the research team and affiliated staff. You can bring in personal devices such as phones, laptops and tablets to watch films, study, work, etc and to call friends and family.

3. Whilst you are in the study, especially in the quarantine unit, the clinical staff will monitor your health closely and medical assistance will be available at all times.

4. You will be closely monitored by the study team with a range of tests and procedures including regular Covid swabs and blood tests.

5. We will treat you with 'rescue therapy' (Paxlovid or alternatives), if you are infected and develop any severe symptoms that concern us. This has been shown to help in other situations of SARS-CoV-2 infection but may not help healthy, vaccinated volunteers at low risk of severe disease. Note, this is for additional safety only and we do not anticipate rescue therapy to be required.

6. You will need to attend follow-up visits for 6 months after we give you the study virus.

7. You will be free to withdraw from the study at any time you wish.

Can I take part?

In order to take part in the study you MUST:

- ✓ Be aged 18-40 when you are given the virus (enrolment).
- ✓ Have evidence of receiving at least one dose of Covid-19 vaccine and the last dose must be more than 3 months before enrolment.
- ✓ Have either a positive Covid-19 antibody test (we will test for this as part of our screening) OR evidence of a prior SARS-CoV-2 infection (e.g. a photograph of a positive lateral flow test on your personal mobile phone) - this must have been more than 3 months prior to planned enrolment.
- ✓ Be normal weight or mildly overweight only - a body mass index (BMI) of over 18.5 and less than 28; a BMI of 30 may be acceptable for a physically fit muscular individual.
- ✓ Be in good health with no history of significant medical conditions (as described in our exclusion criteria) that would affect your safety. This will be based on medical history, physical examination and blood tests. You will also have an Electrocardiogram (ECG), lung function tests and chest X-Ray.
- ✓ Allow the study team to discuss your medical history with your General Practitioner (GP) and other relevant health care professionals.
- ✓ Agree to abstain from sex or use effective contraception from the start of treatment with Paxlovid and for 7 days after stopping treatment (if you need to take it). If you are taking the combined oral contraceptive you will need to use condoms in addition to the pill until you have completed one menstrual cycle after finishing the course of Paxlovid.
- ✓ For people of childbearing potential: practise effective contraception from 4 weeks before entering the quarantine unit until discharge and have negative pregnancy tests on the day(s) of screening and enrolment.
- ✓ Be able and willing (in the investigator's opinion) to comply with all study requirements.

✗ You CANNOT participate in this study if any of the below exclusion criteria applies to you. If you are unsure if they apply to you then please discuss fully with a member of the study team.

- × Clinically significant history of skin disorder, allergy, atopy (e.g., eczema and dermatitis), cancer, cardiovascular disease (conditions affecting the heart or blood vessels), metabolic disease, gastrointestinal disease (conditions affecting the stomach and intestines), liver disease, kidney disease, endocrine disorder (conditions affecting the glands, including diabetes), haematological disease (conditions affecting the blood), neurological illness (conditions affecting the nervous system).
- × Any clinically significant respiratory disease (a condition which affects your lungs), including asthma.
- × Migraine with aura (warning signs just before the migraine starts). Cluster headache (a type of headache that lasts for a long period)/migraine requiring prophylactic treatment (treatment you take regularly to stop you from having attacks).
- × Any clinically significant autoimmune conditions (a condition in which your immune system attacks your body) or immunodeficiency (a condition which affects your body's ability to defend itself against infections), including Human Immunodeficiency virus (HIV).
- × Clinically significant history of severe psychiatric illness at any time (e.g. inpatient stay, psychosis) or current significant active symptoms of anxiety and/or depression (e.g. your daily life is severely impacted by anxiety/depression despite the active treatment).
- × Current smoker (including e-cigarettes and vaping) or ex-smokers who have smoked in the last 3 months.
- × Significant history or presence of drug or alcohol misuse.
- × History of anaphylaxis (severe allergic reaction) or any allergy likely to be worsened by any component of the study agent or proposed treatment regime.
- × Active rhinitis (including hay fever) or history of moderate to severe rhinitis (including seasonal hay fever) if it will likely require at least weekly nasal steroid sprays within 30 days prior to enrolment

- Any significant abnormality affecting your nose or throat including frequent or very heavy nose bleeds or any nasal or sinus surgery within 6 months of the planned date of enrolment.
- Current Hepatitis B, Hepatitis C or HIV infection.
- Use within the last 6 months of steroid oral medication or infection, or other immunosuppressive agents (steroids used as a cream or ointment are permitted).
- Receipt of immunoglobulins (antibodies) and/or any blood products (such as blood transfusions) within the 3 months preceding the planned date of enrolment.
- Current use of any medication or drug taken through the nasal (nose) or inhaled route (breathed in) including cocaine or other recreational drugs.
- Current pregnancy, pregnancy within 6 months of enrolment, current breast-feeding or intention to become pregnant during study period (6 months).
- Sharing a household or caring for or in daily face to face contact with someone who is >65 or <2 years old or with a clinically significant immunodeficiency (either from infection, medication or pregnancy), or who have moderate to severe lung conditions around the time of quarantine.
- Current participation in any other research study or trial which involves drawing of blood or receipt of an investigational product (experimental medicine) in the 30 days before enrolment, or at any time during the study period.
- Confirmed Covid-19 within 3 months before enrolment.
- Evidence of ongoing post Covid-19 symptoms or complications (e.g. abnormal Chest x-ray, altered sense of smell).
- Hospitalisation with prior Covid-19 infection or related complications or unusually severe or long-lasting symptoms (e.g., long Covid).
- Family history of 1st degree relative aged 50 years or less with sudden cardiac or unexplained death.
- Family history of severe Covid-19 disease or severe response to any other viral disease e.g. Guillain-Barré.
- Any other significant disease, disorder, or finding, which, in the opinion of the investigator, may either put you at risk, affect your ability to participate in the study or impair interpretation of the study data.
- Individuals who are difficult to take blood from.
- Use of medication that interacts significantly with Paxlovid (unless an alternative rescue therapy is available, the study doctor will be able to advise on this).
- Have plans to receive any vaccine in the 30-day period before enrolment or before the D28 follow-up visit (you must not have had a Covid-19 vaccine for 3 months before enrolment).

Contents

Part 1

1 Introduction

Human challenge studies (also known as controlled human infection models) involve deliberately exposing healthy volunteers to infectious organisms in a controlled manner to learn more about the diseases they cause. These human challenge studies may allow faster testing of vaccines and answer other important questions about diseases. This study plans to expose healthy volunteers to the Omicron BA.5 subvariant of SARS-CoV-2, the virus that causes Covid-19 disease, via liquid drops into the nose. The full purpose and details of the study are explained below.

2 Why are we doing this challenge study?

The SARS-CoV-2 virus is a member of the coronavirus family, a group of viruses which cause respiratory infections with symptoms ranging from no or mild symptoms only, to severe and life-threatening illness. It is the cause of the coronavirus disease 2019 (Covid-19).

The roll out of licensed vaccines is a positive step towards combatting the disease. However, there are still lots of unanswered questions regarding the immune response to Covid-19. To help with this, we would like to develop a "challenge model" where volunteers who have been previously vaccinated against Covid-19 are exposed to the SARS-CoV-2 virus ("challenged") in a controlled manner. Three similar studies have been conducted to date, with different SARS-CoV-2 variants. The key aim of this study is to establish a safe human challenge model with the Omicron variant of the virus, which would then allow us to closely examine how the body fights off the virus. This study will provide information about immune responses and enable further studies to answer key questions related to Covid-19. We hope to learn what makes some individuals less-likely to get the disease than others and what immune responses protect against getting the disease. Although existing vaccines against SARS-CoV-2 are effective at preventing hospitalisation and deaths, they are less good at stopping people from getting infected. A safe human challenge model would help us to understand why this is and develop vaccines that provide better protection against infection.

To do this, we need to find a dose of the virus which causes infection but with the aim of producing little or no symptoms. For this study, a participant is counted as infected when they shed the virus from the nose or throat (which we will pick up on a swab). However, we cannot guarantee that the dose you receive will *only* cause mild symptoms. For safety purposes, we will have strict selection criteria for who can take part, to make sure we only include those with the lowest predicted risk of becoming unwell from infection. We will also closely monitor participants after infection (including 14-17 days of inpatient quarantine stay).

3 How is the study going to work?

We plan to recruit up to 45 participants initially across two groups (see **Table 1**). Each individual will receive SARS-CoV-2 as liquid drops into the nose. The study virus is the **Omicron BA.5 subvariant**, a variant that dominated in the UK during the summer of 2022.

Table 1*:* Study Groups

Group	Cohort	Number of volunteers	Dose
1	1A	5-12 +/- 5-12 antibody-selected volunteers	Starting dose: $1x10^5$ TICD50
	1B	5-12 +/- 5-12 antibody-selected volunteers	Dose 2
	1C	5-12 +/- 5-12 antibody-selected volunteers	Dose 3
	1D	5-12 +/- 5-12 antibody-selected volunteers	Dose 4
2	[redacted]	Up to 24	Dose determined from Group 1

"TCID50" is a standardised unit of measurement of amount of virus. The exact doses given in groups 1B-D will be decided with the advice of an independent Data Safety Monitoring Board (DSMB) and will depend on the concentration of virus available.

Group 1*- Safety and dose finding group*:
The starting dose has been selected based on prior results from human challenge studies using the original 'wild type' variant of SARS-CoV-2, the delta variant of SARS-CoV-2 and human challenge studies using other viruses like flu. An independent Data Safety Monitoring Board (DSMB) will be monitoring the study and will tell us to continue, increase or decrease doses (and if so by how much) with the aim of infecting 50-75% of volunteers. You will be informed which group and cohort you are assigned to. We will give the virus to up to 5-12 volunteers in the first cohort. If the SARS-CoV-2 virus doesn't cause infection in at least half of participants in the first cohort then we will move to the next available higher dose (the next cohort) after reviewing the data with the independent Data Safety Monitoring Board. We will keep increasing the dose, either via single or multiple administrations, until we infect 50-75% of the volunteers enrolled. Furthermore, once we have enrolled 5-12 volunteers at a given dose we may start selecting volunteers with lower antibody levels against SARS-CoV-2 in order to improve the rate of infections. A further 5-12 volunteers will be recruited into antibody-selected subgroups at a given dose. If we are selecting volunteers for lower antibody level you will need to attend for a pre-screening visit (see section 7.3) to see whether your antibodies are in the right range before we go ahead with a full screening. The study team at your chosen site will be able to advise you whether you need to attend a pre-screening visit before a full screening visit. Once we find a dose that infects 50-75% of volunteers, we will enrol volunteers into group 2 (below). If we reach the maximum dose and still don't manage to infect 50-75% of volunteers, we may enrol volunteers into Group 2 regardless as we can still learn a lot about the virus even with a lower infection rate.

Group 2* - Safety and dose confirmation groups*: *up to 24 participants*
Once an optimal dose or the maximum dose of the virus has been selected from the dose finding groups (Group 1), we will enrol up to 24 participants in Group 2. These groups are needed to confirm that the dose of virus we have identified in Group 1 does cause infection at the expected rates and remains safe in this wider group of participants. Depending on the findings from the rest of the study we may select volunteers with lower antibody levels for group 2.

You will be in the study for 6 months from enrolment (day you are given the virus) to the last clinic appointment.

4 What is the natural course of Covid-19?

The virus spreads between people either by droplets from an infected person or through contact with contaminated surfaces. Some people do not experience any symptoms at all, which is one reason the virus has spread easily despite isolation measures.

The most common symptoms Covid-19 caused by the Omicron variants include:

- runny nose
- headache
- sore throat
- sneezing
- persistent cough
- hoarse voice

Other symptoms include:

- Muscle or joint aches
- Fever
- Nausea
- Ear ringing/Ear ache
- Stuffy nose
- Chest tightness/pain
- Dizziness/feeling light headed
- Loss or change of sense of taste and/or smell
- Irregular heartbeat
- Shortness of breath
- Rashes
- Swollen glands
- Wheeze
- Blisters
- Skin burning
- Tiredness/feeling generally unwell
- Diarrhoea
- Hair loss
- Eye soreness
- Abdominal pain
- Confusion
- Brain fog
- Feeling down
- Poor appetite
- Difficulty sleeping

"Long Covid"

In most cases, symptoms get better within a few weeks. However, in a small number of cases people have symptoms that can last months or more. This is sometimes called "long Covid". These long-term effects are not limited to those who have required hospitalisation or been seriously unwell with Covid-19, but have also been more commonly seen in women, and those with underlying health conditions. The Office for National Statistics' data showed that 4% (4 in 100) of double vaccinated people self-reported long Covid 12-16 weeks after a first Omicron infection.

Long Covid symptoms experienced most commonly include:

- tiredness
- breathlessness
- palpitations (racing heart)
- chest pains
- joint or muscle pain
- not being able to think straight or focus ('brain fog')
- loss or change in taste and/or smell

These symptoms improve over time in the majority of cases but there is a risk that long COVID symptoms may last for many months or could even be permanent.

Severe Covid-19

Overall, severe disease is uncommon in young adults. The chance of requiring hospital treatment in the 18-40 age group if infected with the Omicron variant of Covid-19 is estimated to be approximately 1 in 150 people (less than 1%). For comparison, the chance of hospitalisation following Covid-19 is therefore similar to the chance of dying in a car accident over a lifetime, which is 1 in 200. These numbers include people in this age range who were unvaccinated and/or had underlying health conditions and so will likely overestimate the risk of taking part in this study. We know that underlying health conditions are strongly associated with severe Covid-19. In one large study in the United States looking at more than 500,000 people hospitalised with Covid-19 across all age ranges, 95% had at least one underlying medical condition. In another study of more than 1 million people in the US who had completed their first course of vaccination, carried out before Omicron was dominant, 2,246 people caught Covid-19, 189 needed to go to hospital and 36 died. All of the people who were hospitalised or died were either over 65 or had a significant underlying condition. Our study has been designed to reduce the risk of hospitalisation and death as much as possible by excluding people who are older, people with underlying health conditions and people who are unvaccinated but this cannot be reduced to zero and severe Covid-19 can rarely occur in young healthy adults.

The complications of severe Covid-19 are given in section 11.2. Most people who develop severe Covid-19 are older and/or have underlying health problems such as diabetes, heart disease, lung disease and obesity, but even young healthy adults have developed severe Covid-19 and a small number have died. Data from England during the Omicron period suggests the risk of death in our study target group (aged 18-40 years) is less than 0.005%, which means less than 1 person per 20,000 infected would die. Again, this is likely to be an overestimation for the risk of death in our study, as this study includes people with pre-existing health problems and other risk factors for becoming unwell with Covid-19 that we will screen for.

Studies testing the available Covid-19 vaccines have demonstrated that vaccination reduces the risk of hospitalisation or death from Covid-19 but are less effective at preventing mild or asymptomatic infection. Why some people remain unprotected is unknown. It is known that infection in vaccinated individuals is less likely to cause severe symptoms due to the body's improved immune response, having learnt how to fight off the virus. Whilst, we believe that prior vaccination against Covid-19 reduces your risk of developing severe symptoms we cannot guarantee that you will not become severely unwell if you take part in this study

5 Are there any advantages of taking part?

You will not gain any direct benefit from the study, however, during the screening process, you will get information about your health from the assessments and tests that we will perform (see section 8.2). These assessments are not carried out for diagnostic purposes and should not be considered a substitute for a doctor's visit.

We hope that the information we gather from this and future studies may eventually lead to a test of protection against Covid-19 and better vaccines/treatments that could help many people around the world. There is a theoretical possibility you could boost your immune responses against Covid-19 but we cannot be certain of this, and we would not know whether this would protect you against further Covid-19 infection.

You will also receive approximately £4,935 in compensation for your time, inconvenience and travel for full study participation.

6 Do I have to take part?

No. Participation is entirely voluntary. It is up to you to decide whether 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. However, if we have already given you the study virus, it is

important that you stay in the quarantine unit until we tell you it is acceptable and safe to leave (be discharged). We want to be sure that if you get Covid-19 symptoms, we can monitor you and give you treatment if necessary. We also want to be sure that you cannot spread the virus to other people. You need to be available and willing to stay in the quarantine unit for at least 3 weeks.

The University of Oxford does not urge, influence, or encourage any employees or students of the institution to take part in this research study. Your decision to not participate, or a decision on your part to withdraw from the study, will have no effect whatsoever on your employment/student status at Oxford.

7 What will happen if I decide to take part?

7.1 Study timeline

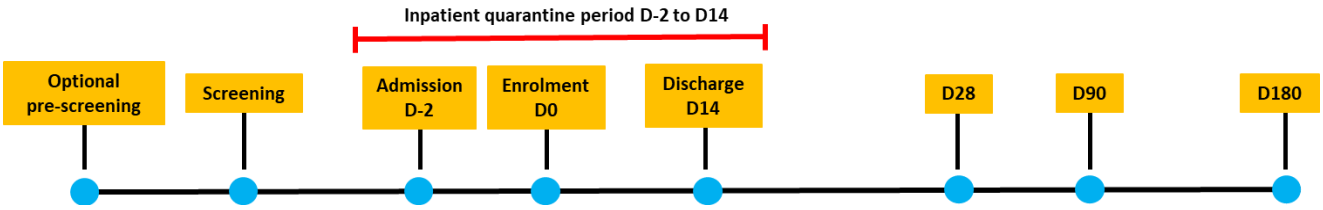
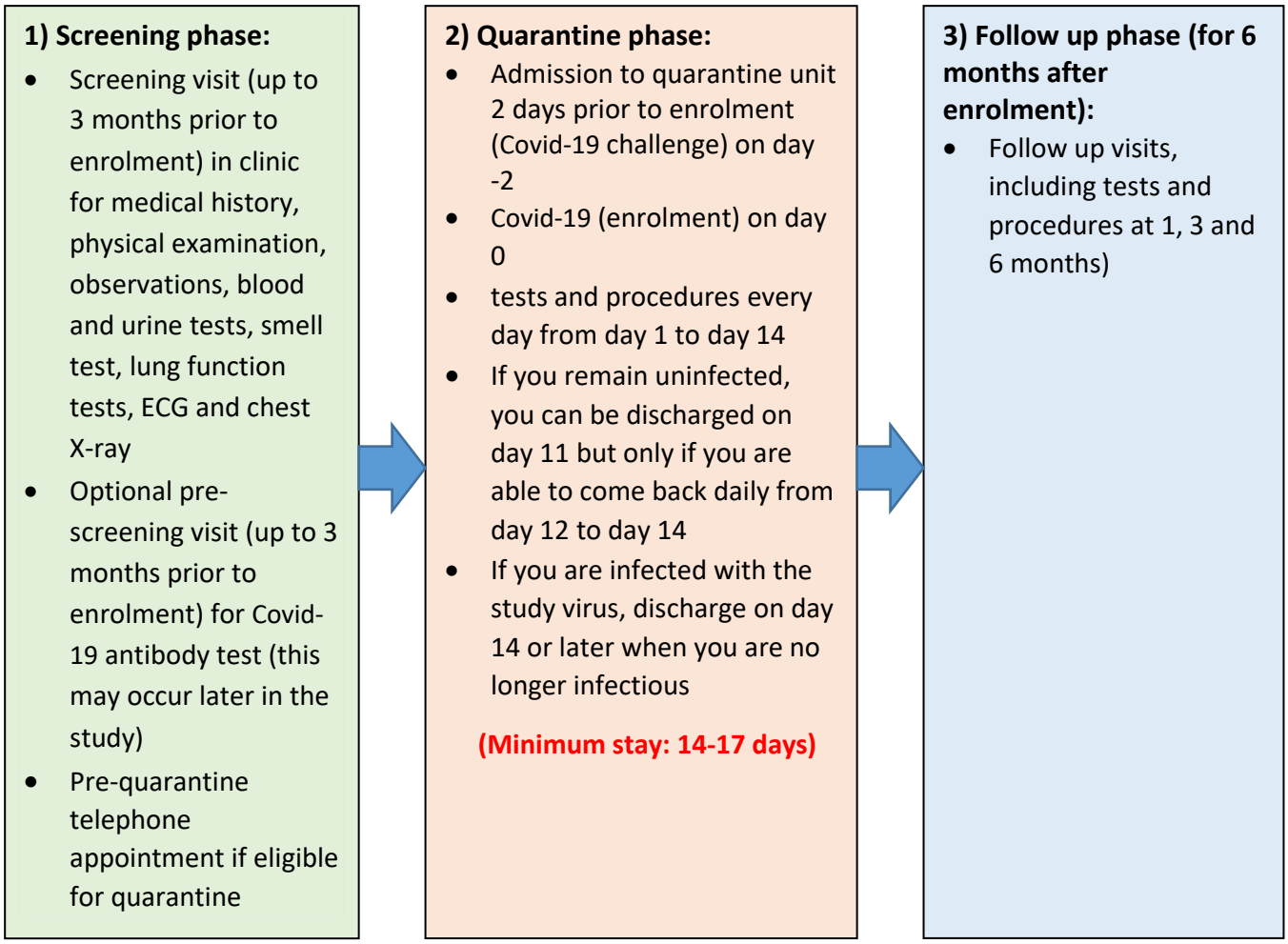


Figure 1: Study timeline ***(Note that the inpatient quarantine period may extend beyond D14 as described in Section 8.4)***

The Study timeline (Figure 1) details the number of visits involved in the study. The screening phase comprises up to 1-2 visits – the screening visit itself, and an optional pre-screening visit that may be introduced later in the study to prioritise which volunteers we invite for full screenings on the basis of their antibody levels. This is followed by the quarantine period and then 3 visits in the follow up phase. Blood tests for research and/or safety will be taken at every visit and during the quarantine period (see Figure 1), and we will not take more than 550ml (approximately 37 tablespoons) in any 8-week period.

The screening, optional pre-screening and follow-up visits will take place at Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) in Oxford. The quarantine phase will be conducted at the Oxford Experimental Medicine Clinical Research Facility (EMCRF), Oxford depending on bed availability.

The study will consist of 3 phases:



7.2 Screening phase

If you would like to take part, you will need to complete an online questionnaire via our study website to register your details. This will take no longer than 10 minutes to complete. Additionally, there will be a few brief questions to check whether you are eligible for the study, this will include a few questions about your medical history. We may clarify any of your answers on the online questionnaire over the telephone.

If eligible based on the preliminary information provided, you will be booked in for a screening visit and will be sent a copy of the participant information sheet (PIS) prior to the visit. You must finish reading PIS before attending the visit and we encourage you to discuss it with friends and family and also your GP if relevant. If you have any additional questions at this stage you will be encouraged to contact us by phone or email to discuss them. At the screening visit, you will be met by one of the study doctors who will discuss the study with you again and you will be given the opportunity to discuss any questions you may have.

Once the study doctor has discussed the study with you, and you have had the opportunity to ask any questions, you will be asked to complete a short quiz to check your understanding of the study. If you get any answers wrong, although your participation would not be affected, the study doctor will go over that area with you again until they are satisfied that you have understood everything. If you would still like to take part, you will be asked to sign a consent form that will be kept at the study site. You will be given a copy of this consent form to take away and keep. You will be asked to allow the study team to contact your own doctor (GP) to obtain your medical information, to make sure there are no medical reasons why you should not participate. You will be

asked to agree to being registered on a confidential database (The Over-volunteering Prevention System, TOPS), which is designed to prevent people entering multiple studies at the same time. Registration on the TOPS database will require your National Insurance or Passport Number. The study doctor will then go through a few administrative questions as well as detailed questions related to your health. This will be followed by a physical examination and blood tests to see if you are suitable for this study (see more details below). You should allow approximately 3.5 hours for this first screening visit and it will occur up to 90 days prior to enrolment in the study. You will receive £125 compensation for this visit.

Medical examination and clinical observations

A medical examination of your skin, chest, abdomen, mouth and the lymph glands in your upper body will be performed. Your blood pressure, pulse, temperature, breathing rate and oxygen levels will be recorded. We will record your weight and height. You will also be asked to provide a urine sample to check for any health problems and for the presence of drug misuse and nicotine use. Additionally, for people of childbearing potential a urine pregnancy test will be performed.

Mental Health Assessment Questionnaires

Due to the potential effects of isolation during quarantine on an individual's mental health, we will perform two questionnaires to ensure that a participant's mental health is good prior to starting the quarantine period. We will therefore ask you to complete the following two questionnaires:

- Patient Health Questionnaire (PHQ-9) which is commonly used for diagnosing, monitoring and measuring the severity of depression.
- Generalised Anxiety Disorder (GAD-7) questionnaire commonly used for diagnosis of generalised anxiety disorder.

ECG (Electrocardiogram)

We will record an ECG to look at your heart's activity. This procedure requires small pads to be stuck to your arms, legs and chest whilst you lie still for a few minutes. This will require you to undress to the waist. The pads can sometimes cause minor skin irritation.

Blood tests

To check you are safe to take part, we will take blood to test for:

- Anaemia (low blood level) or problems with your blood cells (e.g. immune cells)
- Blood clotting problems
- Liver, kidney and heart function
- HIV (the virus that leads to AIDS), Hepatitis B and Hepatitis C (viruses that affect the liver) infection.
- Diabetes/ impaired blood sugar control
- SARS-CoV-2 antibodies in your blood to assess baseline immunity against the virus

You may feel dizzy when you have blood taken. Sitting or lying down when blood is taken should stop you feeling lightheaded or fainting. The total volume taken at this visit will be up to 21ml, the equivalent of just over 4 teaspoons.

Smell identification test

The University of Pennsylvania Smell Identification Test (UPSIT) is a test used to assess your sense of smell. We will perform it at the screening visit to make sure you have no existing abnormalities in your sense of smell. The test takes only a few minutes and consists of 4 booklets of different scents, containing a total of 40 scents across the booklets. On each page, there is a different "scratch and sniff" strip embedded with a scent and a multiple-choice question pertaining to the scent with four possible answers. The scents are released by scratching with a pencil. After each scent is released, you will need to smell the strip and answer the multiple-choice question based on what you smell. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. We can then assess your score against expected scores made up from a database of individuals with normal smell.

Lung function test and Chest X-ray

To check your lungs are healthy, we will measure your lung function using a handheld spirometer and arrange an x-ray of your chest. The lung function test is done by taking a deep breath and then breathing out through a mouthpiece attached to a machine which gives us readings.

A chest x-ray is a routine medical test that shows us the appearance of your airways and lungs. These tests may be performed at the same time or may require you to make a separate visit.

Optional nose swabs for exploratory research

We may ask to take nose swabs that we will use for research purposes such as developing assays. These swabs could include the swabs that are taken in quarantine like the nasosorption and deep nose swabs described in section 7.4.3 or other similar swabs. The study staff will tell you exactly what swabs will be required and what the sampling procedure will involve. If you would prefer not to have these swabs taken then you may still take part in the study.

What happens if any tests are abnormal?

Sometimes test results may be considered "out of range", which means the results do not fall within the usual or expected range for healthy individuals. If this is the case with any of your results, you may be asked to return for a repeat test so that it can be checked again. (You will be compensated pro rata for any additional visits required - see Section 14 for details). If the test results are still out of range, or if the chest x-ray show a significant abnormality, this will mean you cannot participate and we will ask your permission to contact your GP or a specialist doctor (whichever is the most appropriate), to ensure the abnormality is followed up. At no point will your test results be shared to anyone outside the study team without your permission, unless the abnormal results indicate notifiable diseases and/or causative organisms that need to be notified to the public health authorities as part of our legal obligation.

7.3 Pre-screening visit

An additional pre-screening visit may be introduced in later groups. This may take place prior to a full screening visit. In this case, you will be provided with the PIS in advance, this must be read prior to the pre-screening visit. At the pre-screening visit a nurse or doctor will go through a summary of the PIS to ensure you understand what to expect if you decide to take part in the study and you will have the opportunity to ask any questions and have them answered. Once you are happy that you fully understand what the study involves and if you have decided that you would like to go ahead, the study doctor or nurse will ask you to sign a consent form that will be kept at the study site. You will be given a copy of this consent form to take away and keep. The study staff will go through a few administrative questions and confirm your Covid-19 infection and vaccination history before taking a blood test. This blood test will be measured for antibodies against the SARS-CoV-2 virus. We may also take a nasosorption sample (see section 7.4.3) at this visit and use this to measure your antibodies against the SARS-CoV-2 virus as well. We will use this information to decide who to invite for a full screening. Only those with antibodies in the lower range will be invited for a full screening, this is in order to increase the chance that volunteers given the study virus will go on to be infected.

At the pre-screening visit we may also ask to take nose swabs for exploratory research but just like at the screening visit, these will be optional and you can decline this and still take part in the study.

If you receive any vaccines or develop Covid-19 like symptoms after attending either a pre-screening or a screening visit, a repeat blood test may be taken prior to enrolment to re-assess your Covid-19 antibody level, as it may have gone up following this event. We may also have to postpone your enrolment, as the last dose of Covid-19 vaccine or the latest episode of Covid-19 must be more than 3 months prior to enrolment.

7.4 Quarantine phase

We will admit you to our inpatient quarantine unit at EMCRF, Oxford 2 days before you are given the study virus (Day -2). You will stay inside your allocated quarantine room for a minimum of 14-17 days (starting on Day -2), but you may be asked to stay longer if the study doctor thinks it is necessary (see section 8.5 discharge criteria).

During this time, you will be fully isolated in your own room (with your own en-suite bathroom). The only face-to-face contact will be with the research team and affiliated staff. The research team will wear protective clothing every time they enter your room.

You can bring in your mobile phone and laptop, to watch TV, films, play games, study etc and to call friends and family. However, you cannot have any visitors. There will be Wi-Fi. You will have sole use of an en-suite bathroom attached to your room. There will be no cooking facilities; meals will be provided by staff.

Medications
Some over-the counter or prescribed medications and supplements are prohibited during the study and need to be stopped prior to the quarantine period to allow for a 'wash out period'. This is to ensure that these are no longer present in your body prior to the challenge.

A brief summary of some of the medications which are not permitted prior to the challenge date is shown below (**Table 2***)*. This is not an exhaustive list so please do check with the study team regarding any medications that you take including over the counter medications and supplements.

Before your admission to the quarantine unit, the study doctor/nurse will provide you with personal advice about medications if you require.

Table 2. Medications not permitted prior to the challenge

Medication	Washout period required
Systemic (oral or injection) steroid containing medications	6 months prior to enrolment
Systemic (oral or injection) antiviral drugs, except Truvada® being used as pre-exposure prophylaxis against HIV (PrEP)	6 months prior to enrolment
Non-Covid-19 vaccines	30 days prior to enrolment until D28 visit
Covid-19 vaccines	3 months prior to enrolment until D28 visit
Antihistamine	7 days prior to enrolment
Any medication or product (prescription or over-the-counter), for symptoms of nasal congestion or respiratory tract infections including nasal steroids	30 days prior to enrolment
Herbal supplement	7 days prior to enrolment
Any product known to be an inducer or inhibitor of cytochrome P450 enzymes	30 days prior to enrolment
Any medication with significant interaction with Paxlovid (unless an alternative rescue therapy is available)	30 days prior to enrolment

7.4.1 Day -2 & Day -1

When you arrive at the quarantine unit, we will perform some checks to confirm that you are still healthy, free of any active infection and suitable for the study. These tests will include ECG, nose and/or mouth swabs (to look for evidence of different types of airway infections including Covid-19, and for research purpose), blood tests, vital signs (including weight, pulse, blood pressure, breathing rate, oxygen level measurements and temperature), physical examination, smell test, lung function test and urine tests (including urine screening for drug misuse and nicotine use). People of child bearing potential will have a blood test to check for evidence of pregnancy.

If we identify any abnormalities we may cancel or postpone your quarantine stay.

If there are no abnormalities on these tests and you remain well in the first 2 days in the quarantine unit, we will proceed with the enrolment/challenge on Day 0 (deliberate infection with SARS CoV-2 Omicron BA.5 subvariant "the study virus"). Once you have been given the virus, you will be considered to have been enrolled into the study.

Additional baseline research procedures will be carried out on Day -2 or Day -1 including mask wearing samples (please see below for further detail).

Reserve Participants
We may invite extra participants to the quarantine part of the study in case another participant becomes ineligible to take part between admission day and being infected on Day 0. The study team may invite you to be a reserve participant. If you agree, you will be invited to the quarantine unit on the same day as the other participants and will be staying in one of the rooms in the quarantine unit. You will undergo the same study procedures on Day -2 and Day -1 as the other participants.

Should one of the other participants no longer be taking part, you will then continue in the study and be enrolled (be given the study virus) on Day 0 and stay for a further 10-14 days in the quarantine unit. Should none of the other participants drop out, you will be discharged and invited for the next quarantine group, or the next convenient quarantine based on your availability.

If you agree to be a reserve participant for the quarantine part of the study, you will be paid for the time you spend in the quarantine unit at £200 per day.

7.4.2 Day 0: the day of enrolment

On the day of enrolment (Day 0), the study doctor will "inoculate" (administer) you with the study virus. We will administer SARS-CoV-2 Omicron BA.5 subvariant, which was the dominant variant in the UK during summer 2022.

We will drop a small amount of solution containing the virus into each of your nostrils whilst you are lying on your back. After receiving the nose drops, you will be monitored to check that you do not feel unwell or have any side effects. The exact amount of the solution that we give you will depend on the planned dose of inoculation and the concentration of the virus in a drop. We may give you a full amount of the study virus in a single administration, or partial amount through multiple administrations.

In most Covid-19 cases caused by the Omicron BA.5 subvariant in the community the virus takes between 2 to 5 days to start showing up in your nose. Once infected, most people shed "live" (infectious) virus from the nose and/or mouth for up to 9 days. This can occur through talking, shouting, and singing even in individuals who aren't sneezing or coughing. Therefore, your study doctor will ask you to stay in your room in the quarantine

unit for at least 14 days after inoculation if you are infected and until you are no longer infectious. We will also ask you to wear a mask whenever staff members are in the room to reduce risk of spreading the virus.

7.4.3 Procedures during the quarantine phase (Day -2 to Day 14)

Several tests and procedures will be carried out during the quarantine phase, to check the effects of the study virus, to monitor your safety and for research purposes. The table on the next page shows you which tests will be carried out and how often.

Your identifiable details (e.g. name, date of birth) may be used when NHS healthcare IT systems are used for vital signs, safety blood tests, and other investigations for safety monitoring (e.g. the chest x-ray taken during the screening phase). They will be processed and reported using NHS IT systems and they may automatically be linked to your NHS medical records. Whilst you are in the quarantine unit medical information collected about you will also be stored using the NHS healthcare IT system under your identifiable details. Please discuss with the study doctor if this would raise any concerns. Otherwise, all research information and samples will be stored under a unique study number and only the study team will be able to link the study number back to you.

Study Day	(Pre-screening)	Screening	D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	Extended quarantine days	D28	D90	D180
Window		D-90 to D-3																			+/- 5 days	+/- 14 days	+/- 21 days
Written informed consent	(x)	x																					
Eligibility criteria	(x)	x	x		x																		
Medical history	(x)	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Medication history		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demographics	(x)	x																					
Weight and BMI		x	x																				
Mental health questionnaire		x	(x)																	(x)			
Urine samples		x	x	(x)	(x)	(x)	(x)	(x)	x	(x)	(x)	x	(x)	(x)	(x)	x[7]	(x)	(x)	x[7]	(x)	(x)	(x)	(x)
Urine drugs of abuse & nicotine screen		x	x																				
Urine pregnancy test		x			x[1]																		
Physical examination		x	x		(x)																(x)	(x)	(x)
Vital signs[2]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Study Day	(Pre-screening)	Screening	D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	Extended quarantine days	D28	D90	D180
Window		D-90 to D-3																			+/- 5 days	+/- 14 days	+/- 21 days
Symptom diary				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Smell test[3]		x	x			x			x			x				(x)			(x)		(x)	(x)	(x)
Chest X-ray		x																					
ECG[3]		x	x						x			x				(x)			(x)		(x)	(x)	(x)
Lung Function Test		x	x		(x)														x	(x)	(x)	(x)	(x)
Intranasal SARS-CoV-2 challenge (enrolment)					x																		
Rescue therapy						(x)																	
Serum pregnancy test in POCBP			x																				
Hepatitis and HIV blood test		x																					
Blood tests for safety & research		x	x			x		x		x		x		x		x			x		x	x	x
HLA typing[4]		(x)	(x)																				
SARS-CoV-2 antibodies for screening[5]	(x)	(x)																					

Study Day	(Pre-screening)	Screening	D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	Extended quarantine days	D28	D90	D180
Window		D-90 to D-3																			+/- 5 days	+/- 14 days	+/- 21 days
Nose swab for airway pathogens			x																				
SARS-CoV-2 nose swab[7]			x			x	x	x	x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	x			
SARS-CoV-2 throat swab[7]			x			x	x	x	x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	x			
Optional nose swabs for exploratory research[6]	(x)	(x)																					
Nose and throat swabs for exploratory research[9]				x			x		x		x		x					x			x	x	x
Lateral flow antigen test[7]						x	x	x	x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	x			
Mask wearing sampling[8]			x			x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			
Environmental sampling[8]			x			x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			

Study Day	(Pre-screening)	Screening	D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	Extended quarantine days	D28	D90	D180
Window		D-90 to D-3																			+/- 5 days	+/- 14 days	+/- 21 days
Nasosorption[10]	(x)	(x)	x		(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x
Saliva sampling[7]			x			x	x	x	x	x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)			
Deep nose swab			x			x		x		x		x				x			x		x	x	x
Stool sample[9]			(x)			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)

1. After day 11 these tests will only be carried out routinely in participants who have positive swabs for Covid-19 from D2 onwards during the quarantine phase. They will be optional in all participants during the follow-up phase.

2. Pre-challenge.

3. Once daily on D-2 and D-1. Four times daily from D0 to discharge. Once daily from D11 to D14 for participants eligible for discharge on D10.

4. HLA typing can be completed at either screening or D-2.

5. SARS-CoV-2 antibodies can be used for optional sero-screening subgroups if included.

6. Additional nose swabs may be collected for exploratory research, should you consent to this separately

7. In participants with no PCR positivity from D2, throat & mid-turbinate FLOQ virology swabs, lateral flow antigen tests, saliva sampling and routine urine samples may be discontinued from D11 onwards.

8. Subject to PCR positivity from D2, environmental sampling and mask wearing sampling may be discontinued from D8 onwards.

9. Carried out in group 2 only.

10. Twice daily apart from D0 when nasosorption should be completed only once at 6 hours post enrolment.

() Optional: To be carried out only in certain participants.

Diary card

On the day before enrolment, we will set up an electronic diary for you to record any symptoms you may develop from the day before you are given the virus until 14 days afterwards. This needs to be filled in three times a day online, using either a smartphone/tablet/computer or paper diary alternative if required. If any symptoms last beyond 14 days post enrolment, we will ask you about them and record them on your electronic file. It is important that you let us know about any symptoms or medical issues that you have whilst you are in the study.

Nose swabs

Nose swabs will be obtained by placing a swab into your nostrils. Swabs may be taken from the middle or back of the nose. Because we will be asking you to record any symptoms on the electronic diary we will not tell you the swab results until day 10. This is to avoid any unintentional differences in the way you might experience or report symptoms knowing you are, or are not, infected. If you need rescue therapy or any other changes to study procedures (e.g. because you become unwell), we will tell you the results then. See section 7.4.4 for further information about rescue therapy.

We will also collect deep nose swabs by inserting the swab approximately 2 inches into the nasal passage and gently rotating it for a few seconds, for research purposes other than monitoring whether you are, or are not, infected. These swabs will be collected regularly during the quarantine period and at each follow-up visit.

Nasosorption

In addition to the nose swabs, we will perform a nasosorption test regularly whilst in quarantine and then at each follow up visit. This involves the placement of a short soft sterile strip into one or both nostrils. We will then ask you to pinch your nose or put on a nose clip for 2 minutes, before removing the strip(s). This allows us to collect samples from the fluid in your nostrils. We may collect up to 4 swabs 2 times per day.

Lateral flow tests

You will be provided with a lateral flow antigen test and asked to the test yourself following the manufacturer's instructions. Once performed, the lateral flow test will be immediately removed by study staff so you cannot read the result and will be kept blinded from your infection status.

Throat swabs

We will ask you to tilt your head back and open your mouth while a swab is rubbed along the back of your throat. You will need to resist gagging and closing your mouth.

Mask wearing samples

We want to capture and analyse the droplets coming from your lungs. To do this you will be asked to wear an adapted facemask containing strips that capture droplets as you breathe out. You will do this at pre-specified timepoints starting on Day -1, one or two occasions a day for 60 minutes on each occasion.

Saliva samples

You will be asked to provide a saliva sample each day in a container of around 2mls.

Blood sampling

We will take your blood samples for safety and/or research at pre-specified timepoints. The amount of blood samples taken each time would be variable. Overall, we will not take more than 550ml in any 8-week period.

Environmental sampling

During quarantine, we will enter your room up to two times a day to take samples from the air and surfaces to see if the virus stays in the environment.

Stool samples

You may be asked to collect stool samples by using the special containers provided after opening your bowels during the quarantine stay and follow-up phase. Instruction on collecting stool samples will be given when you are admitted to the quarantine unit. Only some participants will be asked to do this, depending on the site they are quarantining with and the phase of the study.

Urine samples

Urine samples will be mandatory at certain time points to monitor your health. We may take additional samples throughout quarantine and at follow ups for research purposes. Only some participants will be asked to provide additional samples, depending on the site they are quarantining with and the phase of the study.

Additional study procedures may be performed to monitor your safety.

7.4.4 Rescue therapy

To help prevent volunteers going on to suffer severe disease, an antiviral treatment may be offered to you if you develop symptoms or other features (such as a severe persistent cough) and if the study team believe this would benefit you.

Potential treatments include:

1. Paxlovid (PF-07321332/ritonavir):

- Is an antiviral drug (a drug that stops SARS-CoV-2 from multiplying) licensed in the UK for treating mild Covid-19 patients who are at risk of progression to more severe illness, as it has been shown to reduce hospitalisation and severe disease if given earlier.
- This would be the treatment you would most likely receive should you require rescue therapy, and it is the preferred treatment to be used.
- It has not been used to treat young healthy people in the early stages of infection, so we cannot be sure how useful it is in this situation.
- Is taken as an oral tablet, for a duration of 5 days.
- Common side effects (up to 1 in 10 people):
  - Headache
  - Diarrhoea
  - Nausea
  - Altered sense of taste

You can find the latest patient information leaflet for Paxlovid here:
https://www.medicines.org.uk/emc/product/13145/pil

You must agree either to use effective contraception or not to have sex from the start of treatment with Paxlovid until 7 days after completing treatment. All people of child bearing potential using the combined oral contraceptive pill will also need to use a barrier method of contraception during treatment and until completion of one menstrual cycle after stopping Paxlovid. This is because Paxlovid can interfere with the effectiveness of the pill. The study doctor will discuss all of this with you in detail should it apply to you.

2. Veklury (Remdesivir):

- Is an antiviral drug licensed in the UK for treating either mild Covid-19 patients who are at risk of progression to more severe illness, or hospitalised Covid-19 patients who require supplementary oxygen.
- Is administered through infusion over the course of 3 days if used as rescue therapy to prevent deterioration from mild illness.
- Very common side effects (may affect more than 1 in 10 people)
  - Blood tests may show an increase in liver enzymes, called transaminases. Mild or moderate rises have been seen in healthy volunteers. In patients with Covid-19 rises in liver enzymes have been seen in both volunteers given placebo (an inactive substance that appears similar to the drug) and volunteers given remdesivir. In some of these studies increased liver enzymes were seen less commonly in the Remdesivir group when compared with the placebo group.
  - Blood tests may show it takes longer for blood to clot. In the study that identified this, there was no increase in bleeding events in the patients given remdesivir over the patients given placebo
- Common side effects (up to 1 in 10 people):

  Nausea
  Headache
  Rash

Side effects associated with the infusion site such as brief pain, bleeding, bruising of the skin, soreness, swelling and possible infection at the infusion site.

You can find the latest patient information leaflet for Remdesivir here:
https://www.medicines.org.uk/emc/product/11597/pil

It is unlikely that we will use Remdesivir during the study. If you were to receive these drugs, the study doctor would provide you with further information at the time.

7.5 Discharge from the quarantine unit

You will only be discharged from the quarantine unit when we are confident that you are well in yourself and that you do not pose an infection risk to others.

If you are not infected with Covid-19 at day 10 after enrolment (13 days since starting quarantine) you may go home on the morning of day 11 but you will need to come back every day to complete the procedures done on days 12-14. If it is difficult for you to attend these visits from home you may be given the option to stay in the quarantine unit until day 14 if agreed in advance with the study team but you would need to stay in your room. This may not be possible in all cases and should be discussed with the study team.

If you are infected with Covid-19, it is important that you stay in the unit for at least 14 days after enrolment (17 days since starting quarantine) and until we tell you it is acceptable and safe to leave (be discharged). We want to be sure that if you get Covid-19 symptoms, we can monitor you and give you treatment if necessary. We also want to be sure that you cannot spread Covid-19 to other people.

We would therefore advise that you need to be available and willing to stay in the unit for at least 3 weeks. You should make plans for childcare needs or emergencies that may occur during the study**.**

If you do not think you can stay in the quarantine unit for the whole duration you should not join the study.

Prior to discharge you will receive lateral flow tests to take home so that you can test yourself if you develop new suspected Covid-19 symptoms. We would like to know about any suspected symptoms or tests you undergo for Covid-19. We ask that if you develop any new symptoms following discharge that would normally require a Covid-19 test, you need to contact our study doctor using the mobile number on a contact card. This contact card will be given to you at discharge from the quarantine unit. We may ask that you test yourself using the lateral flow tests provided to you.

An up-to-date list of Covid-19 symptoms can be found by following the link below

https://www.nhs.uk/conditions/Covid-19/Covid-19-symptoms-and-what-to-do/

Covid-19 vaccination
You need to have had at least one Covid-19 vaccine to take part. However, to avoid confusing changes in your immune system following vaccination and changes in your immune system following challenge with SARS-CoV-2 we ask that you wait for 3 months after your last vaccination before enrolment ("D0"). In addition, we ask that you don't have any Covid-19 vaccine until *after* your day 28 follow up, for the same reason.

We ask that you avoid other non-Covid-19 vaccines for 30 days before enrolment and until *after* your day 28 follow up visit.

You will be asked to contact the study team if after discharge you:

- **Develop any new symptoms concerning for Covid-19**
- **Have any positive tests for Covid-19 (outside of the study tests)**
- **Receive a Covid-19 vaccine**
- **Receive any medical care outside of the study (e.g. GP or hospital attendances)**

7.6 Follow up phase

You will be provided with a 24/7 contact number to get through to a member of the study team should you have any concerns. You will return for clinic appointments at 1, 3 and 6 months after enrolment at the CCVTM, Oxford (where you attended your screening visit) so we can carry out more tests and procedures to check your health and to collect samples for research.

Each follow-up clinic visit will include tests, sample collection and assessments similar to those conducted at the screening visit. At each visit we will check your vital signs, take a blood test, and take a nasosorption test (see section 8.4.3). At the Day 28 visit you will also have deep nose swabs performed. We will also discuss any changes to your health or symptoms since we last saw you. Based on this discussion we may do a physical examination, lung function test, smell test, nose and/or throat swabs to look for evidence of airway infections, or a mental health assessment. You should allow up to 2 hours for the D28 visit. All other follow-up visits will last approximately 60 minutes.

If necessary, depending on the results of these tests and assessments, the study doctor may ask you to come back for additional appointments for extra test(s). The reasons for any additional tests will be explained to you. You will be compensated for each additional visit.

If you miss any follow up visits, we will endeavour to contact you. If despite repeat attempts, we are unable to get hold of you, we will contact your next of kin to check that you are safe. If repeated visits are missed such that it affects the integrity of our study data you may be withdrawn from the study.

7.7 Transferring between study sites

Ideally, participants will attend all aspects of the study at the same site. If we notice that you live closer to a study site than the one you have applied to after submitting your registration questionnaire, we may suggest that you apply to the other study site.

There may be circumstances where you wish to permanently transfer to the other study site after enrolment, for instance, because you have relocated. There may also be circumstances where we ask you to participate in the quarantine phase of the study at the other study site.

This could be due to one site being oversubscribed for the quarantine you wish to join, or other instances such as staffing requirements. We will discuss with you if you would be willing to join the other study site for the quarantine part of the study in these circumstances. You do not have to agree to do this, and we will do our best to accommodate you at the site you signed up with. If you do agree, we will liaise closely with yourself and the transferring site about this. Only after your agreement will we share your personal details with the study team at the transfer site. You will be provided all relevant information about the quarantine at the new site. Your records will be securely sent to the study team at the new site so they have the information they need to care for you. If you have been asked to go to the other study site for the quarantine, your reasonable travel expenses will be paid for travelling to and from this quarantine site upon proof of receipt. You can also choose whether you would like to stay at the new site for your follow up visits or return the original site that you signed up with. When you transfer to a new site, they will provide you with their localised version of this participant information sheet and highlight any important differences between the study sites. You will be asked to re-consent at your first visit with the new study site.

8 What are my responsibilities?

- ✓ You should not donate blood during the study period or take part in other studies that involve blood sampling or the administration of drugs or vaccines.
- ✓ You must tell the study staff if you take/use any medicines or treatments (e.g. tablets, sprays, creams, medicines and inhalers) that your GP/doctor told you to take, and/or any you have bought for yourself (e.g., over the counter medications, multivitamins, homeopathic medicines, herbal remedies, supplements). You will be told which medications are allowed prior to and during the quarantine period of the study and which are not.
- ✓ You must follow the requirements for contraception during the study. The study doctor will advise you appropriately.
- ✓ Smoking is not permitted during quarantine, and you must not be an active smoker or using any nicotine-containing products (e.g. gum, nicotine patches, inhalers, e-cigarettes) during the study period from screening visit to your D180 follow-up visit. You must have a negative test for nicotine before the study virus is given to you.
- ✓ You must not receive <u>any Covid-19 </u>vaccines within the 3 months prior to enrolment or before your D28 follow-up visit.
- ✓ You must not receive any vaccines of any kind within 30 days prior to enrolment or before your D28

follow-up visit.

- ✓ If during the study you require any vaccinations for health, travel, or occupational reasons, you should inform the investigators who can advise you if and when it is safe to receive them.
- ✓ You must not use any recreational drugs during the study period from the screening visit to your D180 follow up appointment.
- ✓ People who are breastfeeding, pregnant, trying to conceive or who have been pregnant within the past 6 months, cannot take part in this study.
- ✓ You should not participate in this study if you are not able to attend the quarantine period for its planned duration and/or the subsequent follow-up visits.
- ✓ You must tell us if you develop any Covid-19 symptoms or have any tests for Covid-19 regardless of the results (except for those performed by the study team) during the study period from the screening visit to your D180 follow up appointment.

9 What are the possible drawbacks of taking part?

The known effects of the study virus are described below. Although, we have designed this study to minimise any risks to your health, there may be unexpected and unforeseen risks related to the study virus and study procedures. **In particular, not all of the long-term effects of Covid-19 are yet known**. Whilst you are in the study, especially in the quarantine unit but also throughout your participation in the study, the medical staff will monitor your condition closely and medical assistance will be available at all times. Therefore, you must tell us immediately if you have any symptoms or changes in your health and wellbeing.

If we find any abnormalities during the study, we will inform you and also inform your GP or a specialist if necessary and with your permission

We will tell you as soon as possible if we become aware of new information that could change your mind about taking part in the study.

If you have any insurance policies, you should check whether taking part in this research study affects them.
If you are in receipt of state benefits you should check if the compensation received from taking part in this study affects any state benefit payments to which you are entitled.

Incidental findings

Undertaking the eligibility tests may result in us noticing something that could be important to your health. If so, we will contact you to explain what was noticed and support you with information regarding where to go for further advice. Future private healthcare or life insurance may be affected if a previously unrecognised problem is found during screening.

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

This virus is still causing disease ranging from asymptomatic or mild illness to severe respiratory disease that can also affect other parts of the body in large numbers of people throughout the world. Humans have only experienced infections with this virus since late 2019 and the full range of symptoms or diseases caused by Covid-19 is still being investigated. Therefore, at present it is not possible to predict completely the risks to you from participating in this study.

Some people when infected with Covid-19 experience no symptoms at all. More severe cases of Covid-19 disease are usually seen in the elderly (over 65 years of age) and those with pre-existing medical conditions (such as diabetes). Although the risks of hospitalisation and death are thought to be very low in young healthy people the factors that might increase the risk of such events in young persons are not completely known and therefore may not be detected in the screening process prior to entering the study.

10.1 Potential risks due to infection with Covid-19

- Common risks from the Covid-19 infection (one or more of these symptoms are seen in almost all identified cases) include: flu-like symptoms such as fatigue, headache, sore throat, persistent cough, shortness of breath, fever, loss of appetite, body aches, and runny nose.
    - You will be offered over the counter medication such as paracetamol and ibuprofen for relief of these symptoms while in quarantine.
- You could lose your sense of smell and/or sense of taste or experience changes in your sense of smell and/or taste.
- You could have abdominal symptoms including abdominal (tummy) pain, diarrhoea, nausea and vomiting.

On average, for people infected with the Omicron variant of SARS-CoV-2, symptoms last for up to 8 days and in 95% of cases are better within 18 days. However, some people have symptoms that last for longer, particularly tiredness/fatigue, cough and changes in their sense of smell or taste. Rarely these have gone on for over 3 months. We currently do not know exactly what proportion of people develop these "long Covid" symptoms but they seem to be more common in people who have a larger number of symptoms initially and those who are unvaccinated. If you develop symptoms of "long Covid", you will be followed up closely and referred to the NHS specialist service for treatment if necessary.

There have been 3 preceding 'human challenge' studies using SARS-CoV-2 but this will be the first study using the Omicron BA.5 subvariant. In the first challenge study participants 18-29 years old were unvaccinated and had not been infected with Covid-19 before. They were inoculated with the "Wuhan-like" virus and all infections were mild, with most infected participants developing symptoms that peaked after about a week and then got completely better. Nobody required rescue therapy, with most participants back to normal by the time they were sent home and 2 out of 18 infected volunteers having no symptoms at all. Reduction in sense of smell and/or taste were common but in most affected participants this was back to normal within a month. One infected person still had reduced sense of smell 9 months after they were infected, but this steadily improved over time and had resolved by the end of the study. Vaccination is known to reduce the likelihood and severity of symptoms, with "long Covid" symptoms halved in some studies, so these symptoms are likely to be less in this study as all participants will have had at least one vaccine.

In addition, during that study, participants were asked to carry out several cognitive tests every day. These showed small differences in a minority of the test scores between infected and uninfected groups, with lower scores on average mainly in the Object Memory tests after infection. None of the participants described symptoms related to these changes, with these differences fluctuating towards the end of the quarantine and afterwards. What these differences mean is currently unclear as these research tools have not been fully tested in the context of infection. Much bigger studies will need to be done to see if differences of this type and size have any impact on health. Changes like this have also been seen after common colds as well as Covid-19 earlier during the pandemic. These studies generally suggest that test scores normalise with time. Preliminary data looking at Omicron infections in the community suggest that, in mild illness, Omicron is less likely to cause long term changes in cognition therefore we will not be carrying out cognitive testing in this study but we will be monitoring all participants for symptoms of brain fog.

There have been two further human challenge studies using SARS-CoV-2 to inoculate healthy volunteers. In these studies, the volunteers were also 18-30 years old and healthy. One study also used the "Wuhan-like"

virus but in people who had either been infected with or vaccinated against Covid-19 before they entered the study. This study has completed enrolment of 48 volunteers with no safety concerns identified and another study using the delta variant is still ongoing and has not identified any safety concerns so far. If any safety concerns were to be raised by these studies and they were thought to be applicable to you, you would be informed. We will be using the Omicron variant in our current study, which is thought to cause less severe illness than both the delta and the "Wuhan-like" virus, although complications from Covid-19 can still occur in young health people.

10.2 Less common and more serious risks from Covid-19 infection

These are listed below. It is not possible to predict at this time what your risks of developing these complications are. However, based on current knowledge they appear to occur in fewer than 1 in 10 cases, and mostly, but not only, in older adults:

- *Covid Pneumonia*: You may develop pneumonia (inflammation in the lungs due to infection). This can make you feel short of breath and can cause oxygen levels to drop. In some cases, individuals need supplemental oxygen by a mask or tubes in their nose. In life threatening cases, individuals with pneumonia need to be placed on a ventilator (a mechanical breathing machine). About one-half of patients who reach this state of severity will die.

- *Severe immune response*: You may develop a newly described complication in which the body's immune system turns against your body's tissues, destroying blood vessels, the skin, and other organs. This syndrome is seen primarily in children and young adults and can very rarely be fatal.

- *Blood clots*: You may develop blood clots. These could cause swelling in your legs (deep vein thrombosis), or they could lead to a stroke. Clots in the legs can break free and get stuck in the blood vessels of the lungs. This is known as a pulmonary embolism (PE).
    - Symptoms from a pulmonary embolism vary from minor symptoms to severe. Symptoms include shortness of breath, a drop in your oxygen levels and in some instances can cause death. If a clot is identified, it can be treated using blood thinning medication. We will routinely offer all participants a daily injection of preventative blood thinning medication to minimise this risk.
    - A stroke is a clinical event that occurs when a blood vessel that brings oxygen and nutrients to your brain becomes blocked by a clot. A stroke may be minor, or it may be more serious, leading to paralysis of one side of your body, inability to speak, or other serious nervous system problems. These outcomes from a stroke could be long lasting or even permanent. If you have a stroke you could be permanently disabled or you could never recover your full strength, or, in a few instances, you may die.

- *Low blood pressure*: Although the risk is small, you could develop a dangerously low blood pressure also known as 'shock'. If this happens you will be given medication and other support to maintain your blood pressure. Treatments for shock in Covid-19 are not always successful, and death is in such circumstances regrettably common.

- *Kidney damage*: In rare circumstances, there may be kidney damage. Normally this gets better but permanent kidney failure may require use of an artificial kidney system (dialysis) or may require that you receive a kidney transplant.

- *Liver damage*: You could develop liver disease (your liver will not work as well). Normally this gets better but it could be permanent. Severe liver disease can be fatal or require a liver transplant.

- *Inflammation of the heart*: Covid-19 can rarely cause inflammation of the heart (myocarditis). This can occur with many viral illnesses. Common symptoms include chest pain or chest tightness on exertion, fatigue and shortness of breath. In severe cases, myocarditis can cause abnormal heart rhythms, heart failure and rarely death.

- *COVID toes*: You could develop painful swelling of your toes ("COVID toes"). This usually lasts 3 to 4 weeks and then resolves.

- *Epididymo-orchitis:* Epididymo-orchitis which means inflammation of the epididymis (structure next to testicles that is involved in making sperm) and orchitis means inflammation of a testicle. This condition can occur with many viral illnesses including mumps and chicken pox. It has been seen in males with Covid-19 disease, and is more common in those severely unwell. This inflammation is temporary and would be treated with pain killers and antibiotics if necessary. It is not yet firmly established whether this has any long-term effect on male fertility when it occurs with SARS CoV-2 infection. In the case of mumps (another viral infection that can cause epididymo-orchitis), we know that approximately 25% of males who get mumps infection after puberty get testicular inflammation, and approximately 1 in 10 of those who get testicular swelling have a drop in sperm count. This is rarely enough to cause infertility.

Since the first pandemic our knowledge of how to manage Covid-19 disease has improved. Several treatments have been approved for use in Covid-19 of different disease severity, from mild cases in the community, to moderate to severe cases requiring hospital care. Should you become unwell with Covid-19 (i.e. to the extent that you would require hospitalisation if you were at home with Covid-19), you will be transferred to the local NHS hospital and given the current recommended treatments to help you get better. These may include giving you oxygen, putting you on a breathing machine, giving you medications to help your blood pressure, or other treatments.

If you develop severe disease you may need to be transferred to an intensive care unit.

There is a very small risk that you could die if you develop Covid-19 illness during this study.

10.3 Risks of Transmission

When an individual with Covid-19 coughs, sneezes, sings and speaks they produce respiratory droplets carrying the virus. A close, unprotected contact within 2 metres of an infected individual can in turn be infected by inhaling these contaminated droplets. These droplets can also land on surfaces or objects and an individual may also be infected by touching these contaminated objects and then touching their own mouth, nose or eyes.

The virus that causes Covid-19 is very contagious. By agreeing to participate in this study, you are agreeing to stay in the unit for a minimum of 14-17 days after you are admitted to prevent spreading infection to others. You may be discharged earlier after 14 days if you are not infected or later if you are still infectious. You will be tested for the presence of the SARS-CoV-2 virus on a daily basis whilst in the quarantine unit. To minimise

infection spread it is important that while you are on the unit, you remain in your room. For their safety you are not allowed to have any visitors, but friends and relatives may leave things for you at the quarantine unit and there will be free WIFI to allow communication with friends and family. You are not allowed to send materials out, such as mail or packages, whilst you are in the quarantine unit.

10.4 Risk of treatment with Paxlovid

The Paxlovid medication has not been used to treat young healthy people in the early stages of infection, so we cannot be sure how useful it is in this situation. However, there are grounds to think it might work. In people at high risk of severe Covid-19, it has been shown to reduce hospitalisation and severe disease if given earlier. It has also been shown to be safe and cause few side effects in adults.

It does have the following known or potential risks:

- Common side effects: The most commonly reported symptoms after taking Paxlovid are dysgeusia (change in sense of taste), diarrhoea and nausea. These are usually mild.

- Allergic reactions: With any medication administered there is always the risk of an unexpected allergic reaction in an individual. Rarely, this can be life-threatening (called anaphylaxis).

- Risk to pregnant people: As a new treatment, there is currently limited clinical evidence in patients who are breast-feeding or pregnant. The effects on both the foetus and reproductive organs of males and females are unknown. Paxlovid can also reduce the efficacy of the combined oral contraceptive pill, therefore all women using the combined oral contraceptive pill will also need to use a barrier method of contraception for the 5-day duration of treatment and then until completion of one menstrual cycle after stopping Paxlovid. Paxlovid interacts with some medication, and herbal remedies and you will not be eligible for recruitment if these medications are required during the quarantine period.

More information can be found in the patient information leaflet: Paxlovid 150 mg/100 mg film-coated tablets - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

10.5 Radiological procedures

If you take part in this study, you will have a chest x-ray. This procedure will be extra to those that you would have if you did not take part. This procedure uses ionising radiation to form images of your body and/or provide treatment and/or provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will add only a very small chance of this happening to you.
All x-rays will be reported by an NHS Consultant Radiologist and any abnormal findings will be appropriately followed up, with referral to specialists where required.

10.6 Potential harm to an unborn child

Because we know that Covid-19 can harm an unborn baby and that being pregnant increases your risk of severe Covid-19, you cannot be in the study if you are pregnant. If you are pregnant, or likely to become pregnant during the study, you should not take part. To take part in this study, participants that can become pregnant must agree to use an effective method of contraception (as per section 12). If you became pregnant during the study, we would ask you to inform us.

10.7 Risks from other study procedures

Quarantine phase

You may become anxious, lonely or depressed by being confined to the quarantine unit without being able to see family or friends. Your personal private space will be limited. You will be visited frequently by study staff to check on you. To reduce these risks, prior to enrolment into the study, we will discuss with you your plans for activities during quarantine and strategies to promote your mental health well-being during this period. Suggested free online activities and resources (e.g. virtual museum exhibitions, online learning) can be shared with you including links to wellbeing and mental health resources. We strongly encourage you to exercise during quarantine and you will be allowed to bring in basic exercise equipment such as mats and hand weights. You will be able to contact friends and family via video calls etc as you would normally.

We are committed to safeguarding your mental health and if during the study period we are significantly concerned about your mental health status, we may consider stopping your participation in the study early if this was felt to be in your best interests. If needed, we may refer you for specialist mental health assessment and treatment or for follow up with your GP, with your permission.

There may be other psychological or social risks that result from taking part in the study, such as concern about being tested for HIV.

Blood samples & intravenous cannulation

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 study, we will take no more than 550ml of blood in any 8-week period, which is a safe amount for healthy volunteers to give, with blood donors being allowed to donate 470ml every 3-4 months. As we are taking this amount of blood for the study, you should not donate blood during the study period from screening visit to 6 months after enrolment, or take part in any other studies where you give blood. We will not enrol you if your blood counts are significantly low at screening and we will monitor you for signs or symptoms of low blood counts (anaemia) during the study.

Throat swabs, nose swabs, deep nasal swabs & nasosorption testing

Nose and/or throat swabs are both considered a safe way of looking for Covid-19 infection and has been performed across the world during the Covid-19 pandemic. It is not painful but can be uncomfortable. Swabbing the back of the throat can cause individuals to cough or gag. The deep nasal swab (and nasosorption tests) can make your eyes water or rarely cause nose bleeding.

11 What happens if I decide to withdraw from the study?

You are free to withdraw from the study at any time you wish, however If you decide to withdraw your consent and 'leave the study' during the quarantine phase, you will be very strongly encouraged to remain in the quarantine unit until you are no longer contagious. This is for both your safety and that of others whom you could infect as a contact. In this situation, we would continue to optionally offer you all procedures considered important for safety purposes by the study team but would stop any research procedures. This would include:

- Regular vital signs
- Medical review of any symptoms
- Safety blood tests (but not research ones)
- Paxlovid or alternative rescue therapy

Remaining in the unit would therefore allow close follow-up by the study medical team and receipt of the rescue therapy. If you have to leave the quarantine unit before you have been formally discharged, you will be advised to self-isolate at home.

In the event that you decide to leave the unit early:

- You will be advised about hand-washing and other infection control measures by the study medical team.
- You will be transported home in private transport and need to wear protective equipment (e.g. facemask etc.) during the trip if you test positive on the day of withdrawal.
- You will be advised to self-isolate for at least 10 days after enrolment and until you have two negative daily lateral flow antigen test results from 9 days after enrolment onwards.
- If you return home and there are other people in your household, we would advise you to avoid contact with them to reduce risk of transmission.
- You may not be eligible to receive the rescue therapy with Paxlovid (if being offered) if you leave quarantine before the planned date of treatment.
- With your agreement, you will be contacted daily by the study staff (i.e. study doctor or nurse) via phone calls to check on your health and to remind you of self-isolation requirements until the study doctors are satisfied that daily follow up can end.

If you withdraw from the study, any samples and data collected before your withdrawal will be used/stored unless you specifically request otherwise. However, if any of your pseudo-anonymised data has been incorporated into the study, it will not be withdrawn or erased in order to comply with our legal obligations and to maintain the scientific integrity of the study.

12 What advice on contraception must I follow during the study?

Please share the following information with your partner and talk to your GP or the study staff to decide the best method of birth control.

If you are able to have a baby you must be using acceptable birth control from 4 weeks before entering quarantine and until discharge from the quarantine unit. Thereafter you must not be trying to get pregnant and must agree to practise effective contraception from 4 weeks before admission to the quarantine unit until discharge from the quarantine unit.

Acceptable forms of contraception include:

a. Established used of oral, injected or implanted hormonal methods of contraception, starting at least 4 weeks prior to admission to quarantine
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods such as condoms
d. Vasectomy, if the vasectomised partner is the sole partner and appropriate post vasectomy documentation of success is available
e. Same sex intercourse only
f. True abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle

You must notify the study doctor if you become pregnant during the study. If you become pregnant, your study participation will be stopped and your pregnancy will be monitored, and we will follow up on your health to ensure there are no long-term complications.

Volunteers who are not of childbearing potential are those who have had a complete absence of menstrual periods for at least 12 months (and this is not due to the use of hormonal contraception or a medical condition) or practise same sex intercourse only, or provide documented proof of surgical sterilisation or hysterectomy.

In addition to the contraceptive requirements above, volunteers who receive Paxlovid during quarantine must agree to abstain from sexual activity or use effective contraception from the start of treatment until 7 days after finishing the course of treatment. People who are taking the combined oral contraceptive pill as their sole form of birth control will also need to use a barrier method of contraception (such as condoms) during the 5-day course of Paxlovid and until completion of one menstrual cycle after stopping Paxlovid.

13 Will I be compensated for taking part in this study?

You will be compensated for your time, inconvenience and travel expenses. The total amount compensated will be £4,935. If you are required to have any repeat or extra visits or are required to stay longer than the full 17 days in quarantine, then you will be compensated pro rata in addition to this payment. Note, travel will not be reimbursed separately and is included in the below payments.

Study reimbursement will be made by bank transfer after each of the following study time points:

1) £125 will be paid following attendance for screening
2) £2,590 will be paid after discharge from quarantine
3) £1,110 will be paid after the Day 90 follow-up appointment
4) £1,110 will be paid after the Day 180 follow-up appointment (last visit)

Additional days in the quarantine unit will be paid at £200 per day. Compensation for additional follow up visits are calculated based on any procedures performed and length of the visit.

If you attend an additional pre-screening visit, this will be paid at £35.

If you withdraw or are ineligible for the study, we will pay you up to the timepoint at which you withdrew/became ineligible.

It can take up to several months for payments to show in your account, all payments will be made prior to the study closing.

No cash payments can be made so please bring your bank details to the screening visit. If you do not complete the study (e.g. should you decide to withdraw from the study before it is completed, are excluded or are considered as a reserve participant), payment will be pro rata (you will receive a proportion of the total amount based on the visits completed). Your bank details will be stored beyond the end of the study, in accordance with site financial policies.

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

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

I have read and understood this section and had my questions answered (please initial):	

Part 2

1 What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. If you experience harm or injury (above the expected mild symptoms over the 2-4-week post-infection period) as a result of taking part in this study, you will be eligible to claim compensation without having to prove that the University of Oxford is at fault. This does not affect your legal rights to seek compensation. The amount of compensation you receive will be assessed independently based on any harm or disability you suffer and is unlimited.

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 need to be admitted to hospital. At any time during the study, you will be entirely free to change your mind about taking part, and to withdraw from the study. This will not affect your subsequent medical care.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient (for the study investigations performed at the hospital including chest x ray). PALS is unable to provide information about this research study. If you wish to contact the PALS team of Oxford, please call 01865 221473, or email PALS@ouh.nhs.uk.

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

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

All information that is collected about you during the course of the study will be kept strictly confidential. It is available to the study team, the NHS trust staff who are involved in your care, regulatory agencies and the sponsor (The University of Oxford), who can ask to assess the study. Responsible members of the University of Oxford, the external monitor/ monitoring service provider and/or NHS trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Your GP will be informed about your participation, as mentioned in Part 1.

Furthermore, we may share personal details (name, address and contact details) with taxi companies in order to facilitate private transport if required during the study.

Every effort will be taken to maintain confidentiality. Information about you may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the research site.

3 Will you require any photographs?

During the study, if you develop any unexpected or adverse reactions (e.g. rashes or Covid toes) it may be useful for us to photograph these to enable comparison at later time points.

Additionally, we may request use of photographs for scientific publications and/ or media documentation. Any photographs we take will not include your personally identifiable features (i.e. we would remove or black out your face) unless you gave separate explicit consent for inclusion of your personally identifiable features.

Consenting to photography during the study is optional and your consent can be withdrawn at any point. However, once photographs have been published they cannot be retracted.

4 What tests will be done on my samples?

The blood tests which we will perform at the screening visit have already been described in Part 1. The research and safety blood tests taking up to about 550mL of blood in any 8-week period, will test for the different types of cells in your blood as well as your kidney, heart, liver function and blood clotting. The immunology blood and nasosorption tests that will be done throughout the study will look at your body's response to the challenge agent you have been given. We will look for evidence of activation of your immune system, to see if the infection has triggered any response specifically against the study virus. Nose and throat swabs and facemask strips will be assessed to look for evidence of Covid-19 caused by the study virus. Some of the samples we collect will be sent to collaborating academic study teams in both the UK and abroad, which may include collaborators outside of the United Kingdom and may not be restricted to virology and immunology research. For example, we may look into the bacteria that usually reside within your nose and/or throat. Any samples will be sent and stored securely in a pseudo-anonymised form (under a unique study ID which only the study team can link back to you) except during the quarantine phase where investigations may have your personal details attached as part of standard of care.

If you consent, your leftover samples may be stored indefinitely under a University Human Tissue Authority (HTA) license and may be used for further related research, including the human body's immune response or vaccine research. As part of the consent form, you will be given the option of consenting to long-term storage for future research, or not. Your participation in this study will not be affected by your decision regarding storage and future use of your leftover samples. When your samples are stored, we will attach some demographic data to them, collected during your study. This will allow us to see if there are links or patterns between immune responses and other factors such as age or sex. This data may include but not be limited to, month/year of birth, immunisation history, medications, ethnicity, sex. No identifiable information would be included. If you decide not to participate in storage under a University HTA license then samples will be disposed of in accordance with HTA guidance at the end of the study.

5 Will any genetic tests be done?

We will do genetic tests on your blood samples to look at the patterns of genes that regulate your own individual immune response (these are called Human Leukocyte Antigen HLA genes). Doing this helps us to work out which aspects of the immune response to vaccines are due to genetic differences between individuals. We may also try to identify and study the genes that appear to be important in response to challenge. Samples will be tested in pseudo-anonymised form; however, your DNA is unique to you so it can never be completely anonymous.

6 Who is organising and funding the research?

This study is funded by the Coalition for Epidemic Preparedness Innovations (CEPI). The study is designed and organised by the investigators. The study is sponsored by the University of Oxford and the Chief Investigator is Professor Helen McShane. Neither your GP nor the researchers are paid for recruiting you in this study.

7 Who has reviewed the study?

This study has been ethically reviewed and approved by the Specialist Research Ethics Committee (ref: 24/SC/0404).

8 What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is a task we perform 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 in order to undertake this study and will use the minimum personally-identifiable information possible.

The University of Oxford will keep identifiable information about you for up to 7 years after the study has completed. If you agree to your samples being used in future research, your consent form will be held securely until the samples have been used up. Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

We will store any research documents with personal information, such as consent forms, securely at the University of Oxford for 25 years after the end of the study (January 2028) as part of the research record.

If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form securely until such time as your details are removed from our database. We will keep the consent form and your details separate from one another and any research data.

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

We may disclose your personal data to our third-party service providers to carry out activities specifically for the purpose of this research and as explained in this information sheet. Any third-party service providers are required to take appropriate security measures to protect your personal data in line with University of Oxford policies. We do not allow our third-party service providers to use your personal data for their own purposes, but rather to only process your personal data for specified purposes and in accordance with our instructions.

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

9 What will happen to the results of the research study?

The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until one or more years after the study is completed. A summary of published reports will be sent to all study participants for information purposes. You will not be identified in any report or publication. Data from this study may be used as part of a student post-graduate degree, for example a PhD. The anonymised data from this study will be shared with the collaborating partners who are organising and funding this research. 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.

10 Taking part in future 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 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 study.

Your details will be stored electronically on a secure server and only authorised individuals at the University of Oxford 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.

11 Further Information and contact details

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 study you may wish to contact your GP. If you would like to speak to one of our study doctors or Professor Helen McShane (Chief Investigator) to discuss any aspect of this study, or if you would like to take part in this study, please contact:

Covid19-challenge@paediatrics.ox.ac.uk

If you have any medical problems during your participation in this study, please contact the study doctor via the number given to you on your emergency contact card (24-hour emergency number). Alternatively, if your query is not urgent you can email Covid19-challenge@paediatrics.ox.ac.uk.

Please note this PIS document, as well as Quarantine Information Sheet, consent form and PIS summary have been reviewed by members of the Oxford Vaccine Centre PPI group for review and feedback.

I have read and understood this section and had my questions answered (please initial):	