



## **A SARS-CoV-2 challenge study in previously infected and/ or vaccinated healthy adults**

### **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 questions and there will be time for you to discuss it with friends, relatives and your General Practitioner (GP) if you wish.

**And remember, it is entirely your choice.**

Our study aims to develop a safe human infection model with SARS-CoV-2 (the virus that causes COVID-19 disease) in healthy volunteers who have previously been infected with SARS-CoV-2 and/or received a vaccination against the SARS CoV-2 virus. Information 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 develop a test that tells people if they are protected from the virus.

You will be compensated a maximum of £4,845 for your time, travel and inconvenience.

### **Could I be eligible to take part?**



**You must**

- Be aged 18-30 years old
- Be in excellent health
- Be willing to travel to Oxford
- Either:
  - 1) Have previously been infected with SARS-CoV-2 virus (the virus that causes COVID- 19 disease). In this group you may be vaccinated or unvaccinated against SARS CoV-2.
  - 2) OR No prior history of COVID-19 infection but have received a vaccine against SARS-CoV-2.



**You must not**

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

**If you decide to join our study:**

1. You will be exposed to SARS-COV-2 virus with its attendant 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 17 days and will not be able to receive any visitors. The only in person contact will be with the research team. 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 medical staff will monitor your health and mental condition 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.. You may have CT scans of the chest depending on when you are enrolled.
5. We will treat you with a medicine, Paxlovid, if you are infected and develop any symptoms that concern us. This has been shown to help in other situations of SARS-CoV-2 infection but may not help in people who already have antibodies
6. We will need to follow you up for 12 months.
7. You will be free to withdraw from the study at any time you wish.



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## **Part 1**

### **1 Introduction**

Human challenge studies (sometimes also called 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 SARS-CoV-2, the virus that causes COVID-19 disease, as liquid drops into the nose. The full rationale 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-19 (COVID-19) currently responsible for a global pandemic which has infected over 100 million people across the world.

Recent 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 sensitised to COVID-19 (either due to prior infection and/ or vaccination) are exposed to the SARS-CoV-2 virus (“challenged”) in a controlled manner. The key aim of this study is to establish a safe human challenge model, which would then allow us to closely examine the immune response (human biological response to fight the virus). This study will provide information about immune responses in its own right and crucially enable further studies in future 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 again. We hope this will help develop a blood test or “test of protection” that could help develop and test future vaccines or treatments and even inform policy, such as who is safe to travel or return to school or work. Despite the recent positive news of effective vaccines against COVID-19, ongoing studies are needed as one vaccine is not likely to be suitable for everyone and we need a selection of vaccines to protect the whole population and protect against new strains of the SARS-CoV-2 virus. Furthermore, as more of the population are vaccinated and there is less COVID-19 in the community, being able to test new vaccines will become increasingly difficult which is why we need these controlled human infection models (also known as ‘challenge’ models).

To do this, we need to find the lowest dose of 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 a 2-3 week inpatient quarantine stay). This study will be carried out in close collaboration with a study at Imperial College London in healthy adult participants who are negative for SARS-CoV-2 antibodies.

### 3 How is the study going to work?

We plan to recruit up to 112 participants initially (possibly up to 132) across four groups (see **Table 1**, **Table 2** and Figure 2). Each individual will only receive the SARS-CoV-2 virus once as liquid drops into the nose. The study virus is based on the original virus from Wuhan, China and NOT one of the newer strains that have been identified since December 2020.

**Table 1: Arm 1 Study Groups – for individuals who have previously been infected with COVID 19 (+/- vaccination)**

Group	Cohort	Number of volunteers	Dose
1	1A	6-8	Low dose (10 TCID50)
	1B	6-8	Medium dose 1 (100 TCID50)
	1C	6-8	Medium dose 2 (1000 TCID50)
	1D	4-8	Medium dose 3 (10,000 TCID50)
	1E	4-8	High dose (100,000 TCID50)
2		10- 20 initially (possibly up to 30)	Dose determined from Group 1

“TCID50” is a standardised unit of measurement of amount of virus.

**Table 2: Arm 2 Study Groups – for individuals who have never been infected with COVID-19 but have received at least one COVID-19 vaccine**

Group	Cohort	Number of volunteers	Dose
3	3A	4-8	Medium dose 1 (100 TCID50)
	3B	4-8	Medium dose 2 (1000 TCID50)
	3C	4-8	Medium dose 3 (10,000 TCID50)
	3D	4-8	High dose (100,000 TCID50)
4		10 - 20 initially (possibly up to 30)	Dose determined from Group 3

**Group 1- Safety and dose finding group for individuals who have previously been infected with COVID-19 (+/-vaccination):** Each dose will be tested in 4 to 8 participants.

We will start by testing the lowest dose of the virus and then test higher doses if needed. An independent Data Safety Monitoring Board (DSMB) will be monitoring the study and will tell us to continue, increase or decrease doses. You will be informed which group and cohort you are assigned to. We will infect up to 8 volunteers in the first cohort. If the SARS-CoV-2 virus doesn't cause a positive swab in at least 3 participants in the first cohort (i.e. no evidence of re-infection) then we will move to the next higher dose (the next cohort) after review with the independent Data Safety Monitoring Board. Depending on whether people are infected, and what symptoms, if any, they get from this dose of SARS-CoV-2 virus, a higher dose may be studied in another cohort of up to 8 volunteers. If we reach the high dose (100,000 TCID50) then we will inoculate a minimum of 4 individuals at this dose before proceeding to group 2 (see below). We will not dose beyond this level even if our target infection rate is unmet but will proceed to group 2 at this dose as long as there are no safety concerns identified. If you are unvaccinated you may be given a lower dose than the dose we are currently testing, this is because we want to ensure we have sufficient data in unvaccinated volunteers prior to dose escalating in case of differing immune responses.

**Group 3 - Safety and dose finding group for individuals who have never been infected with COVID-19 but have received at least one COVID-19 vaccine:** Each dose will be tested in 4 to 8 participants

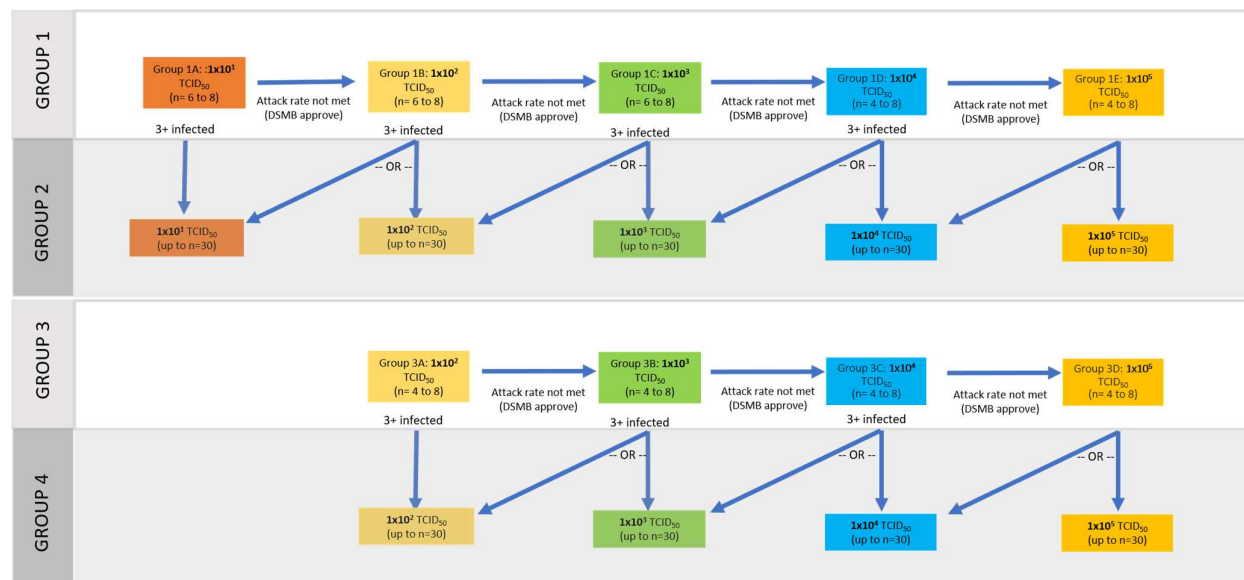
We will start this dose finding group at the medium dose of the virus then test higher doses if needed. The decision to start at the medium dose is based on safety data from group 1A and 1B (See Table 1). An independent Data Safety Monitoring Board will be monitoring the study and will tell us to continue, increase

or decrease doses. You will be informed which group and cohort you are assigned to. We will infect up to 8 volunteers in the first cohort. If the SARS-CoV-2 virus doesn't cause a positive swab in at least 3 participants in the first cohort (i.e. no evidence of infection) or we inoculate 4 participants and none are infected, then we will move to the next higher dose (the next cohort) after review with the independent Data Safety Monitoring Board. If we reach the high dose (100,000 TCID<sub>50</sub>) then we will inoculate a minimum of 4 individuals at this dose before proceeding to group 4 (see below). We will not dose beyond this level even if our target infection rate is unmet but will proceed to group 4 at this dose as long as there are no safety concerns identified.

**Groups 2 and 4: - Safety and dose confirmation groups: up to 20 participants initially (possibly up to 30)**

Once an optimal dose or the maximum dose of the virus has been selected from the dose finding groups (Group 1 and 3), we will enrol up to 20 participants in group 2 and 4. These groups are needed to confirm that the dose of virus we have identified in group 1 and group 3 does cause infection at the expected rates and remains safe in this wider group of participants. The findings from the first 10-20 participants in this group will be carefully reviewed and if needed (to achieve statistical significance of results generated) then a further up to 10 participants may be enrolled.

You will be in the study for 12 months from enrolment (Day of administration of the virus) to the last clinic appointment.



**Figure 2: Groups 1-4: Dose Escalation and Dose Confirmation**

## 4 What is the natural course of COVID-19?

The virus spreads between people either by droplets in the air following exhalation 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 common symptoms of COVID-19 include:

- Fever
- Headache
- Fatigue
- Dry cough

- Loss or change in taste and/or smell
- Sore throat
- Diarrhoea
- Body aches

### **“Long COVID”**

In most cases, symptoms get better within 2 weeks. However, up to 10% of people who have had COVID-19 may still be experiencing fluctuating symptoms more than 3 weeks following infection. In a small number of cases these after-effects can last months. This is sometimes called “long COVID” or “post-COVID syndrome.” These long-term effects are not limited to those who have required hospitalisation or been seriously unwell with COVID-19, but have been more commonly seen in older women who have a larger number of symptoms when initially infected. The current estimated risk of “Long COVID” after natural infection in the 18-30 age range is that 1% of individuals are still experiencing symptoms 8-12 weeks after 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

Unfortunately, there is currently no way to predict how long recovery from “long COVID” will take. It is important to note that this isn’t unique to COVID-19 – other viral illnesses can also have lasting effects. Experience with other viruses suggest most symptoms should gradually resolve within 3-6 months, and there are some treatments that may reduce them. However, this may not apply to everyone and as COVID-19 is a new disease, it is still unclear exactly how long these symptoms can last and how many people they might affect.

Emerging data suggests that prior immune sensitisation from infection and/or vaccination may protect against the development of long COVID. The COVID symptom (ZOE) study has shown that a full course of vaccination halved the risk of symptoms persisting beyond 4 weeks as well as reducing the total number of symptoms reported when compared to unvaccinated individuals. There is less data available about the risk of long COVID symptoms following a second infection (“re-infection”) with SARS-CoV-2. One large UK study, the SIREN study (Sarscov2 Immunity & REinfection EvaluationN) is looking at COVID-19 re-infection in healthcare workers. This study suggests re-infection may lead to development of COVID-19 disease with fewer symptoms compared to the initial episode. This may indicate that there is a reduced risk for prolonged symptoms following a secondary infection.

However, we do not have enough information to know you are not at risk of long COVID and we will therefore be monitoring for ongoing symptoms throughout the study.

### **Severe COVID-19**

Overall, about 10-20% of people who get COVID-19 get severe disease but this is uncommon in young healthy adults. The chance of requiring hospital treatment in the 18-30 age group if infected with COVID-19 is estimated to be less than 0.4% (1 in 250 people infected with COVID-19). 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.

The complications of severe COVID-19 are given in section 12.2. Most people who develop severe illness from 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 disease and a small number have died. Data from the last peak suggests the risk of death in our study target group is less than 0.0016%, which means 1-2 people per 100,000 infected would die. This is likely to be an overestimation for the risk of death in our study, as this value doesn't take into account existing health problems and other risks for becoming unwell with COVID-19 that we will screen for. As part of this screening process we will be using a risk assessment tool called QCOVID. **A member of the study team will inform you of your calculated risk. It is important to remember that your calculated risk is an estimate derived from population-based studies and may over or under represent your actual risk. A member of the trial team will discuss the risks posed to you by taking part in the trial and you will not be eligible if you are judged to be at significantly increased risk of severe illness.**

#### **Is it possible to get COVID-19 infection if I have already been infected or I have received a COVID-19 vaccine?**

Recent studies following healthcare workers have shown that having antibodies to SARS-CoV-2 (from previous infection) appears to protect most individuals from a second infection ("re-infection") for at least 6 months. However, a small collection of individuals in these studies seem to get re-infected, despite having antibodies. Of those who got a second infection in the healthcare studies no one was hospitalised. Additionally, data from the office of national statistics (ONS) has demonstrated milder symptoms with re-infection compared to initial infection. However, there is still limited data on re-infection with COVID-19 and it is also possible that the immune response could cause a more severe illness on re-infection. There have been a few reports of individuals who have had a more severe illness on second infection.

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 felt that re-infection or 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. There are however many unanswered questions regarding infection in individuals who have been sensitized to the virus, which, we hope in part to answer in this study. Variables such as the infecting strain of COVID and dose of infection may affect why some people are infected and others are not.

Whilst, we believe by being sensitized to the virus via prior infection or vaccination that your risk of developing severe symptoms is reduced. There are still large gaps in our knowledge and we **cannot guarantee that will be the case.**

## **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 8.1). 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 chance you could develop or boost antibodies and T cells (the two arms of the immune system that fight infection) against COVID-19 but we don't know if you will develop antibodies or T cells and whether they would protect you against further COVID-19 infection.

You will also receive compensation for your time, inconvenience and travel a maximum of £4,845 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 symptoms of COVID-19 disease, 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 2-3 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 the University (if applicable).

## 7 Can I take part?



In order to take part in the study you **MUST**:

- ✓ Be normal weight or mildly overweight only (a Body Mass Index (BMI) of over 18.5 and less than 28).
- ✓ 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.
- ✓ For women of childbearing potential, practise continuous effective contraception during the study and have a negative pregnancy test on the day(s) of screening and challenge and if requiring rescue therapy must also use a barrier method of contraception with spermicide during treatment with Paxlovid and then for 30 days after stopping Paxlovid.
- ✓ Be able and willing (in the investigator's opinion) to comply with all study requirements

For Groups 1& 2:

- ✓ Written or electronic proof of SARS-CoV-2 infection. For example: a text or email confirming a positive PCR or a photograph of a positive lateral flow test on your personal mobile phone. This must have been more than 3 months before enrolment.
- ✓ OR documentation of a positive antibody test for anti-nucleocapsid (anti-N) antibody, a type of antibody developed in response to natural infection but not vaccination. Where the timing of your SARS-CoV-2 infection is known, this must have been more than 3 months before enrolment.

For Groups 3& 4:

- ✓ Evidence of at least one dose of SARS CoV-2 vaccination over 21 days prior to planned enrolment



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.

- ✗ Any clinically significant respiratory disease (a condition which affects your lungs), including asthma.
- ✗ Current smoker (defined as any smoking, including e-cigarettes, in the last 3 months) or have smoked the equivalent of more than 20 cigarettes daily for a 2-year period at any time or currently using nicotine containing products .
- ✗ History of anaphylaxis (severe allergic reaction) or any allergy likely to be worsened by any component of the study agent or proposed treatment regime.
- ✗ Clinically significant history of skin disorder, allergy, atopy (e.g., eczema and dermatitis), cancer, cardiovascular disease (conditions affecting the heart or blood vessels), gastrointestinal disease (conditions affecting the stomach and intestines), liver disease, kidney disease, endocrine disorder

(conditions affecting the glands, including Type I or II diabetes), neurological illness (conditions affecting the nervous system).

- ✗ 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 or significant claustrophobia.
- ✗ Significant history or presence of drug or alcohol misuse.
- ✗ Any significant abnormality affecting your nose or throat including frequent or very heavy nose bleeds or any nasal or sinus surgery within six months of the planned date of enrolment.
- ✗ Active rhinitis (including hay fever) or history of moderate to severe rhinitis (including seasonal hayfever) or mild rhinitis if it will likely require weekly nasal steroid sprays during the enrolment period.
- ✗ 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).
- ✗ Active Tuberculosis (TB) disease or latent TB infection.
- ✗ Previous Varicella-Zoster Virus (VZV) pneumonia.
- ✗ Current Hepatitis B, Hepatitis C or HIV infection
- ✗ Use within the last 6 months of steroid medication or other immunosuppressive agents (steroids used as a cream or ointment are permitted)
- ✗ Use of medication contraindicated for use with paxlovid
- ✗ Immunoglobulin (antibodies) and/or any blood products within the three months preceding the planned study challenge date.
- ✗ 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 the last 6 months, current breast-feeding or intention to become pregnant during study period (1 year).
- ✗ Shares a household with someone with a clinically significant immunodeficiency (either from infection, medication or pregnancy), or who is extremely clinically vulnerable (i.e. anyone previously shielding under Public Health England guidelines)
- ✗ Current participation in any other research trial which involves receipt of an investigational product or drawing of blood. Additionally participants must not have had an investigational product within the 30 days preceding enrolment into COV-CHIM01.
- ✗ Evidence of ongoing post COVID-19 symptoms or complications (e.g. abnormal Chest x ray)
- ✗ Hospitalisation with prior COVID-19 infection or related complications
- ✗ Have plans to receive any live vaccine in the 30 day period before or after enrolment
- ✗ Have plans to receive any non-live vaccine (including a SARS CoV-2 vaccine) in the 21 day period before enrolment or 30 day period after enrolment. (For more detailed information please see section 8.3 & 8.4).
- ✗ 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
- ✗ Individuals who are difficult to take blood from
- ✗ 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

For Groups 3 & 4:

- ✗ Previous positive test for SARS CoV-2 infection (PCR or lateral flow antigen test)
- ✗ A history suggestive of COVID-19 disease at any time
- ✗ Positive antibody test for SARS CoV-2 (not explainable by prior vaccination).

## **8 What will happen if I decide to take part?**

### **8.1 Pre-Screening**

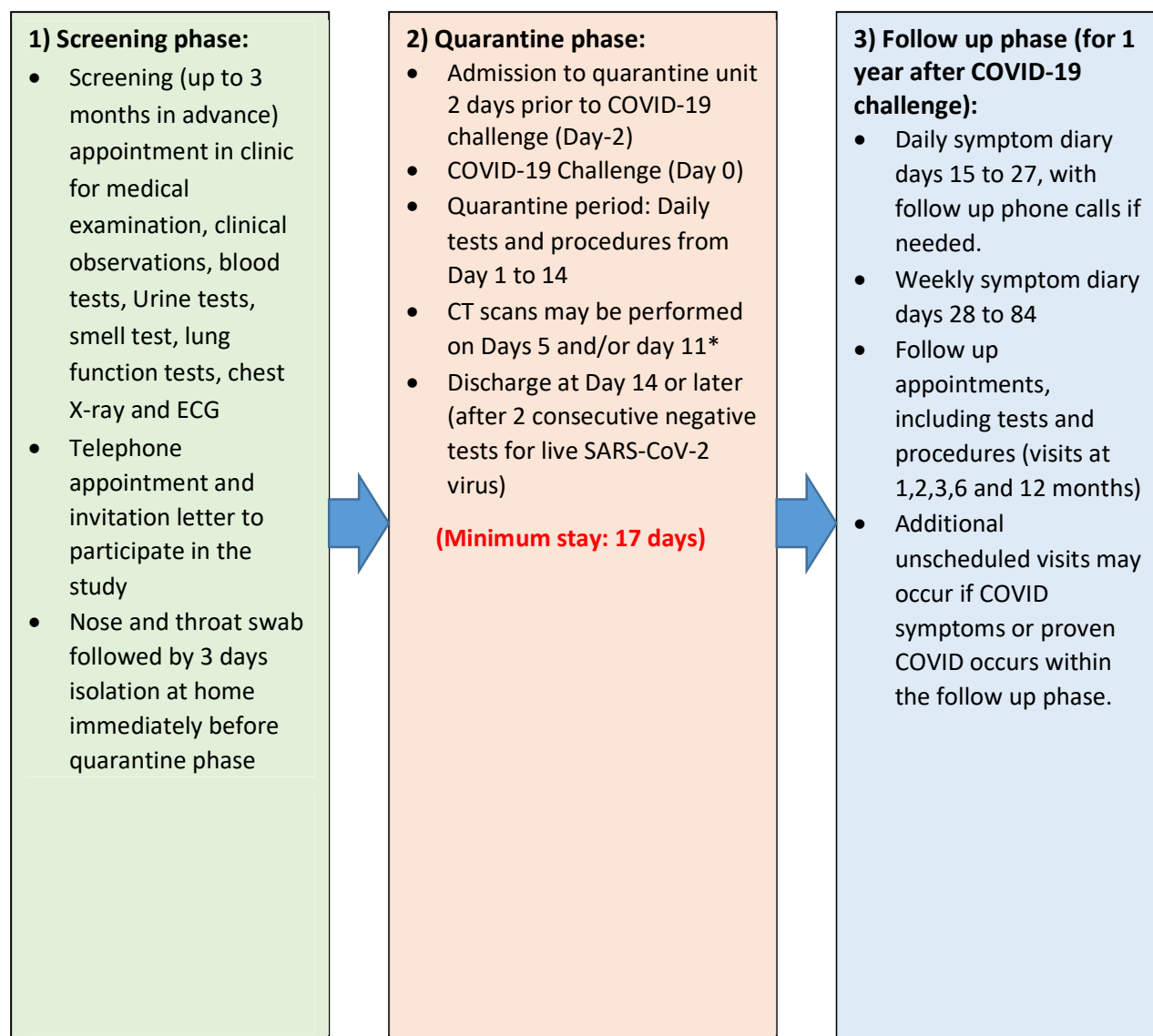
If you would like to take part we will ask you to complete an online questionnaire to register your details. This will take no longer than 10 minutes to complete. Additionally, there will be a few brief questions to check that

you are eligible for the study, this will include a few questions about your medical history. Additionally, we may clarify any of your answers on the online questionnaire over the telephone.

If eligible, a pre-recorded video will be made available to you providing a detailed explanation of the study information sheets (Participant Information Sheet and the Quarantine PIS) to ensure you understand what to expect if you decide to take part, the risks involved and what side-effects you might experience. Once you have confirmed that you have watched the video and read the information sheets, you will then be booked in for a video Pre-Screening appointment. During this appointment the research Doctor will discuss the study with you . and you will receive full and comprehensive answers to any questions you might have. This video appointment will be recorded (audio only). This is in order to make sure that we have properly given you all the important information and you are able to give fully informed consent. You will not be identified in this recording other than by a participant number and your voice. We will take your verbal consent to record this appointment. After this appointment you will have time to think about this study 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.

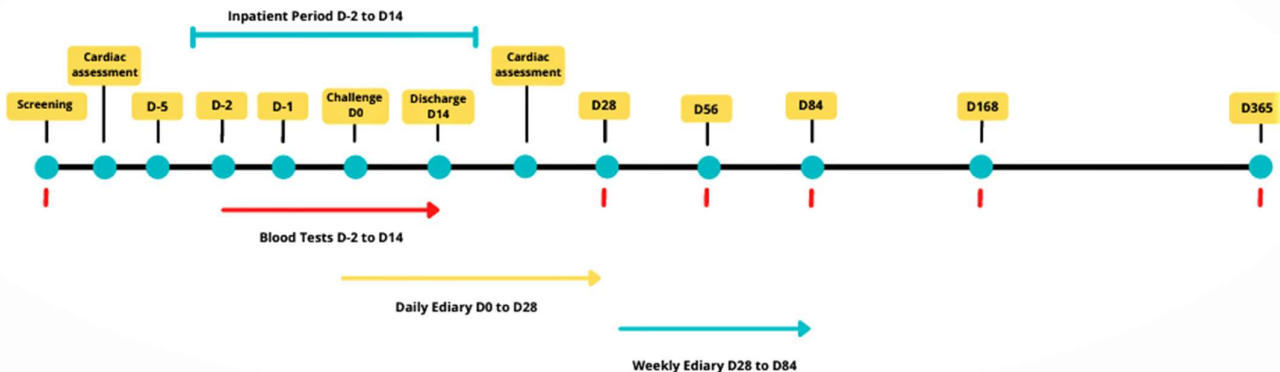
If you decide you would like to proceed then we will then ask you to attend a face to face screening visit. The screening and follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at the Churchill Hospital site in Oxford. The quarantine phase will be conducted at the Experimental Medicine Clinical Research Facility (EMCRF, based at the Churchill Hospital site) depending on bed availability.

The study will consist of 3 phases:



\* Refer to section 8.3.3 for more details on when CT scans may be carried out.

The trial timeline (Figure 1) details the number of visits involved in the study. The screening phase comprises up to 3 visits – the screening appointment itself, and the COVID swab 5 days prior to enrolment (D-5). This is followed by the quarantine period and then a minimum of 5 visits in the follow up phase. Additional visits will include unscheduled visits if you develop COVID in the community. Blood tests for safety and research will be taken at the visits marked in Figure 1 and during the quarantine period, total volume of 838.5ml. Up to an additional maximum total of 125ml for research may be taken if longer than 17 days is spent in quarantine and/or any unscheduled visits are needed.



**Figure 1: Trial timeline** (Note that the inpatient period may extend beyond D14 as described in Section 8.2)

## 8.2 Screening phase

At the screening visit, you will be met by one of the study doctors who will discuss the study again with you and you will be given the opportunity to discuss any additional questions you may have.

Once you are happy that you fully understand what the study involves, the study doctor will ask you to complete a questionnaire to make sure you have understood everything. When the doctor is satisfied that you have understood everything, and 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. We will also seek your consent to contact Public Health England for your previous nose/throat swab results to verify that you have had prior infection with the SARS-CoV-2 virus (if applicable).

The investigator 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 hours for this first screening visit and it will occur up to 90 days prior to enrolment in the study. You will receive compensation for this visit.

### Medical examination and clinical observations

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 both for any health problems and for the presence of drugs of misuse and nicotine use. Additionally, for women 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 screen for the presence of active anxiety or depression that may make the quarantine period less tolerable. The questionnaires used are:

- 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 painless 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 red blood cells) or problems with your immune system,
- Blood clotting problems,
- Liver, kidney and heart function
- Tuberculosis infection
- 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 immune status and to look for evidence of prior or recent COVID infection.

### 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 abnormalities after your initial COVID-19 illness. 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 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. You will also be asked to breathe in air mixed with very small amounts of gases (helium and carbon monoxide), hold your breath for about 10 seconds and then breathe out slowly.

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 to the Oxford University Hospitals NHS Trust.

### QCOVID

The study doctor will perform a personalised risk assessment using the QCOVID tool, based on the latest data and knowledge of risk factors available at the time of your enrolment for the study. This will be performed at the screening visit and then rechecked with your screening results and GP summary. If your risk of both death and hospitalisation from COVID-19 are considered low using the QCOVID tool and your test results, medical history and examination meet our eligibility criteria then you will be contacted to arrange a date to start the study.

### What happens if any tests are abnormal?

Sometimes test results may be “out of range”, which means the results do not fall within the usual ranges for healthy individuals. In this case, you would 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 page 28 for details). If the test results are still out of range, or if the chest x-ray or heart imaging 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 divulged to anyone outside the study team without your permission.

## **8.3 Quarantine phase**

To ensure you haven't been infected with COVID-19 in the community immediately prior to your admission we will perform a COVID-19 nose & throat swab 3 days (+/- 1 day depending on clinic logistics) before you come into the quarantine unit (this is 5 days before the planned challenge date i.e. Day -5). We then ask that you self-isolate at home after the swab has been performed and until you come into the quarantine unit.



These swabs are performed by first wiping the soft tip of a swab (like a long cotton bud) across the back of the throat, then inserting a few cm into the nostril and gently rotating it for a few seconds. This is an important measure both for your safety and to ensure the research data is accurate (we would not want to inadvertently dose you with further virus if you were already infected). We would also request that you inform us if you develop any symptoms prior to coming into the quarantine unit or if you are in close contact with someone with COVID-19. In this situation, if it would fit with our study schedule we would delay your enrolment or in some cases we may have to withdraw you from the study.

In addition to a nose and throat swab, a repeat blood test (5mls) may be taken prior to enrolment to look at any changes in your antibody levels to the SARS CoV-2 virus that may suggest a recent infection.

We will admit you to our Quarantine unit at the Experimental Medicine Clinical Research Facility 2 days (Day-2) before you are given the study virus. You will stay inside your allocated quarantine room for a minimum of 17 days (starting on day-2), but you may be asked to stay longer if the study doctor thinks it is necessary (see section 8.3 discharge criteria).

During this time, you will be fully isolated. The only face-to-face contact will be with the research team. The research team will wear protective clothing every time they enter your room. You will be cared for in line with Oxford University Hospitals NHS inpatient policies.



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 ensuite bathroom attached to your room. There will be no cooking facilities; meals will be provided by staff.

You will receive a supplementary information booklet with further information about what to expect during your stay in the quarantine unit. We will also provide you with a schedule, so you know what tests/procedures will be carried out each day. This will help you organise your daily routines during the quarantine period.

### Medications

Some over-the counter, 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 3**). 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 3 Medications not permitted prior to the challenge**

Medication	When to stop prior to the challenge date
Steroid containing medications (steroids used as a cream or ointment are allowed)	6 months
Antiviral drugs	6 months
Vaccines – Live	30 days
Vaccines -Non-live (including SARS CoV-2). For further information on SARS CoV-2 please see below section 8.4.	21 days
Any medication or product (prescription or over-the-counter), for symptoms of nasal congestion or respiratory tract infections including nasal steroids	30 days
Hay fever medications	7 days
Medications not compatible with Paxlovid	30 days

#### 8.3.1 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, mouth and nose swabs (to look for evidence of different types of viral illness including COVID-19 infection and additionally for research purposes), blood tests, vital signs (including weight, pulse, blood pressure, breathing rate, oxygen level measurements and temperature), physical examination and urine tests (including urine screening for drug misuse and nicotine use). Women of child bearing potential will have a blood test to check for evidence of pregnancy. Repeat mental health assessment questionnaires will be performed to check you remain well.

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 challenge (deliberate infection with SARS CoV-2 virus). If we identify any abnormalities we may cancel or postpone your quarantine stay.



Additional baseline research procedures will be carried out on Day-1 including smell testing, cognitive assessments and mask wearing samples (please see below for further detail).

### **8.3.2 COVID-19 challenge (Day 0)**

On Day 0 (challenge day) the study doctor (or qualified nurse) will “inoculate” you (administer) with the study virus. They will drop a small amount of solution containing the SARS-CoV-2 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.

In most COVID-19 infections (99%) in the community the virus takes between 2 to 12 days to start showing up in your nose, with most cases taking a period of 5 days. Once infected, the average amount of time that people shed “live” (infectious) virus from the nose and mouth is approximately 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 and until you have had two negative tests for ongoing shedding of infectious virus. We will also ask you to wear a mask when staff members are in the room to reduce risk of spreading the virus.

### **8.3.3 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, both to monitor your safety and for research purposes. Table 4 shows you which tests will be carried out and how often.

If your quarantine is undertaken in association with the Oxford University Hospitals NHS Trust, safety blood tests taken during the quarantine phase of the study will be processed using the hospital Electronic Patient Record System. This will use your identifiable patient data, which will link to your NHS medical records.

**Table 4 Tests and procedures during quarantine phase**

Test/procedure	When?
Vital signs (heart rate, blood pressure, breathing rate, oxygen levels, temperature)	Minimum of four times a day (when awake).
Physical examination	Compulsory on Day -2 and then only if needed. Weight will be measured at Day-2, Day 5 and Day 12.
Mental Health Assessment questionnaires	On Day -2, Day 0, 3, 6, 9, 12 and 14
Urine tests	Day -2, Day 4, 9 and 14
Pregnancy test (women only)	Day -2 (blood test) and Day 0 (urine test)
CT scan of lungs	May be performed on Days 5 and/or day 11 as needed
ECG	Day -2, Day 4, 8 and 12 Other days only if needed
Nose and throat swab	Once on Day -2, then twice daily from Day 1 and once in the morning on day of discharge.
Deep nasal swab	3 swabs on Day -2 Two swabs on Days 2, 5, 7, 11 and 14
Smell identification test	Day-1, Day 2, 5, 8, 11 and 14. Other days only if needed (i.e. if reporting symptoms of change in sense of smell or taste).
Cognitive tests	Day-1, then daily from Day 1
Symptom Diary	Twice daily from Day 0 until discharge
Mask wearing	Day-1, and then daily from Day 1 until discharge
Nasosorption	Twice daily on Day -1 and Days 1- 3, Once daily on Days 0, 5, 7, 11 and 14
Blood tests	Day -2(+/- day-1 if not enough sample obtained on day-2), 2, 5, 7, 11 and 14 We may take up to an additional 62.5mls (3-4 tablespoons) if you stay beyond 14 days.
Wearing TED stockings	Daily from Day 0 until discharge

#### Diary card

On Day 0 challenge, we will set up an electronic diary (E-diary) account for you to record any symptoms you may develop over the following 28 days post-challenge. This needs to be filled in twice daily online, using either your smartphone or your personal computer (a tablet or paper diary alternative can be provided if required) during your quarantine stay. After you leave the quarantine unit, we will ask you continue this once a day until day 28. After your Day 28 visit, we will then ask you to continue a once weekly symptom diary until your day 84 (3 month) visit.

### Nose and throat swabs

These swabs are performed by first wiping the soft tip of a swab (like a long cotton bud) across the back of the throat, then inserting the swab approximately 2cm into the nasal passage and gently rotating it for a few seconds. These will be done twice daily (morning and night) during quarantine to see if the inoculation leads to an infection (defined as SARS-CoV-2 virus detected on the swab). Because we will be asking you to record any symptoms on the diary card, for the first 1.5 weeks we will not tell you the swab results. 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 paxlovid therapy, heparin, or any other changes to study procedures (e.g. because you become unwell), then we will tell you the results then. See below for further information about paxlovid therapy and heparin.

### Deep Nasal swabs

In addition to the nose & throat swabs to identify the SARS CoV-2 virus, we will perform additional deep nasal swabs (nasopharyngeal) on the same days we take blood tests during your quarantine stay. Deep nasal swabs are taken by inserting the swab approximately 2 inches into the nasal passage and gently rotating it for a few seconds. Data from these swabs will be used to collect additional data regarding your immune response to inoculation. We will take 2 deep nasal swabs on Days 2,5,7,11 and 14. There will be an additional deep nasal swab (therefore 3 deep nasal swabs in total) on Day -2 to screen for other bacteria or viruses that can cause infection.

### 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 daily starting on Day minus 1, once a day for 30 minutes on each occasion.

### Nasosorption

In addition to the throat and nose swabs performed with a long cotton bud, 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 1 minute, 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.

### Cognitive tests

During your stay in the quarantine unit, we will ask you to perform daily assessments of your cognitive function. We will provide you with a study tablet that contains a pre-loaded App called "CogAssess." This App will contain a selection of tasks and questionnaires designed to assess how quickly you process information, memory function, attention and executive function (ability to plan, organise and multi-task). These tasks will take approximately 20-30 minutes each day and we will ask you to perform them at around the same time daily during your stay on the quarantine unit. In addition, a questionnaire about your previous night's sleep will be included on the App. We will also ask you to complete these tasks at each follow up visit.

### Computed Tomography (CT) scan

On day 5 and/or day 11 a CT scan may be performed to take pictures of your lungs. The CT scan is a type of scan that uses X-Rays to obtain detailed pictures of your body in 'slice sections' (cross sections). These pictures are examined by a radiologist (a doctor who specialises in reading X-ray images). The CT scanner is an open ring-like structure which resembles a giant doughnut. You will be asked to lie on your back with your arms above your head. The scanning table moves your body through the scanner so that the relevant areas can be scanned. You may be asked to hold your breath whilst the scanner takes pictures. The scanner is not noisy, and the procedure should not be painful. Each scan takes approximately 20 minutes. The radiographer who performs the scan and the radiology assistants can see and hear you at all times via a connecting window and an intercom.



Example of a CT scanner

Initially, CT scans will be carried out on everyone at D5 and repeated in those who have evidence of COVID infection at D11. As the study progresses, the need for CT scans at D5 and D11 will be reviewed by the Data Safety Monitoring Board (DSMB), who may conclude that these should be reserved for people who have findings that suggest that COVID has caused inflammation of the lungs. Therefore, after the DSMB review, CT scans may be reserved for people who have findings like a severe cough or crackles when the doctor listens to your chest with a stethoscope. The study doctor will discuss this with you, and tell you whether or not you would have a CT scan as a routine part of the study.

### **8.3.4 Blood clot prevention**

Blood clotting is a vital process to ensure that when we cut ourselves it stops bleeding. However, in some cases overactive blood clotting can lead to unhelpful clot formation in blood vessels in the legs (deep vein thrombosis), lungs (pulmonary embolism) or brain (stroke). COVID-19 is known to increase the risk of blood clots, this occurs more commonly in severe COVID compared to mild disease. Although, considered rare in mild disease, these conditions can be life threatening. Lack of movement (e.g. sitting for long periods in quarantine or being confined to bed) can also increase the risk of blood clots. There are several things we shall do to reduce this risk in quarantine:

- Encourage gentle exercise in your rooms (lack of movement increases blood clot formation).
- Keep you well hydrated.
- We will provide you with fitted thromboembolic deterrent stockings (TED stockings) and recommend that you wear them throughout your quarantine period. These are thin, specifically designed snug-fitting medical compression stockings that gently squeeze the lower leg, which lessens the ability of blood to pool and form clots.



Example of medical compression stocking.  
Exact variety used may differ.

Because your risk of blood clotting increases with COVID-19 infection and also with lack of movement, if you become unwell with COVID-19 and this results in reduced mobility then daily injections of a preventative blood thinning medication (called low molecular weight heparin) will be started in addition to the TEDs. Low molecular weight heparins injected with a small needle subcutaneously (just beneath the skin) over either your stomach or thighs.

### **8.3.5 Paxlovid rescue therapy**

Paxlovid is a treatment designed specifically to treat COVID-19 disease. For participants in the dose finding arms (Group 1 & Group 3), you will be given this treatment if you demonstrate any symptoms related to COVID-19 disease beyond the mild symptoms expected. This will be given as a 5 day course of oral tablets.

After we have completed dose escalation, an independent safety committee will review whether this treatment is necessary for those in group 2 and group 4.

The purpose of Paxlovid treatment:

- Paxlovid is a combination of two antiviral medications called Nirmatrelvir and Ritonovir.
- Further information can be found regarding treatment on <https://www.gov.uk/government/publications/covid-19-antiviral-treatment-paxlovid/patient-information-for-paxlovid>
- The active part of Paxlovid (Nirmatrelvir) is a type of protease inhibitor which was specifically designed for the SARS-CoV-2 virus. It works by stopping the virus from replicating and therefore helping the body's immune system to fight off the infection more quickly.
- The second part of Paxlovid (Ritonovir) is used with other antiviral medicines such as those used for HIV and is used to boost the level of the active drug (Nirmatrelvir) in the body for longer.
- Paxlovid has recently been licenced in the UK (December 2021), to prevent people who have recently caught COVID-19 disease from getting more unwell
- By taking Paxlovid we hope to reduce the risk of getting severe COVID-19 disease, such as a lung infection. In clinical trials, it has been shown to reduce the risk of hospitalisation by up to 89%.
- To date Paxlovid treatment has been safe and generally well tolerated. It is important to note, however, that there is limited data on its benefit in people, like you, who may already have antibodies to SARS-CoV-2 from prior infection or vaccination.

Please note, if you were enrolled in the study prior to this version of the PIS, you may have been offered an alternative intravenous rescue therapy (Ronapreve) during your quarantine period. This change has been made to avoid additional intravenous cannulation in study volunteers and because of the logistical benefits of using an oral over an intravenous medication. Furthermore, although data is very limited in people like you who are young and healthy with some immunity to COVID-19 (either from infection or vaccination), it is possible that Paxlovid may be more effective than Ronapreve.

## 8.4 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. We will confirm this by making sure that there is no more live virus present on two swabs (taken 12 hours apart) from your mouth and nose. It is important that you stay in the unit until we tell you it is acceptable and safe to leave (be discharged). We want to be sure that if you get symptoms of COVID-19 infection, 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. You need to be available and willing to stay in the unit for at least 2-3 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 a thermometer (we will provide this), training regarding the signs and symptoms of potential complications of infection, and how and when to contact study staff. You will be asked to record your temperature on an electronic diary daily until your first follow up visit after discharge from the quarantine unit (1 month follow up visit). If you develop a fever or develop new or worsening symptoms of infection, we may ask you to attend for evaluation and repeat testing for the SARS-CoV-2 virus (see section 9 for full details). You will also receive lateral flow tests (LFTs) to take home so that you can test yourself if you develop new suspected COVID symptoms (see Section 9 below).

### **COVID-19 vaccination**

You are allowed to take part in this study if you have received a COVID-19 vaccine. However, to avoid confusing potential vaccine side effects and COVID-19 side effects we ask that you wait for 21 days after vaccination (1<sup>st</sup> dose or booster doses) before enrolment (“D0”).

In addition, vaccinations for COVID-19 should not be administered for 30 days *after* COVID-19 infection. Therefore, we will ask that once enrolled, you delay any COVID-19 vaccinations (1<sup>st</sup> vaccine if not had previously, or booster doses, as applicable) for a minimum of 30 days from date of enrolment (receipt of virus) *or* 30 days from your first swab positive for SARS CoV-2 infection, whichever is latest. Volunteers who receive the paxlovid rescue therapy should also await a minimum of 30 days from date of enrolment (receipt of virus) *or* 30 days from your first swab positive for SARS CoV-2 infection, whichever is latest. All other non-COVID-19 vaccines can be received 30 days from enrolment (D0) as per section 8.2.

The study team can give you individualised guidance at the end of your quarantine stay on the earliest date you can safely receive a COVID-19 vaccination.

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

- **Develop any new symptoms concerning for COVID-19 (see section 9)**
- **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)**

### **8.5 Follow up phase**

Following discharge from the quarantine unit, the clinical team will monitor your symptom diary. This is to be completed daily from discharge until your 1 month follow up visit and then weekly until your 3 month follow up visit. The study team may contact you (telephone or email) to make sure you are well or to clarify any symptoms from your E-diary. Additionally, you will be provided with a 24- hour contact number to get through to a study doctor should you have any concerns.

You will return for clinic appointments at 1, 2, 3, 6 and 12 months after challenge at the CCVTM (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 appointment will include tests and assessments similar to those conducted at the Screening appointment. At each visit we will check your vital signs, take a blood test, a mouth/nose swab, a nasosorption test and perform the cognitive tests (see section 8.2.3). Volunteers who have had a positive swab for SARS CoV-2 at any timepoint during the study will also have the deep nasal swabs performed at each follow up visit. We will also discuss any changes to your health or symptoms since we last saw you. Based on this discussion we may also do a physical examination, smell test, deep nasal swab to look for evidence of other bacteria or viruses or a mental health assessment. At your first visit after the quarantine phase (1 month visit), everyone will have lung function, smell and mental health assessments regardless of symptoms. You should allow up to 2 hours for the one month visit. All other 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.

## 9 What if I develop new suspected COVID symptoms after discharge from quarantine?

We are only discharging you from quarantine when we are confident that you are no longer an infection risk. This requires you to stay for a minimum of 14 days following inoculation and have two sequential tests immediately prior to discharge that confirm you are not shedding live virus (i.e. not contagious). However, as explained in section 4 it is possible for individuals to become re-infected with COVID-19 despite recent infection. At present, it's also not known if prior infection with one strain of the virus protects you against new strains. **We therefore ask that all current government guidance is adhered to regarding testing and isolation throughout the 12 month study period.**

Additionally, 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 challenge that would normally require a COVID-19 test, that you self-isolate as per government guidelines and contact our study doctor using the 24 hour medical emergency on call number. This will be given to you on a contact card at discharge from the quarantine unit. We may ask that you test yourself using the lateral flow tests provided to you for this purpose, or arrange for a PCR test to be performed if this option is available to you. If the test is positive we would arrange to see you at a *"COVID-19 positive visit."* If your symptoms are highly suspicious for COVID-19 we may ask you to attend a *"suspected COVID-19" visit* regardless of test result. This is because sometimes the tests we do for COVID-19 can be falsely negative.

At both "suspected COVID-19" and "COVID-19 positive" visits we will review any symptoms you have, undertake a physical examination (if necessary based on symptoms), check your vital signs, take nose and throat swabs for SARS CoV-2 infection (which may include an additional swab for variant testing if available), a deep nasal swab to look for presence of alternative bacteria or viruses that could be responsible for your symptoms, nasosorption testing, smell testing and some safety and research blood tests. We additionally, would like to repeat some research samples including blood tests, nasosorption, nose and throat swabs, deep nasal swabs 4 weeks (- 1 week/+ 2 weeks) after your COVID positive visit. If this falls within a period for which you are attending for a routine study visit (1,2,3,6 or 12 month visit) then these samples will be undertaken at that visit. If we cannot time this within your routine study visit schedule we will arrange an additional "4 weeks post COVID infection" visit. You will be compensated for any additional visits.

The most up to date national guidance on when you and your household contacts should be self-isolating can be found here:

<https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-and-treatment/when-to-self-isolate-and-what-to-do/>

Suspected COVID-19 symptoms include:

- **a new continuous cough;**
- **a high temperature** (37.8°C or higher or you feel hot to touch on your chest or back if unable to check your temperature)
- **a new loss of, or change in, your normal sense of taste or smell** (anosmia)

If you have any of these symptoms, or are concerned that you have COVID-19, please contact the team on the 24 hour contact number. The study team may advise you to take a test for COVID-19 and/or attend for a suspected COVID-19 visit. For an up to date list of symptoms compatible with COVID-19 please see the following link:

<https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/main-symptoms/>

## 10 What are my responsibilities?

- ✓ You should not donate blood during the 12 month study 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 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 should not have smoked or used any nicotine-containing products (e.g. gum, nicotine patches, inhalers, e-cigarettes) for at least 3 months before you enter the quarantine unit. You must have a negative test for nicotine before the study virus is given to you.
- ✓ You must not receive any live vaccines within the 30 days prior to challenge; any vaccines (live or non-live) 21 days prior to challenge or plan to receive any vaccinations for 30 days after challenge. Furthermore, vaccinations against COVID-19 should not be received until a minimum of 30 days from the date of your first positive swab for SARS CoV-2 infection (or date of challenge if you do not develop infection) .
- ✓ 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 (from the Screening appointment to the last follow up appointment).
- ✓ Women 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 the subsequent follow-up appointments.
- ✓ You must tell us if you develop any COVID-19 symptoms/ or have any tests for COVID-19 (except for those performed by the study team) during the trial.

## 11 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.

## **12 Are there any risks from taking part in the study?**

This virus is currently causing a world-wide pandemic of respiratory disease ranging from asymptomatic or mild illness to severe respiratory disease that may also affect other parts of the body. Humans have only experienced infections with this strain of 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 accurately and 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).

However, severe COVID-19 disease can rarely occur in young, healthy adults. In England up to 6th November 2020, 95 adults between the ages of 18-30 had died from COVID-19 from the total number of deaths with COVID-19 recorded at over 49,000 by this date. During the pandemic, it is therefore estimated that 1-2 people per 100,000 aged 18-30 have died (although, most have had other health conditions before developing COVID-19). It has also been estimated that 1 in 200 people aged 20-29 with COVID-19 needed to go into hospital. The factors that might increase the risk of such events in young persons are not fully known and therefore may not be detected in the screening process prior to entering the study.

### **12.1 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, these symptoms last for 5 days and in 90% of cases are better by 2 weeks. 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 older people who have a larger number of symptoms initially. If you develop symptoms of “long COVID”, you will be followed up closely and referred for treatment if necessary.

## **12.2 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 known if 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 including steroid therapy, Remdesivir (an anti-viral medication) and different anti-inflammatory treatments (Tocilizumab and Sarilumab). These medications are currently only used for individuals with moderate to severe COVID requiring hospital admission.

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 trial.**

### **12.3 Risks of Transmission**

When an individual with COVID-19 coughs, sneezes, sings and speaks they produce respiratory droplets carrying the virus. A close 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 17 days after you are admitted to prevent spreading infection to others. You will be tested for the presence of the SARS-CoV-2 virus on a twice 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, unless accompanied by staff for study procedures. 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.

## 12.4 Risk of treatment with Paxlovid

The Paxlovid medication has been given to over 3500 adults in clinical trials for the treatment and prevention of COVID-19 and has been found to be generally well-tolerated with no serious safety risks identified.

It does have the following known or potential risks:

- **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).
  - The most commonly reported symptoms after taking Paxlovid are dysgeusia (change in sense of taste), diarrhoea, hypertension (high blood pressure) and myalgia (muscle pain) these are usually mild.
- **Risk to pregnant women:** 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. Currently, Paxlovid is not routinely recommended for use in pregnancy and breastfeeding but could be used if the potential benefit is felt to outweigh any potential risks with individual health factors taken into account. In this study we will perform a pregnancy test on volunteers of childbearing potential at screening and prior to infection with SARS-CoV-2 and ask that volunteers of childbearing potential use effective contraception for the duration of the study. Paxlovid can reduce the efficacy of some combined oral contraceptive pills, therefore all women using the combined oral contraceptive pill will also need use a barrier method of contraception with spermicide for the 5 day duration of treatment and then for 30 days after stopping Paxlovid. Medications and herbal remedies: Paxlovid interacts with some medication, and herbal remedies and will not be eligible for recruitment if these medications are required during the quarantine period as dictated by the study doctor.

## 12.5 Radiological procedures

If you take part in this study you will have a chest x-ray and a maximum of two CT chest exams. These procedures use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study may increase the chances of this happening to you to about 50.01 % if you were to receive a chest x-ray and two CT scans.

The chest x-ray is a routine medical examination that uses a low dose of radiation approximately equal to 3 days of natural background radiation. The additional risk of cancer attributable to one chest x-ray is about one extra case in every 900,000 people. The radiation from CT scans is higher, but we will minimise this by using low-radiation dose CT scans. Each dose of radiation from a low dose CT scan is equivalent to no more than 6 months background radiation. If you take part in the study you may receive between 0 and 2 CT scans depending on when you are enrolled in the study, whether you have evidence of COVID infection and whether or not you have symptoms or signs of inflammation of the lungs from COVID (see section 8.3.3 for more details).

All scans will be reported by an NHS Consultant Radiologist and any abnormal findings will be appropriately followed up, with referral to specialists where required.

## 12.6 Potential harm to an unborn child

Because we do not know how COVID-19 affects an unborn baby, you cannot be in the study if you are pregnant. Furthermore, pregnant women can sometimes be more at risk of getting seriously ill from viruses like flu and therefore have been included in the list of individuals who may be vulnerable to getting seriously ill from COVID-19. Therefore, 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 a highly effective method of contraception (as per section 14). If you became pregnant during the study we would ask you to inform us.

## **12.7 Risks from other study procedures**

### **Quarantine phase**

You may become anxious, lonely or depressed by being confined to the Quarantine unit for 2-3 weeks 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.

The study team will monitor your mental health during the study period using regular health questionnaires. 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. We have access to NHS psychological services whilst you are in the quarantine unit and our study team are trained in assessing mental health.

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

### **Thromboembolic deterrent stockings (TEDS)**

You will be given fitted TEDS to reduce the risk of blood clots. Poorly fitted stockings (overtight) can occasionally cause numbness, tingling, pins & needles, pain or soreness in the foot or leg and a pale/cool/discooured foot or leg. These symptoms will go away if the stockings are removed. Rarely individuals can be allergic to the material in the stockings, if this occurs an alternative can be provided. Trained staff will ensure good fit of stockings to minimise any discomfort.

### **Low molecular weight heparin (only given if study clinicians decide this is needed in addition to the TEDs)**

This injection is routinely given to many hospital inpatients to reduce the risk of blood clots. Possible side effects from the medication include bruising and prolonged bleeding if you cut yourself (this is rare). Very rarely (<1 in 5000) individuals develop an abnormal immune response to the medication which actually increases their risk of blood clotting. This is easily picked up on safety blood tests that will be performed during your stay and reversed by stopping the medication. Thromboembolic deterrent stockings will continue to be used even if you cannot receive low molecular weight heparin.

### **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 120mls of blood (approximately 7 tablespoons) at a single visit. The total amount we plan to take over the 12-month period of the study is 838.5ml. We may take up to an additional 125ml if you are in quarantine for more than 17 days or attend for a “suspected COVID 19” or “COVID-19 positive” visit during the follow up phase.

This is a safe amount for healthy volunteers to give over a 12 month period, 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 (12 months), or take part in any other studies where you give blood. We will not enrol you if your blood counts are low at screening and we will monitor you for signs or symptoms of low blood counts (anaemia) during the study.

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

The combined oropharyngeal and nasopharyngeal swab is 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.

## **13 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)
- Blood thinning treatment
- Paxlovid rescue therapy (if being offered)

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 as per the latest government guidance.

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 you will need to wear protective equipment (e.g. facemask etc.) during the trip.
- 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 call 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 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.

## **14 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 use acceptable birth control for the full 12 month duration of the trial (including at least 4 weeks before trial start to ensure effective contraception in place). See **14A**.

### **14A:**

If you are a volunteer of childbearing potential, you must agree to practise a highly effective form of contraception for the entire course of the study (1 year).

Acceptable forms of contraception include:

- a. Established use of oral, injected or implanted hormonal methods of contraception, started at least 4 weeks prior to admission to quarantine
- b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- c. Vasectomy, if the vasectomised partner is the sole partner and appropriate post vasectomy documentation of success is available
- d. Same sex intercourse only
- e. 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 documented proof of surgical sterilisation or hysterectomy.

Volunteers who receive Paxlovid during quarantine 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 with spermicide during the 5 day course of Paxlovid and for another 30 days after stopping Paxlovid

## **15 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 at least £4,845. If you are required to have any repeat or extra visits or are required to stay longer than the minimum 17 days in quarantine, then you will be compensated pro rata in addition to this payment.

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

- 1) £2000 will be paid after discharge from quarantine
- 2) £1330 will be paid after the Day 168 follow-up appointment .
- 3) £1515 will be paid after the Day 365 follow-up appointment.

Additional days in the quarantine unit will be paid at £195 per day. Compensation for additional follow up visits such as COVID positive visits are calculated based on any procedures performed and length of the visit.

It can take 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 for 7 years in accordance with University of Oxford financial policy.

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):	
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## 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, CT scan, ). PALS is unable to provide information about this research study. If you wish to contact the PALS team please call 01865 235855 (Churchill Hospital), 01865 221473 (John Radcliffe Hospital), or by email at [PALS@ouh.nhs.uk](mailto: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](mailto: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](mailto: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 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. Additionally, we will contact Public Health England and use your personally identifiable details to verify your prior infection with SARS-CoV-2, if applicable. 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 trial 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 baseline and safety blood tests taking up to about 26mL of blood 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 SARS-CoV-2 virus. Nose and throat swabs and facemask strips will be assessed to look for evidence of the SARS-CoV-2 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 European Economic Area. Any samples will be sent in an anonymised form 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 at the Oxford Vaccine Centre Biobank and may be used for further related research, including the human body's immune response or vaccine research. More information around the procedures for long-term storage of your samples is available in the Oxford Vaccine Centre Biobank information booklet and you will be asked to sign a separate biobank consent form if you agree. Your participation in this study will not be affected by your decision regarding storage and future use of your leftover samples in the biobank. If you decide not to participate in Biobank storage then samples will be disposed of in accordance with Human Tissue Authority 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 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 both a Wellcome Trust grant held by Professor Helen McShane in addition to funding from the Department of Health and Social Care. The study is designed and organised by the investigators. Neither your GP nor the researchers are paid for recruiting you in this study.

#### **7 Who has reviewed the study?**

This trial has been ethically reviewed and approved by a Specialist AdHoc Research Ethics Committee (ref: 21/UK/0001).

## 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. The audio recording of the pre-screening video appointment (identifiable only by your voice and screening number) will be stored on a secure server at The University of Oxford for up to 7 years. If you decide not to consent to partake in the study after the pre-screening video call then this recording will be destroyed.

The 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.

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 [\[https://compliance.web.ox.ac.uk/individual-rights\]](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](mailto: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 trial 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 an MD or DPhil. 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 trial.

Your details will be stored electronically on a secure server and only authorised individuals at the Oxford Vaccine Centre 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: [\[http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx\]](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](mailto: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](mailto:Covid19-challenge@paediatrics.ox.ac.uk).

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