



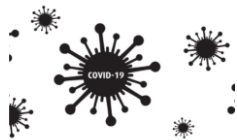
## Participant Information Sheet: COV-CHIM01

### SARS-CoV-2 challenge study in healthy adults

Title: "A dose finding human experimental infection study with SARS-CoV-2 in healthy subjects with previous, microbiologically confirmed, SARS-CoV-2 infection".

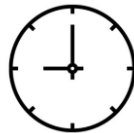
Thank you for showing an interest in this study. The first page of this information sheet sets out a brief summary. The rest of the document provides more detail. You can ask us for more information at any point.

#### Condition Studied



COVID-19 infection

#### Study Length



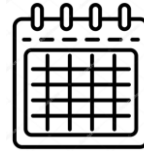
12 months

#### Inpatient quarantine unit



Minimum 17 days stay

#### Number of visits



Eight

The study will consist of 3 phases:

- 1) Screening phase
- 2) Quarantine phase ( Following intentional SARS-CoV-2 infection) with a minimum 17 days in quarantine
- 3) Follow-up phase

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



You must

- Be aged 18-30 years old
- Be in excellent health
- Live in or around Oxford
- Must have previously been infected with SARS-CoV-2 virus (the virus that causes COVID- 19 disease)



You must not

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

#### Why participate?

Information gained from this study may help us understand what kind of immune response stops people from being re-infected with COVID-19 and the impact of the virus on the immune system. This may help with the development of better COVID-19 vaccines and treatments, and might help develop a test that tells people they are protected from the virus. You will be compensated at least £4995 for your time, travel and inconvenience.

**Dear Volunteer,**

Thank you for showing an interest in taking part in this research study. Before you make a decision, it is important you take the time to understand why the research is being done and what it would involve. Please read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish.

- Part 1 tells you the purpose of the study and what will happen to you if you take part
- Part 2 tells you more information about the conduct of the study

Please ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not to take part.

[Insert local contact details here](#)

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## Part 1

### 1 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, much is not yet known about immunity to re-infection in individuals who have already had COVID-19. To help with this, we would like to develop a ‘challenge model’ where volunteers who have previously had COVID-19 are re-exposed to the SARS-CoV-2 virus in a controlled manner. The key aim of this study would be to allow us to closely examine the immune response (human biological response to fight the virus) and we hope to learn what makes some individuals less-likely to get the disease than others and if previous infection protects 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 re-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.

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

We plan to recruit up to 44 participants across two groups (see Table 1). 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.

“TCID50 “is a standardised unit of measurement of viral load.

Group	Cohort	Number of volunteers	Dose
1	1A	3 to 8	Low dose (10 TCID50)
	1B	3 to 8	Medium dose (100 TCID50)
	1C	3 to 8	Higher dose (1000 TCID50)
2		Up to 20	Dose determined from Group 1

Table 1: Study Groups

**Group 1- Safety and dose finding group:** *Each dose will be tested in up 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 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. The first cohort of any dose will be divided into 2 subgroups. The first subgroup will have only 3 participants. If the SARS-CoV-2 virus doesn't cause a positive swab (i.e. no evidence of re-infection) in the first 3 participants then we will move to the next higher dose (the next cohort) after review with the independent Data Safety Monitoring Board. If there is evidence of a positive swab in any of the first 3 participants, a second subgroup of 5 participants will be given the same dose in that cohort. 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 volunteers.

***Group 2 - Safety and dose confirmation group: up to 20 participants***

Once an optimal dose of the virus has been selected from the dose finding group (Group 1), we will enrol up to 20 participants in group 2.

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

### **3 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

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')

Unfortunately, there is currently no way to predict how long recovery from "long COVID" will take. It's 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.

## 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 11.2 (page 23). 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 which we will screen for. As part of this screening process to see if you are eligible to take part, we will be using a risk assessment tool called QCOVID. **You will only be enrolled if your estimated risk of hospitalisation from COVID-19 infection is less than 1 in 5000 (0.02%) and risk of death less than 1 in 250,000 (0.0004%).**

## Re-infection with COVID-19

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. Why some people remain unprotected is unknown. It is felt that re-infection is less likely to cause severe symptoms than the first episode of COVID-19 due to the body's improved immune response, having learnt from the first infection. Of those who got a second infection in the healthcare studies no one was hospitalised. However, very little is known about 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.

## 4 Are there any advantages of taking part?

You will not gain any direct benefit from the study, however, during the screening assessment you will get information about your health from the assessments and tests that we will perform (see section 7.1, page 10). However, 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 study will 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 of at least £4995 for full study participation.

## 5 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 in the study, 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).

## 6 Can I take part?



In order to take part in the study you MUST:

- ✓ Have had a positive nose/throat swab for SARS-CoV-2 infection. This must have been more than 3 months before enrolment.
- ✓ Positive SARS-CoV-2 antibody blood test (tested at your screening visit).
- ✓ When assessed by the study team using the QCOVID tool, have an absolute risk of COVID-associated death of less than 1 in 250,000 (0.0004%) and COVID-associated hospital admission risk of less than 1 in 5000 (0.02%). The QCOVID is a risk assessment tool that predicts those at highest risk of hospitalisation and death from COVID-19 using a range of factors including age, ethnicity and existing medical conditions.
- ✓ 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, chest X-Ray and either Magnetic Resonance Imaging (MRI) or an Echocardiogram to check your heart and lung health (see pages 10-12 for details)
- ✓ Allow the study team to discuss your medical history with your General Practitioner (GP) and other relevant health care professionals.
- ✓ Refrain from blood donation during the study (1 year). If REGN-COV-2 rescue therapy is received you will not be eligible to donate blood for 12 months after receipt of this medication (see section 7.2.5 REGN-COV-2 rescue therapy).
- ✓ 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. For men, practise continuous effective contraception from day of challenge to 6 months post treatment with REGN-COV2 if offered (see section 7.2.5 REGN-COV2 rescue therapy ).
- ✓ Be able and willing (in the investigator's opinion) to comply with all study requirements.



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

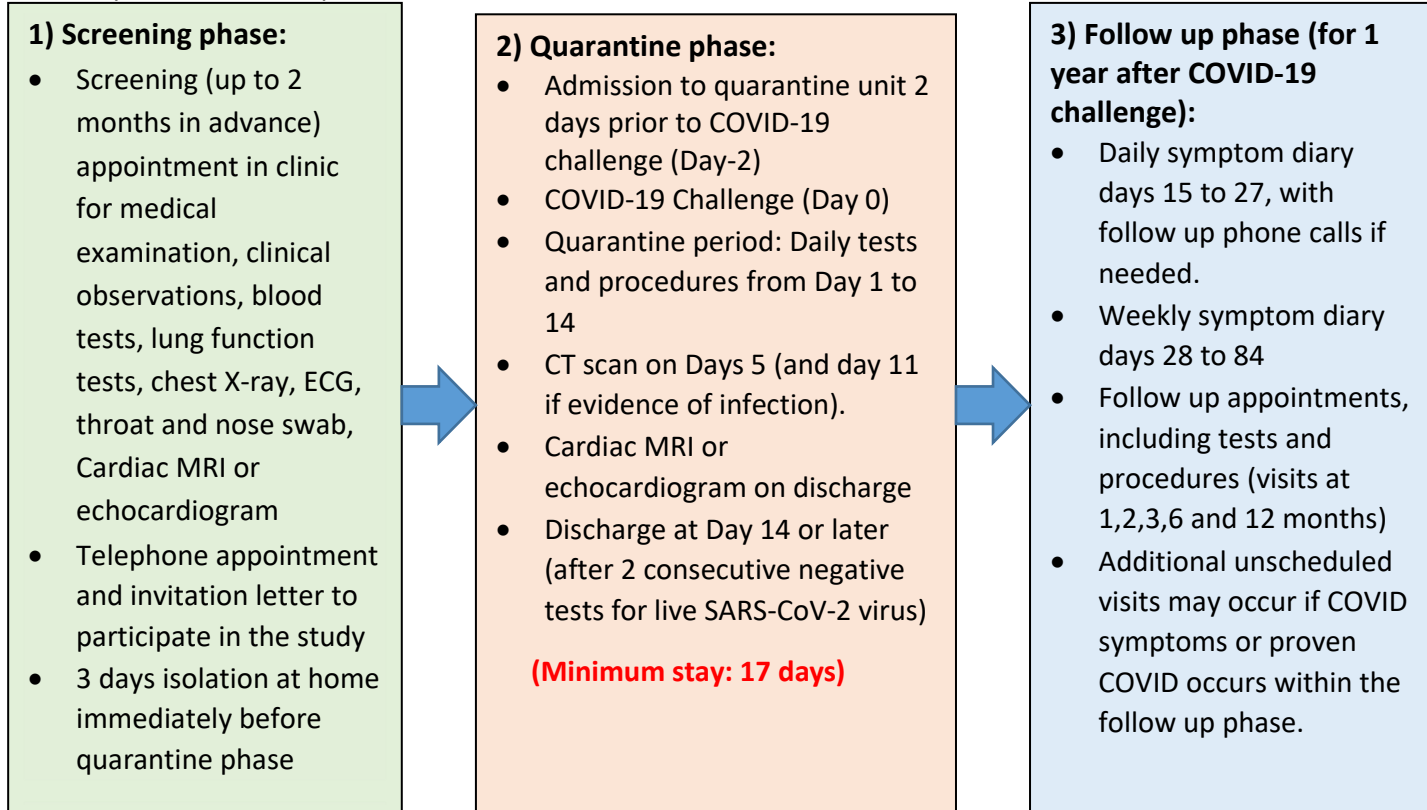
- ✗ Any clinically significant respiratory disease (a condition which affects your lungs), including asthma.
- ✗ Current smoker (defined as any smoking, including e-cigarettes, in the last 3 months) or have smoked the equivalent of more than 20 cigarettes daily for a 2-year period at any time or currently 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.
- ✗ 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 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)
- ✘ 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 (or bubble) with someone with a clinically significant immunodeficiency (either from infection, medication or pregnancy), or who is extremely clinically vulnerable as per Public Health England guidelines (i.e. anyone told to shield).
- ✘ Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period
- ✘ 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 received a vaccination for SARS-CoV-2 prior to enrolment. Further information, on when vaccination against COVID-19 disease is permitted after enrolment can be found in section 7.3.
- ✘ Have plans to receive *any* vaccinations in the 30 day periods before and after enrolment.
- ✘ 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



## 7 What will happen if I decide to take part?

The study will consist of 3 phases:



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. If eligible a member of the team will get in touch to see if you would like to arrange a face to face screening visit. Additionally, we may clarify any of your answers on the online questionnaire over the telephone.

If you decide you would like to take part in this study, you will need 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 either the Oxford University Hospitals NHS Trust or the Oxford Clinical Research Facility (based at the Churchill Hospital site) depending on bed availability.

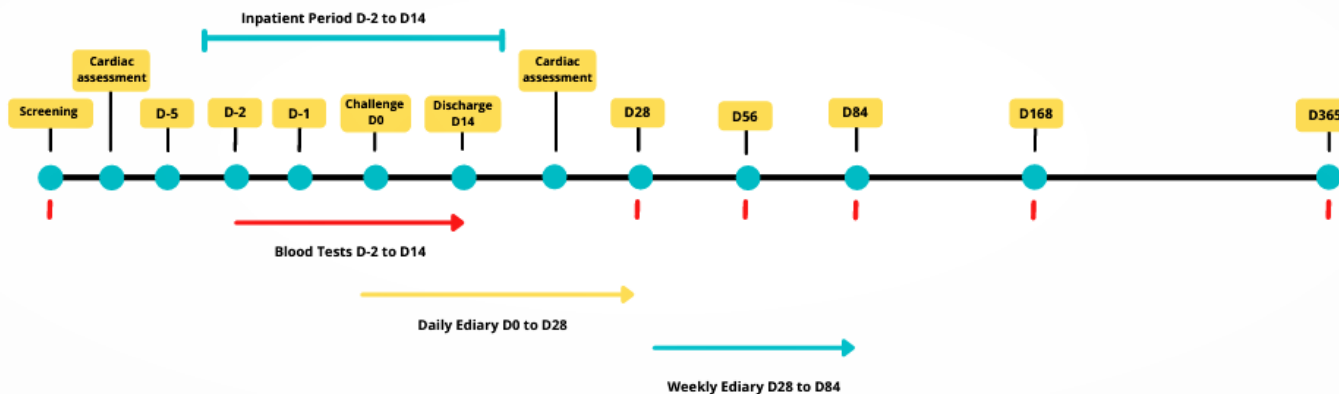


Figure 1: Trial timeline

## 7.1 Screening phase

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

Once you 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.

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 60 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 affects 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.

### Throat and nose swab

We will take a swab from the back of the throat and nose to look for evidence of COVID-19 infection. We will first wipe the soft tip of a swab (like a long cotton bud) across the back of the throat, then insert the swab deeply into the nasal passage (approximately 2 inches), and gently rotate it for a few seconds.



### 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 or Hepatitis C (viruses that affect the liver) infection.
- Diabetes/ impaired blood sugar control
- SARS-CoV-2 antibodies in your blood to confirm you have previously had COVID-19 and still have antibodies present.

### 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.

### Cardiac MRI or echocardiogram

Cardiac MRI will be performed to ensure you don't have any underlying heart conditions. This test will only be performed if all your other tests show that you may be suitable for the study and will require a separate visit to Oxford University Hospitals NHS Trust.

An MRI is a safe test that uses magnets, radio waves and a computer to make detailed pictures of your heart and major blood vessels. The scanner is a large machine with a hole in the middle. You will be asked to remove any metal jewellery before having the scan. You will be asked to lie on your back on a sliding table that goes into the scanner. The scan usually takes between 30 and 60 minutes. Cardiac MRI is painless and harmless but can be quite noisy and individuals with claustrophobia may not like going into the scanner. You may be asked to wear headphones. You will need to lie very still during the test because any movement can blur the images. The doctor or radiographer will talk to you through the headphones and ask you to hold your breath for 6-10 seconds at a time, to ensure your chest is still whilst the pictures are being taken. A dye (Gadolinium contrast) is often used to make the images clearer. This is a clear, colourless fluid injected into one of your veins via a cannula (a soft, thin plastic tube) during your scan. The cannula is inserted through your skin into a vein using a needle. Once the cannula is in place the needle is removed, leaving the small, thin plastic tube in the blood vessel. This should be comfortable and will only be in place until your scan is finished.



For participants who cannot safely have a cardiac MRI scan (metallic implanted objects are not safe in MRI scanners or individuals with an allergy to the gadolinium dye used), an echocardiogram will be performed instead.

An echocardiogram uses ultrasound (sound waves beyond our normal range of hearing) to produce pictures of moving heart structures and blood flow. The procedure is carried out by a trained clinical physiologist or a specialist heart doctor (cardiologist). It is painless and there are no side-effects or risks from the sound waves used.

The echocardiogram takes place in a darkened room to help see pictures of the heart on a screen. To enable the ultrasound to penetrate the chest it is necessary to undress to the waist. You will usually be asked to lie on your left side during the procedure, as this provides the best views of the heart. The operator will hold a device, which is coated in a harmless gel, directly and quite firmly against several positions on the chest surface. Pictures of your heart will appear on a screen.

### 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. You do not need to be present for this assessment. If your risk of both death and hospitalisation from COVID-19 are considered low using the QCOVID tool (see section 6 for detailed values) 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.

## **7.2 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 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. 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 told to self-isolate by test and trace due to being a contact of 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.

We will admit you to our Quarantine unit at either the Oxford University Hospitals NHS Trust or Oxford 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 7.3 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.



Insert localised picture of Quarantine room

You can bring in your mobile phone and laptop, to-watch TV, films, play games, study etc and to call friends and family. However, you cannot have any visitors. There will be Wi-Fi. You will have sole use of an 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 2).

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

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 (see below for COVID-19 vaccine information)	30 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
Herbal supplements	7 days
Chronically used medications, vitamins or dietary supplements,	21 days

**Table 2 Medications not permitted prior to the challenge**

### 7.2.1 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 (for evidence of different types of viral illness including COVID-19 infection), blood tests, vital signs (including 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 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 assessment and mask wearing samples (please see below for further detail).

### 7.2.2 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.

### 7.2.3 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 3 shows you which tests will be carried out and how often.

Test/procedure	When?
Vital signs (heart rate, blood pressure, breathing rate, oxygen levels and temperature)	Minimum of four times a day (when awake).
Physical examination	Compulsory on Day -2 and then only if needed
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	Days 5 (and repeated on day 11 if you have shown any evidence of infection with the virus).
ECG	Day -2, Day 4, 8 and 12 Other days only if needed
Nose and throat swab	Day -2, then twice daily from Day 1
Smell identification test	Day-1, then daily from Day 1
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	Once daily on Day -2 and Day 0, Twice daily from Days 1-3, then once daily on Days 5, 7,11 and 14
Blood tests	Day -2, 2, 5, 7,11 and 14 We may take up to an additional 60mls (3-4 tablespoons) if you stay beyond 14 days.
MRI scan or echocardiogram	On day of discharge, or after discharge but before your next follow up visit (depending on availability).
Blood thinning injection	Daily from Day 0 until discharge

**Table 3: Tests and procedures during quarantine phase**

### 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.

### 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 1 - once a day for 60 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.

### Smell identification test

The University of Pennsylvania Smell Identification Test (UPSIT) is a test used to assess your sense of smell. The test takes only a few minutes and consists of 4 booklets of different scents, containing a total of 40 scents across the booklets. On each page, there is a different “scratch and sniff” strip embedded with a scent and a multiple-choice question pertaining to the scent with four possible answers. The scents are released by scratching with a pencil. After each scent is released, you will need to smell the strip and answer the multiple-choice question based on what you smell. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. We can then assess your score against expected scores made up from a database of individuals with normal smell.

### 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 a CT scan will be performed to take pictures of your lungs. If you display any evidence of infection (e.g. a positive swab test, any COVID-19 symptoms or any signs on other tests) an additional scan will be undertaken at day 11. 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.





#### 7.2. 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. There are several things we shall do to reduce this risk after administration of the virus:

- Encourage gentle exercise in your rooms (lack of movement increases blood clot formation).
- Keep you well hydrated
- We will give you a daily dose of a blood thinning medication known as low molecular weight heparin. This is injected with a small needle subcutaneously (just beneath the skin) over either your stomach or thighs. Its use is routinely recommended for individuals with COVID-19 in hospital, as long as they have no increased bleeding risk or allergy to the blood thinning medication.
- If you are unable to receive the blood thinning injection, we will offer you the routine 2<sup>nd</sup> line blood clot prevention therapy which is the use of fitted thromboembolic deterrent stockings (TED stockings). These snug- fitting stockings gently squeeze the leg, which lessens the ability of blood to pool and form clots.

#### 7.2.5 REGN-COV2 rescue therapy

All participants in group 1 who show any signs, symptoms or tests suggestive of COVID-19 disease will receive a treatment called REGN-COV2. We will not administer this if you have a swab positive for re-infection but develop no symptoms. This will be given intravenously (via a cannula, into a vein in your arm) over 60 minutes. This is an investigational (unlicensed) treatment designed specifically to treat COVID-19 disease.

After we have completed all participants in group 1 an independent safety committee will review whether this treatment is necessary for those in group 2.

The purpose of REGN-COV2 treatment:

- REGN-COV2 is a cocktail of monoclonal antibodies developed by Regeneron.
- Further information can be found regarding this treatment at <https://www.regeneron.com/>
- Antibodies are produced naturally by your body and help the immune system recognize germs that cause disease, such as bacteria and viruses, and mark them for destruction. Monoclonal antibodies are immune system proteins (or antibodies) created in a lab. Like your body's own antibodies, monoclonal antibodies recognise specific targets and mark them for destruction by the body's immune system.

- REGN-COV2 is the only treatment currently in production that has been designed to specifically target and destroy the SARS-CoV-2 virus.
- REGN-COV2 has received emergency authorization by the U.S Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in adults and adolescents with an increased risk of being hospitalised with COVID-19. The Medicines and Healthcare products Regulatory Agency (MHRA) is currently deciding whether to approve it as recommended treatment for some Covid-19 patients in the UK.
- By giving you REGN-COV2 we hope to further reduce the chance of you developing severe COVID-19 disease, such as a lung infection. In clinical trials, it has been shown to reduce by 57% the need to see a medical professional within a month of COVID-19 infection. However, it is still an investigational treatment and there is limited data on its benefit in people who already have antibodies to SARS-CoV-2.
- To date, REGN-COV2 treatment has been safe and generally well tolerated .

### 7.3 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 8 for full details).

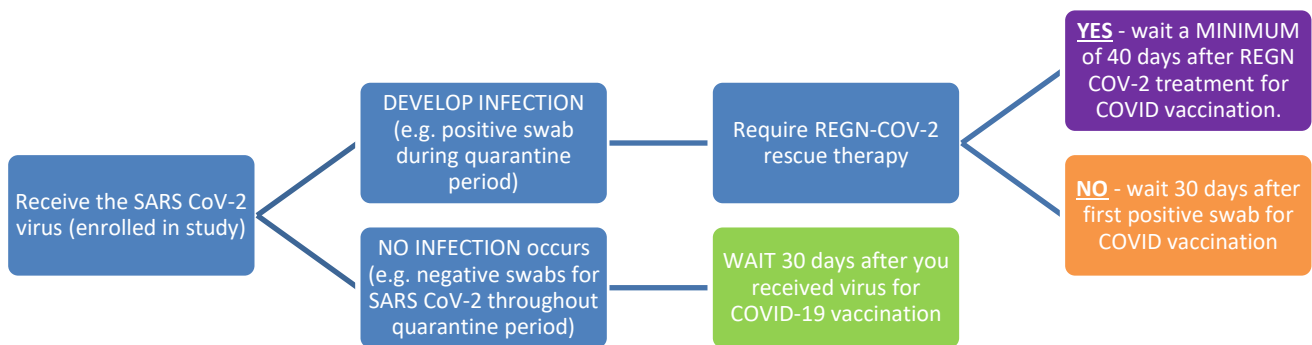
#### COVID-19 vaccination

To take part in this study you must not have already received a vaccine for COVID-19.

Following completion of the quarantine period, if a COVID-19 vaccine is offered to you as part of the national roll-out it can be received. However, in line with national guidance, vaccinations for COVID-19 should not be administered for 30 days after COVID-19 infection. We will therefore ask that vaccination is delayed for a minimum of 30 days after challenge (in line with other vaccines as described in section 7.2) BUT if you do become infected with SARS CoV-2 during the quarantine period then vaccination should additionally be delayed for 30 days after your first positive nose and throat swab.

Additionally, it is not known if the antibodies from the REGN COV-2 rescue therapy (see section 7.2.5) would dampen the protective effect of COVID-19 vaccines. It is therefore recommended that if you require the REGN COV-2 rescue therapy whilst in the quarantine unit, COVID-19 vaccination is further delayed until the medication has started washing out of your system. We ask you wait a **minimum** of 40 days after receipt of REGN COV2 to receive a COVID vaccination, although this may be up to 90 days depending on discussions with your study clinician.

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. Figure 2 summarises this guidance.



**Figure 2: COVID-19 vaccination guidelines after the quarantine period**

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

- **Develop any new symptoms concerning for COVID-19 (see section 8)**
- **Have any positive tests for COVID-19 (outside of the study tests)**
- **Receive a COVID-19 vaccine**
- **Receive any medical care outside of the study (e.g. GP or hospital attendances)**

## 7.4 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 7.2.3). 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 or 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.

## **8. 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 3 it is possible for individuals to become re-infected with COVID-19 despite recent infection. At present, it is 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 study.**

Additionally, we would like to know about any suspected symptoms or tests you undergo for COVID-19. After infection, individuals can still have evidence of dead virus on nose and throat swabs for up to 90 days. The dead virus is not an infection risk to others, but tests performed routinely for COVID-19 will not be able to differentiate live or dead virus. Therefore, we ask that if you develop any new symptoms in the first 90 days following challenge that would normally require a COVID-19 test, that you and your household self-isolate as usual and contact our study doctor on the on call number:

**Insert Local number**

We can arrange a “*suspected COVID-19*” visit to perform swabs to look for evidence of live virus thus ensuring you only have to continue isolation if there is evidence of infectious (live) SARS-CoV-2 virus.

If more than 90 days has elapsed since enrolment we would not expect persistent dead virus in your throat or nose. Therefore, if you develop new symptoms more than 3 months after enrolment we would ask that you and your household self-isolate and contact the study doctor as above. In the first instance, we will request you arrange a test via the usual means (e.g. test & trace). We will ask that you keep us informed of any test results and if the test is positive we would arrange to see you at a “*COVID-19 positive visit*.”

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 a nose and throat swab, nasorption testing, smell testing and some safety and research blood tests. 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.gov.uk/government/publications/covid-19-stay-at-home-guidance>

At the time of writing, suspected COVID-19 symptoms requiring testing are defined by Public Health England as:

- **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 are advised by our team to organise a test for COVID-19 using the NHS test and trace system this can be done at the following website:

<https://www.nhs.uk/conditions/coronavirus-covid-19/testing-and-tracing/get-a-test-to-check-if-you-have-coronavirus/>

## 9 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. Furthermore, if you receive REGN COV-2 rescue therapy you will not be allowed to donate blood until 12 months after this medication was given.
- ✓ 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). 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 vaccines within the 30 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) and a minimum of 40 days from receipt of REGN COV-2 rescue therapy but ideally 90 days (if applicable).
- ✓ 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.

## 10 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.

## **11 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.

### **11.1 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 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.

## 11.2 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.**

### 11.3 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.

### 11.4 Risk of treatment with REGN-COV2 (Regeneron)



The REGN-COV2 medication (which is in development and currently unlicensed) has been given to over 2000 adults for the treatment 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 and Infusion-related reactions:**
  - To date, a small number of people (less than 1 in 100) have developed a reaction during or shortly after the infusion.
  - 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).
  - Additionally, this type of medication can also trigger an over-reaction of the immune system, known as an infusion-related reaction.
  - The symptoms and signs of infusion-related reactions include fever, chills (feeling of coldness), nausea (feeling sick), abdominal (tummy) pain, headache, feeling short of breath, low blood pressure, angioedema (swelling underneath the skin), throat irritation, rash, itchy skin, muscle aches, and/or dizziness.
  - These reactions are manageable risks and can be treated by slowing or stopping the infusion plus the provision of supportive therapies.
- **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. We know that natural antibodies can cross the placenta from the mother to the developing foetus so there is a chance that the synthetic antibodies may potentially be transferred to the foetus. It is not known whether this would provide a treatment benefit or risk to the developing foetus. Currently, REGN-COV2 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 females at screening and prior to infection with SARS-CoV-2 and ask that females use effective contraception for the duration of the study, and males use effective contraception for 6 months after receiving REGN COV-2 (see section 13).

## 11.5 Radiological procedures

If you take part in this study you will have a chest xray 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 %.

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. We will perform a CT scan at day 5 in all volunteers. An additional CT scan will be performed at Day 10 in individuals who have shown any evidence of COVID-19 infection (e.g. positive swab, symptoms or other tests suggestive of infection). Each dose of radiation from a low dose CT scan is equivalent to no more than 6 months background radiation.

The MRI scan performed at screening and after discharge from quarantine is a safe procedure that does not use radiation to make pictures and there are no risks or side effects associated with the scan itself. Gadolinium contrast dye administered for the MRI scan is widely used for cardiac MRI scans and is safe. Occasionally, it may cause a mild headache, nausea, itching and very rarely (1 in 5000) a more severe allergic reaction (anaphylaxis). It is cleared within hours by the body. Availability to treatment for anaphylaxis is

readily available in the unit where these procedures are carried out and participants will be accompanied by staff appropriately trained in the management of anaphylaxis.

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.

### **11.6 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, female participants that can become pregnant must agree to use a highly effective method of contraception (as per section 13). If you or your partner became pregnant during the study we would ask you to inform us.

### **11.7 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, and you will be visited frequently by study staff to check on you. There may be other psychological or social risks that result from taking part in the study, such as concern about being tested for HIV.

#### Low molecular weight heparin

This injection is routinely given to most 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. Second line therapy with Thromboembolic deterrent stockings will be used if you cannot receive low molecular weight heparin.

#### Thromboembolic deterrent stockings (TEDS)

If you cannot receive low molecular weight heparin (e.g. a reaction to the medication) then 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/discoLOURED 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.

#### 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 92mls of blood (approximately 5 tablespoons) at a single visit. The total amount we plan to take over the 12-month period of the study is 759ml. We may take up to an additional 120ml 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. Additionally, the NHS blood and transplant service will not accept any donations for 12 months after receipt of REGN COV-2. 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.

REGN COV-2 will be given through an intravenous (IV) cannula (a small plastic tube) placed in your arm vein. Additionally, you may require a cannula for the cardiac MRI scan. This procedure may cause pain, bruising, swelling, redness and very rarely, infection at the site of insertion.

### Throat and Nose 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.

## **12 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
- REGN COV-2 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 legally required to self-isolate as per the latest government guidance and we are legally obliged to inform the NHS test & trace system so that they can ensure adequate self-isolation.

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, they will also need to self-isolate according to government guidelines; this will be explained to you before you leave.
- You will not be eligible to receive the rescue therapy with REGN COV2 (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.

## **13 What advice on contraception must I follow during the study?**

If you are able to have a baby, or if you are a male and your partner is able to become pregnant, you must use acceptable birth control. Please share this information with your partner and talk to your GP or the study staff to decide the best method of birth control.

If you are a female 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 used 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. Male sterilisation, 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

Female volunteers who are not of childbearing potential are those who have had a complete absence of menstrual periods for at least 12 months, or documented proof of surgical sterilisation or hysterectomy.

If you are a male volunteer in heterosexual relationships, you must agree to practise continuous effective contraception from the day of challenge to 6 months post treatment with REGN-COV2 (if offered). You must also agree not to donate sperm during this time.

Effective methods of contraception include:

- a. Use of a condom with a spermicide to prevent pregnancy in a female partner
- b. Male sterilisation with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate
- c. If in a stable relationship with a female partner of childbearing potential, contraception used by the female partner outlined above is also acceptable, as long as it is part of the partner's regular long-standing method of contraception.
- d. True abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle

You must notify the study doctor if you or your partner become(s) pregnant during the study. If you are a female who becomes 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.

## **14 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 £4995. 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 6-8 weeks after each of the following study time points:

- 1) £2000 will be paid after discharge from quarantine
- 2) £350 will be paid after the Day 28 follow-up appointment.
- 3) £350 will be paid after the Day 56 follow-up appointment
- 4) £350 will be paid after the Day 84 follow-up appointment
- 5) £350 will be paid after the Day 168 follow-up appointment
- 6) £1595 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 are calculated based on any procedures performed and length of the visit.

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.

## 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, Cardiac MRI, Echocardiograms). 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 Clinical Trials and Research Governance (CTRG) office on 01865 616480 or the head of CTRG via email: [ctrg@admin.ox.ac.uk](mailto:ctrg@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. We will share data with Regeneron Pharmaceuticals regarding any events that occur in relation to the REGN COV-2 rescue therapy. This data will be sent labelled with your unique study number rather than your name. 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.

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 about 8mL 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. Any samples will be sent in an anonymised form (without any of your personal details).

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 a Wellcome Trust grant held by Professor Helen McShane. 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 XXX Ethics Committee (ref: XX).

### **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 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>]. 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>]. 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:

[Insert local contact details here](#)

If you have any medical problems during your participation in this study please contact [insert local contact telephone number](#): (9am-5pm Mon-Fri), or [insert local mobile phone number](#): (24 hour emergency number). Alternatively, if your query is not urgent you can email [insert local contact email address here](#).