Title: Stratification of Clinically Vulnerable People for COVID-19 Risk Using Antibody Testing (STRAVINSKY)

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The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study as per GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as applicable

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Study Name:	STRAVINSKY- Stratification of Clinically Vulnerable People for COVID-19 Risk Using Antibody Testing
Protocol Version Number:	Version: 2.0
Protocol Version Date:	26.11.2023

CI Name:	Professor Alex Richter
Study Role:	Chief Investigator
Signature and date:	 26/11/2023 __ __ __ ___

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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1.0 Study Summary

Title:	Stratification of Clinically Vulnerable People for COVID-19 Risk Using Antibody Testing (STRAVINSKY)
Funding Body	NIHR- National Institute for Health and Care Research
Rationale:	Although the COVID-19 vaccination program has proved extraordinarily successful, clinically vulnerable (CV) patients remain at risk of SARS-CoV-2 infection, severe COVID-19 and death. Large (inter)national studies have previously identified patient groups who generate sub-optimal immune responses to COVID-19 vaccines, and those at highest risk of severe COVID-19. Although the precise immune correlates of protection against severe COVID-19 are not defined and this may be different in different patient groups. Recent emerging data in patient groups suggest that the serological response to vaccination is a critical determinant in COVID-19 outcomes. In this study we will i) perform a retrospective meta-analysis using previous studies to enhance stratification of patient groups for clinical risk and ii) assess if SARS-CoV-2 serological responses to COVID-19 vaccines can be used to risk stratify CV people for COVID-19 clinical outcomes.
Aim & Objectives:	**Primary objectives**: a) To define and assess the predictive value of SARS-CoV-2 spike serology measurements for COVID-19 clinical outcomes (infection rates and disease severity) in CV people. □ **Secondary objectives:** a) To evaluate the serological vaccine responses (magnitude and durability) of CV patients to bivalent or other vaccines given during the study period 2023 onwards b) To assess the functional activity of anti-spike IgG antibodies against new SARS-CoV-2 variants in CV patients during the study period 2023 onwards c) To perform a detailed retrospective analysis using pre-existing data from large national studies that may further inform the patient groups that will be enrolled in the prospective study. □ **Exploratory objectives**: a) To evaluate alternate methods to predict COVID-19 infection/hospitalisation should antibody testing fail to predict relevant clinical outcomes (e.g. QCOVID4 score and T cell responses). b) To understand whether the serology vaccine response, in those with suboptimal responses to primary course, can be further enhanced with increasing doses of vaccination.□□□ c) To assess T-cell response to emerging variants of concern (VoC) in CV individuals. d) To determine the correlation between antibody and T-cell responses.

Study Design:	The STRAVINSKY study encompasses a multicentre prospective, observational cohort study involving multiple sites within the UK, in addition to retrospective analysis of data previously acquired in national studies. In the prospective study a large number of patients will be recruited from pre-specified clinical groups and enrolled through online/remote consent procedure. Blood samples will be acquired by the volunteer and sent to a central laboratory for serology testing. A subgroup of patients will be recruited and donate blood in a face-to-face visit for more detailed immune analysis. Clinical data, alongside vaccine history and COVID-19 infection outcomes will be recorded at each visit. Volunteers are expected to attend for up to four visits over 2023-2024. The retrospective analysis will use pre-existing data from large national studies that may further inform the patient groups that will be enrolled in the prospective study.
Number of participants in the prospective study:	Up to 3000 individuals will be recruited including: **Remote cohort**: 2600 will be recruited and remotely sampled. **In-person cohort**: 400 individuals will be recruited and attend an in-person appointment for in-depth sampling from selected hospitals (Birmingham, Oxford, Southampton, and Imperial).
Eligibility criteria for the prospective study:	**Inclusion criteria** Participants will meet ALL the following: • The individual meets the diagnostic or treatment criteria set out in **TABLE 2, page 13.** • 18 years or older. • The individual must have capacity to provide written informed consent or in cases where this is not possible, a legal representative who is able to make an informed decision on their behalf. **Exclusion criteria** Participants will meet NONE of the following: • Does not have a legal representative who is able to make an informed decision about consent to the study. • Individuals will be excluded if they have received any monoclonal antibody therapy against SARS-CoV-2 within the 26 weeks prior to the first study blood sampling (either as a treatment for infection or pre-exposure prophylaxis). Recipients of regular immunoglobulin therapy are eligible*. • Age less than 18 years.
Sample collection for the prospective study:	**Remote cohort:** Capillary blood sampling by dried blood spot. **In-person cohort:** Up to 60 ml of blood to assess blood antibody levels, T cell responses and store samples for exploratory studies; Saliva and nasal samples. **All patients** will be given a COVID-19 swab kit at home to return to the investigators when they test positive for COVID-19 infection.

2.0 Background

COVID-19 vaccines are the main strategy employed by governments globally to protect their populations against SARS-CoV-2 infection. However, the protection conferred by these vaccines is not equivalent for everyone.[1] Individuals with immunosuppression, either because of underlying disease or immunosuppressive treatment, comprise ~3 million people in the UK. These individuals have suboptimal responses to vaccination and remain at an increased risk of severe COVID-19. [2,3] The QCOVID team and others have also identified additional disease groups who are increased risk of severe COVID-19, where immune dysfunction is recognised but is mechanistically poorly understood (e.g. renal disease, liver disease, diabetes, and Parkinson's disease).[4] Even in healthy people, current COVID-19 vaccines give limited protection against SARS-CoV-2 infection, but rather protect against severe disease. Healthy people almost universally generate high titre serological responses to vaccines. By contrast, in many disease populations the response to vaccines is suboptimal, however this is heterogeneous, and the antibody response is difficult to predict. The precise correlates of protection against infection and severe disease remain poorly understood, but emerging data particularly in patient groups suggests that the serological response to vaccination is a critical determinant in COVID-19 clinical outcomes. Serological heterogeneity together with clinical phenotypes in disease groups gives an opportunity to define these correlates more precisely, and to identify populations who remain most susceptible to severe COVID-19 clinical outcomes.

Identifying individuals who continue to be at risk of severe COVID-19 despite vaccination, and who might benefit from additional treatment strategies remain challenging. This requires the clinical characterisation of multi-disease patient groups alongside vaccine response assessment using standardised immune assays and correlation with COVID-19 infection outcomes. Furthermore, assessment in real time is required as new Variant of Concern (VoC) emerge and the number of vaccines administered, and more recently vaccine type, continues to evolve over time.

To address this challenge, we will investigate whether SARS-CoV-2 antibody testing can better quantify an individual's risk and enable clinicians to provide targeted advice to those previously requested to shield and have been deemed Clinically Vulnerable.

2.1 Overall summary of Study

There will be two key workstreams to achieve the study aims. Firstly, a retrospective meta-analysis of existing data from clinical studies undertaken during the COVID-19 pandemic. These data have not been analysed in a comparative way to understand the breadth and diversity of clinical vulnerability, and results from this analysis may further inform on the CV groups that require prospective evaluation. Secondly, a prospective study that will recruit up to 3000 CV individuals, to understand how SARS-CoV-2 antibody tests, following COVID-19 vaccines, predicts COVID-19 risk.

3.0 Retrospective meta-analysis (Lead: Willicombe / Richter)

Aim: We will perform a meta-analysis of post-vaccination SARS-CoV-2 antibody concentrations in CV patient populations to discriminate SARS-CoV-2 infection risk and inform the clinical use of serological testing.

Objectives:
1) To investigate if a detectable SARS-CoV-2 antibody response (binary yes/no) post-vaccination predicts infection outcomes (rates and severity) across different CV groups.
2) To investigate if the post-vaccination antibody magnitude can predict infection across different CV groups.
3) To identify and refine CV patients to be included in the prospective study.

Methodology: Using existing combined UK cohorts of >15,000 immunosuppressed patients, a meta-analysis will be performed on published (and unpublished) data reporting linked vaccine immunogenicity and effectiveness outcomes. Studies to be included are shown in **TABLE 1**, with chief investigator approvals already obtained. This will include only anonymised patient data. Patient identifiable data will not be made available to the study team for the retrospective analysis.

The data will be pooled to maximise the statistical power for descriptive and comparative analysis. A minimum number of key characteristics will be collected in all studies (age, gender, primary disease type, treatment, vaccine number and type, anti-spike (S) IgG level and clinical outcome).

Different antibody tests have been used for these studies; to ensure this analysis is transferable across assays, the WHO International Standard will be used to compare platforms. Descriptive statistics will set out the geometric mean titres of IgG antibodies by age, gender, disease type and treatment, and compared with control cohorts within the included studies. Preliminary analysis of the association between antibody concentration and effectiveness will include post-vaccination (≥3rd dose) antibody status in immunosuppressed people-antibody status will be considered as a binary value (detectable versus absent). Clinical outcomes of interest will include infection, hospitalisation and death; first considered as a composite, and then individually, data allowing. The odds ratio of clinical outcome by antibody status will be reported both unadjusted and adjusted for key participant (or patient – terms used interchangeably) characteristics. We will also explore the relationship between antibody concentrations as a continuous variable and clinical outcomes, with estimation of discriminative cut points at concentration levels associated with inferior effectiveness. A repeat analysis will be performed on non-immunosuppressed vulnerable people within these cohorts. Those groups with inadequate response with respect to the clinical outcomes as determined by these analyses would be included in the prospective study.

Data sharing and transfer: We will request ethical approval to use existing data from other studies to achieve the aims of STRAVINSKY. This will enable the development of data transfer arrangements between the existing studies with the STRAVINSKY team. Before doing this the data transfer arrangements will ensure the correct ethical approvals are in place and patients have consented for their data to be used in future ethically approved studies. The data transferred will be at patient level but will be completely anonymised. Data will be stored on secure servers at all times and transferred using encrypted files.

TABLE 1. Examples of studies to be included in the retrospective meta-analysis

Study	Patient Cohort	Numbers of participants
OCTAVE	Rheumatology, Solid Organ Transplants, Renal, Liver, Stem cell Transplant	2,686
OCTAVE-DUO	Rheumatology, Solid Organ Transplants, Renal, Liver, Stem cell Transplant, lymphoma, antibody deficiency	804
PROSECO	Immunodeficiency	592
COVAD	Immunodeficiency	562
CORONACANCER	Cancer	3,555
CLARITY	Inflammatory bowel disease	7,224
COVID-19 RENAL	Renal Transplant, Dialysis, Autoimmune, Renal disease	2,500
PITCH	Health care workers (control)	800

4.0 Prospective observational study (Lead Lim/Barnes)

4.1 Aim

To assess the predictive value of post SARS-CoV-2 vaccination serology measurements in CV individuals.

4.2 Objectives

Primary objectives:

a) To define and assess the predictive value of SARS-CoV-2 spike serology measurements for COVID-19 clinical outcomes (infection rates and disease severity) in CV people.

Secondary objectives:

a) To evaluate the serological vaccine responses (magnitude and durability) of CV patients to bivalent or other vaccines given during the study period.

b) To assess the functional activity of anti-spike IgG antibodies against new SARS-CoV-2 variants in CV patients during the study period.

Exploratory objectives:

a) To evaluate alternate methods to predict COVID-19 infection/hospitalisation should antibody testing fail to predict relevant clinical outcomes (e.g. QCOVID4 score and T cell responses).

b) To understand whether the serology vaccine response, in those with suboptimal responses to primary course, can be further enhanced with increasing doses of vaccination.

c) To assess T-cell response to emerging VoC in CV individuals.

d) To determine the correlation between antibody and T-cell responses

5.0 Study population and eligibility criteria

5.1 Patient selection

Participants in this study will have an underlying disorder which has identified them as being clinically vulnerable. The disease and treatment groups eligible for participation (**TABLE 2, page 13**) in STRAVINSKY may alter throughout the study depending on the results from the retrospective analysis or other new knowledge/discussions such as the report from the Independent Advisory Group for COVID-19 medicines.[5]

TABLE 2. Groups eligible for participation

Group	Disease related groups (n=120-140 per group)	
1	Chronic lymphoproliferative disorders (footnote 1)	
2	Plasma cell disorders (footnote 2)	
3	Myelodysplastic syndrome (MDS) or (myeloproliferative neoplasms MPN) (footnote 3)	
4	Sickle cell disease, thalassaemia, or rare inherited anaemias	
5	Active malignancy diagnosed within 2 years of study consent (excluding non-melanoma skin cancer, non-invasive bladder cancer and localized squamous cell carcinoma of cervix) (Note: participants who have received radiotherapy or systemic anti-cancer treatment within the last 26 weeks should be included in groups 18 and 19 first).	
6	Down's syndrome and learning disability	
7	Neurological diseases (Parkinson's and multiple sclerosis) (footnote 4)	
8	HIV	
9	Common variable immunodeficiency and secondary immunodeficiency (requiring prophylactic antibiotics and/or immunoglobulin)	
10	Cirrhosis (footnote 5)	
11	Chronic respiratory conditions (footnote 6)	
12	Chronic kidney disease (CKD) stage 4-5 (footnote 7)	
13	Diabetes mellitus (Type 1 and 2)	
14	Cardiac failure	
	Treatment-related group (n=120-140 per group)	**Timing**
15	Previous recipients of a solid organ transplant (SOT)	At any time
16	Recipient of a haematopoietic stem cell transplant (HSCT)	Within 52 weeks at time of study consent
17	Recipient of B-cell depleting treatment (**APPENDIX 1** for details)	Within 52 weeks at time of study consent
18	Recipient of systemic anti-cancer therapy e.g. chemotherapy or immunotherapy and others (**APPENDIX 1** for details)	Ongoing or within last 26 weeks at time of study consent
19	Recipient of radiotherapy	Ongoing or within last 26 weeks at time of study consent
20	Autoimmune disease on systemic immunosuppressive* medication (**APPENDIX 1** for details)	Ongoing or within last 26 weeks at time of study consent

If a participant belongs to more than 1 disease/treatment group, allocation will follow the following prioritisation:

Does the patient fit into any of the treatment-related groups?

Yes –> allocation to Treatment-related group. Patients should be preferentially allocated to the first treatment-related group that can be applied to them in the list above from rows 15 to 20 above.

No -> allocation to disease-related group that is considered by the local clinical investigator to be the MAIN disease. Patients should be preferentially allocated to the first disease-related group that can be applied to them in the list above from rows 1-14 above.

Footnotes:

1. Any chronic/indolent/low-grade B or T-cell lymphoproliferative disorder e.g. follicular lymphoma, chronic lymphocytic leukaemia, lymphoplasmacytic lymphoma etc.
2. e.g. myeloma, plasma cell leukaemia and AL amyloidosis and excluding monoclonal gammopathy of undetermined significance (MGUS).
3. Includes myelodysplastic syndrome, myeloproliferative neoplasms, myelofibrosis and chronic myelomonocytic leukaemia.
4. Any rare neurological and severe complex neurodisability e.g. multiple sclerosis, motor neurone disease, myasthenia gravis, Huntingdon's disease, and also Parkinson's disease.
5. Cirrhosis Child-Pugh class A, B and C.
6. Chronic obstructive pulmonary disease, Interstitial Lung disease, Pulmonary hypertension
7. eGFR less than 30 ml/min/1.73m^2

5.2 Inclusion criteria

Participants will meet ALL the following:

- The individual meets the diagnostic or treatment criteria set out in **TABLE 2 on page 13.**
- 18 years or older.
- The individual must have capacity to provide written informed consent or in cases where this is not possible, a legal representative or Welfare Attorney who is able to make an informed decision on their behalf.

5.3 Exclusion criteria

Participants will meet NONE of the following:

- Does not have a legal representative who is able to make an informed decision about consent to the study.
- Individuals will be excluded if they have received any monoclonal antibody therapy against SARS-CoV-2 within the 26 weeks prior to the first study blood sampling (either as a treatment for infection or pre-exposure prophylaxis). Recipients of regular immunoglobulin therapy are eligible*.
- Age less than 18 years.

* This enables assessment of the primary outcome and response to bivalent vaccine. It is highly likely that policy on these licensed treatments will change, in which case we may submit an amendment to individuals receiving SARS-CoV-2 monoclonal Abs.

6.0 Prospective study

6.1 Study design and overview

This is a multicentre prospective, observational cohort study (**FIGURE 1**). Patients will provide samples and clinical data on 4 different occasions over 12-18 months. For each of the 4 visits individuals will be allocated to be involved in the study either remotely or attend in-person.

3000 individuals will be recruited in total; for 2600 of these patients (remote cohort), their commitment to the study will be entirely remote.

400 individuals (in-person cohort) will be invited to attend a sampling appointment at one of the 4 in-person sampling sites (Birmingham, Southampton, Imperial or Oxford), for each of the 4 study visits. The aim will be to recruit between 120 and 140 individuals per disease/treatment group as detailed in **TABLE 2.**

Informed consent and data collection will predominantly be collected online via a REDCap database. Patients and sites without access to devices or internet will be consented via telephone, the signed paper consent form will then be sent to the participant to counter sign, and they will be asked to post this back to the central study team.

Participants without access to devices to internet will also be offered face to face appointments where the patient can either be supported by the research nurse to complete the online consent form or the participant can sign a paper consent form. If paper consent forms are used, they will be transcribed/scanned into REDCap and the original paper source document will be stored at the recruiting site for the duration of the study. Any case report form (CRF) data collected face to face or via telephone will also be transcribed directly into the database by each local clinical care team. Paper CRF data and consent forms will be transcribed/scanned into REDCap. The original paper documents will be stored at the recruiting site.

There will be a baseline visit which will establish an antibody result at the point of recruitment and establish their medical and COVID-19 infection and vaccination history. There will be 3 further visits that will measure the antibody level prior to booster vaccination, the antibody response at 4-10 weeks post vaccination and then a 4th visit at least 24 weeks after vaccination to examine the longevity of this booster response. Patients can be recruited at any point during their vaccine journey (pre or post vaccine). If patients are recruited after their booster vaccination, they will start at visit 1. Clarification of this route is shown in Appendix 6. Patients will receive their antibody test result.

Booster vaccinations are not being given as part of the study; it is the antibody response to any vaccines that are being given as part of the national vaccination policy that are being examined. If an individual chooses not to have a vaccine they will still be able to take part and we will still measure their antibody levels at equivalent timepoints to those being vaccinated.

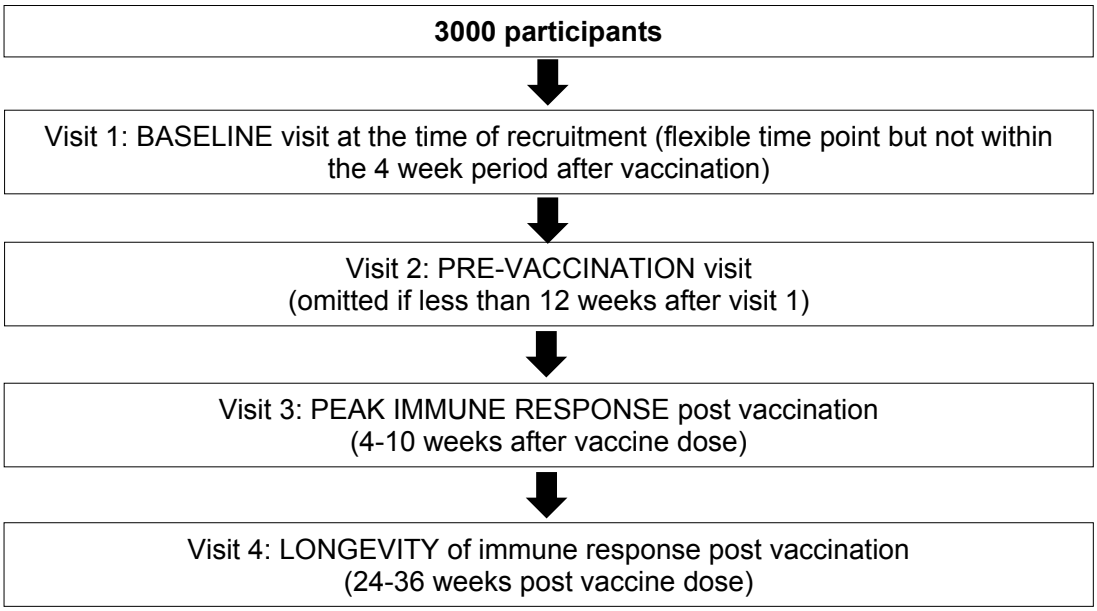
Participants will contact the study team or their local clinic team if they test positive for COVID-19 infection, which will enable the study team or local clinical team to complete an online form relating to their illness and to send swabs back to the study to monitor for persistent viral infection.

For participants in the remote cohort (2600) their 4 visits will be all be undertaken remotely but with the option for in person or assisted consent if required. Their contact with the study will be either over the telephone or electronic. They will receive regular electronic updates on the study from the Central Study Team and will have the email and telephone for the Central Study Team if they would like or require individual contact. In addition to this, individuals may receive a telephone call to clarify any history provided by the participant remotely during visits 2-4 or if they suffer from COVID-19 infection. Patients will also be texted their result.

For participants in the in-person cohort (400) they will be enrolled either remotely or in-person and all 4 visits will be in-person to enable an extended sample collection. Contact about the study will then be similar to the remote cohort.

Participants will be monitored for COVID-19 infection until the study completes.

FIGURE 1. Visit schedule



6.2 Participant identification

Potentially eligible participants (based on underlying conditions) will be identified either through hospital clinics, local hospital clinical databases, localised adverts or through the existing local or ethically approved studies, where patient has given prior consent to be contacted to participate in future studies. They will be contacted either by post, telephone, email, or in-person during routine clinic visits and invited to join the study. They will receive a PIS and copy of the consent form either by post, email or in-person from a member of the study team or clinical team.

Participants whom are not known to local study sites also be able to self-identify for the STRAVINSKY study via the STRAVINSKY webpage and posters and other social media outlets featuring QR codes. Participants will contact the study team through the study email STRAVINSKY@contacts.bham.ac.uk. The Central Study Team will confirm eligibility. Where possible, we will include individuals that attend the chosen clinical sites to enable access to hospital records, however, for those that self-identify and self-consent in the community (having read and agreed to the participant information sheet) we will request clarification of their clinical history through GP data sources and via access to the National Immunisation and Vaccination System and NHS digital clinical data through their NHS/CHI number.

Informed consent and data collection will be collected online via a REDCap database. Patients and sites without access to devices or internet will be consented via telephone or face to face and the data will be transcribed into the REDCap database. Any case report form (CRF) data collected face to face or via telephone will also be transcribed into the database by each local clinical care team. Copies of all paper CRF data and consent forms must be kept in the site master file for the duration of the study.

6.3 Consent

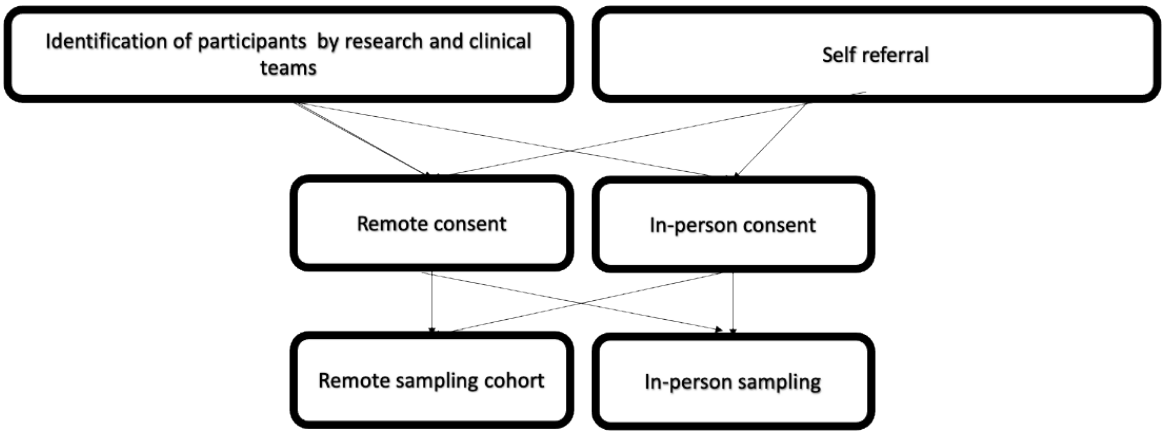
Once individuals have expressed their interest in the study, they will be sent a link to an online consent form within the REDCap database. Having read the participant information sheet, and are content that they have no further questions, they will sign the consent form. Paper options will also be available as an alternative to be undertaken either remotely and returned by post or be completed

during in-person appointments. It is anticipated that most individuals will consent remotely, however, if an individual is identified when they are attending for a clinical appointment, they will be able to undertake informed consent at the time if this is their preference and it is more convenient for them.

Once an individual has signed the online consent, the Central Study Team will receive an alert that this individual has consented and they will email a pdf copy of the consent form to the individual participant for their personal records and with this email the participant will be informed of their study ID number and given a link to complete a REDCap form to provide information about their underlying condition and their contact details. The local study team will also receive an alert that a patient at their site has consented to arrange for a telephone call to complete the CRF for visit 1. The local study team will use a log to document the time of any telephone call, who it was made by, and the purpose of the call or topics discussed.

If a participant requires support with their consent, chooses not to use electronic consent or has no access to email, informed consent can be undertaken remotely by research nurses or members of the study team, who are on the study delegation log and who are trained in GCP and informed consent. Consent can also be undertaken in-person by these members of the study team. For all individuals there will be the option for remote or in-person consent and this does not pre-determine whether they continue with remote or in-person sampling visits. This ensures as much flexibility as possible for participants (**FIGURE 2**).

FIGURE 2. Options for remote and in-person consent



6.3.1 Arrangements for individuals who do not have capacity to consent

Some patients may not have the capacity to consent, e.g. individuals in the learning disability group. For these individuals, the clinician will inform the patient's next of kin, personal consultee or legal representative /Welfare Attorney about the study either through telephone call or face to face at the time of recruitment. If the next of kin or personal consultee is not be able to come to the hospital, the research team will send the consultee information sheet and consultee declaration form to them either by post or email. The research team will then obtain the declaration form from the personal consultee or welfare attorney by telephone call witnessed by another member of the research team.

The potential participants will be provided with a simplified poster outlining the study. If they would like to participate, participants' representatives will be given sufficient time to review the PIS and will be given the opportunity to ask questions, once they are able to make an informed decision they will be asked to sign a consent form.

This alternative arrangement will enable vulnerable adults to participate in this study and so inform care for individuals within these disease groups.

6.4 Enrolment

Once the participants are consented, they will be issued a study ID number and added to the REDCap database. Participants will receive an electronic link to input their contact details into the REDCap database. It is necessary for participants to provide contact details to enable dried blood spot (DBS) tests and swabs to be sent to the patient's address, results to be returned by text and their NHS/CHI number and GP's to be able to retrieve vaccine details and other clinical information from primary care records.

When the patient undertakes consent and enrolment, they will provide the following data:

- Demographics (Age, year of birth, height, weight, self-reported ethnicity, sex, NHS number)
- Contact details- Name, address, email address, contact number (preferably mobile to receive antibody result)
- Occupation
- Name and address of GP
- Which clinical or treatment groups participant self identifies as being part of (**SECTION 5.0, also see TABLE 2 on page 13**)

All participants will be given contact details of the Central Study Team. Participants will be made aware that they will remain in active follow up and the Central or Local Study Team will contact them during the study either electronically or by telephone call to update them on the study.

Once a participant has consented the REDCap system will alert the Central Study Team and also the local study team that someone from their centre has consented as this will enable the local team to arrange completion of the CRF.

6.5 Visits

Visits will either be all remote, or all in-person for any individual. Unless circumstances arise for practical reasons or patient preference, participants will remain in either the remote or in-person sampling cohorts for each of their 4 visits. A visit checklist is provided in **APPENDIX 2**.

6.5.1 Timing and detail of visits

These visits are arranged around the assumption that there will be a booster campaign, but we acknowledge the study will have to be amended if this is not the case.

Visit 1: Baseline – This is a flexible timepoint depending on recruitment.

At the baseline visit (remote and in-person) patients will be contacted by a research nurse or member of the study team to populate the CRF. The research team member will complete the REDCap online CRF form through this telephone call, with the information detailed below, from the participant. The study team will also be able to confirm clinical details through hospital records, GP records and NHS digital records (e.g. hospital episode statistics and the National Immunisation Management Service) which the patient has consented to. This information will be inputted straight into the REDCap database by the research team. Where this is not possible, for contingency the data will be collated on paper and transcribed onto an electronic CRF on the REDCap secure web application.

The research nurse or clinical team will collect the following data from the hospital records, GP records, National Immunisation or Vaccination System or NHS digital.

- Medical conditions / co-morbidities and regular/previous medication as detailed in CRF

· Vaccination history including COVID-19 and other routine vaccinations including influenza or pneumococcal.

Baseline samples will be taken as soon as possible after consent and enrolment into the study. The remote cohort will receive a DBS testing kit in the post and the in-person cohort will provide blood, saliva and nasal samples (described below) during a clinic visit.

Visit 2: This visit is to capture samples just before administration of the booster vaccine.

The purpose of this visit is to measure the lowest antibody level just before vaccination. Ideally this will be within the week prior to the booster vaccination although, patients can be recruited at any point during their vaccine journey (pre or post vaccine).

This visit may be shortly after the Visit 1 depending on when a participant consents. For individuals providing in-person samples the study team can omit this visit if it is less than **12 weeks after Visit 1.** The remote group will continue to complete a dried blood spot sample if they are recruited before September 2023. If recruited after this point this visit can be omitted.

Participants will be asked to complete an electronic REDCap data collection questionnaire or be assisted in this by the research team by telephone if support required. Information collated will include:

- Confirmation of any change in medical and drug history, COVID-19 infection and vaccination history. If the patient answers no to all of these no further action will be taken. If they answer yes they will be asked whether it is a change in their immunosuppressive/chemotherapy/ radiotherapy treatment. This will alert the Central and Local Study Teams to check the individual's medical records to confirm this change and if required the patient will be contacted to confirm. If an individual has tested positive for COVID-19 they will be asked to complete a REDCap survey about their illness and where they were treated (see section on testing positive for COVID-19 17.3.1)
- Remote cohort will receive a DBS kit and in-person cohort will provide the same blood, saliva and nasal samples as per baseline. For the remote cohort, participants will be asked to logon to REDCap to confirm they have sent a sample back to enable sample tracking and their anticipated vaccination date (if known). Or participants can email or telephone the study team with this information.

Visit 3: All participants will provide a sample **4-10 weeks post vaccination**.

Participants will be asked to complete the same electronic REDCap questionnaire as per visit 2.

Participants will be asked to provide the same samples as per visit 2 depending on whether they are the remote or in-person group.

If a participant does not to receive a booster vaccine (either because they chose not to or suffered a COVID-19 infection at this time), they will be asked will to provide an equivalent sample at any time between November-December 2023 and their clinical record will be reviewed as above.

Visit 4: All participants will provide a sample **24-36 weeks post vaccination.**

Visit 4 timelines are flexible and will depend on optimal time according to the planned vaccine schedule. The timing will be at least 24 weeks after the last vaccine but before the next planned vaccine.

Participants will be asked to complete the same electronic REDCap questionnaire as per visit 2.

Participants will be asked to provide the same samples as per visit 2 depending on whether they are the remote or in-person group.

If someone does not want to receive a vaccine during the study (either because they chose not to or suffered a COVID-19 infection at this time), they will be asked will to provide an equivalent sample at any time between October-December 2023 and their clinical record will be reviewed as above.

If someone chooses not to receive a vaccine during the study, they will be asked to provide a blood sample, at any time After April 2024.

Text message reminders and alerts will be sent to patients by the central study team (via FireText as detailed below) prompting them to complete the surveys as timepoints listed.

6.6 Samples

Remote DBS samples will be sent by participants directly to the University of Birmingham Clinical Immunology Service (UOB CIS). In-person samples will be transported to the local research laboratory at UoB, Southampton, Oxford or Imperial for processing. Samples will be transported between the sites under an appropriate material transfer agreement / collaboration contract. To enable this, consent will be obtained from participants for data collection, transfer and storage of all samples.

The following samples will be taken for the in-person cohort:

- 60ml of blood taken by venepuncture
- Saliva – 4-minute passive drool into a universal
- Nasal secretions - synthetic absorptive matrices (SAM) inserted in nostrils for 60 seconds

The samples taken for this study will be used as follows:

In-person sampling (n=400)			Remote sampling (n=2600)	
60ml of peripheral venous blood at each visit			Finger prick blood test at each remote visit	
Cells	Stored as peripheral blood lymphocytes to undertake T cell ELISpots and other exploratory studies.		Finger prick blood test	A capillary sampling method where the blood drop from a finger prick made by a lancet, is dripped onto a filter card. This is then dried (dry blood spot or DBS) and eluted in the laboratory and used to measure antibodies but can be used for other analytes.
Serum/plasma	Enumerate and characterise the antibody responses and storage for other exploratory studies.			
Mucosal samples				

Saliva	Measure antibody in saliva and compare this with serum to determine whether saliva could be used an alternative sample for antibody testing.			
Nasal sections	Measure antibody in nasal secretions and compare this with serum and saliva to determine whether could be used an alternative sample for antibody testing.			

A description of the sample transport to the laboratory and processing and distribution is described in the laboratory manual.

The samples will be stored for up 10 years from the last recruitment date for further ethically approved studies.

6.7 In event of a COVID-19 infection in a participant

In addition to the routine sampling, all participants will be provided with a nasal swab testing kit when they test positive for COVID-19 . These will sent to the participant once they call the central study team or clinical care team and report a positive COVID-19 test. Once the patient tests positive on their lateral flow, or by swab in hospital, they should use their swab and send it to the laboratory (pre-labelled address and pre-paid) where the swab will be tested for presence of virus and sequenced, to enable the variant to be typed and inform our knowledge of viral evolution. Swabs will be sent to participants if insufficient samples are received, and until two consecutive negative swabs are documented. If the participant does not return the swab we will contact them by text or telephone to remind them to return this. In addition to this, a survey link will be issued to each participant via REDCap once they have consented onto the study. This link will be active for the duration of the study and allow the participant to report their episode(s) of COVID-19 infection, trigging further swab testing kits to be issued to their home address should these be required. If an individual thinks they are COVID-19 positive but testing negative (we know that lateral flow tests are not 100% sensitive) they should contact the Central Study Team by email or phone. If there is a high likelihood this is COVID-19 (e.g. family all COVID-19 positive and patient unwell but testing negative) we will record this as a likely episode and still ensure 2 negative swabs returned.

6.8 Antibody test result

The antibody test result will be returned to the participant by text message using a 3rd party provider FireText where a mobile number is provided. The result will inform the patient of their antibody status, and provide further information regarding the results meaning. For individuals who are not able to provide consent, it will be decided at the consent process whether the result is returned to the patient or their legal representative / Welfare Attorney. Where a mobile number is not provided or used, test results will return by email or letter if that is the patient's choice. FireText provide secure SMS security to the NHS and the Government and are ISO27001 certified to meet strict standards for security and redundancy.

6.9 Follow up duration

All participants will remain in the study, for the duration of the study which currently is spring 2025, to monitor for infections and further vaccination.

7.0 Risks and ethical considerations

Blood testing is usually well tolerated. The most common adverse event is an individual feeling faint, during phlebotomy. Facilities, including a bed on which to lie, will be available to mitigate this if required. Sometimes there is bruising at the puncture site. This is a common adverse event and so will not be recorded or reported.

The DBS test may cause minimal discomfort, but this will be transient. Individuals will be sent a paper instruction to do this which has been used previously successfully. Individuals will also be able to access a video of how to undertake a DBS test. Occasionally, the DBS may not have collected sufficient blood to perform the necessary tests, particularly if home-testing. In this case, the patient will be offered repeat DBS testing, access to telephone support via the Central Study Team and leaflets and videos in order for participants to conduct the testing as safely and as comfortably as possible. If a participant finds DBS difficult to perform they will be offered a blood test at one of the in-person centres as an alternative. If the participant does not return the DBS test, we will contact them by text or telephone to remind them to return this.

A separate information sheet has been written about the antibody test, emphasising the limitations of the results. It is made clear that the results are of scientific interest and value, however, they should not reassure or worry the participant. It is emphasized that the result should not change behaviour with regards social distancing, handwashing, and personal protective equipment (PPE). It is also made clear that their employers will not be contacted with the result in case this changed external behaviour towards the participant.

Following the rapid deployment of antibody testing nationwide, many different assays are being used by NHS laboratories for antibody testing. To avoid any confusion arising from differences in the performance between the University of Birmingham assays and those currently being used in other NHS laboratories, we will only issue a result to study participants if they have not enrolled in the parallel government antibody testing programme. If participants have enrolled in the government antibody testing programme, then the sample taken for this research study will only be used for research purposes.

Samples collected from this study will be critical in the future validation of such assays prior to their deployment in the NHS. Participants will specifically consent to their samples and data being used for future ethically approved research studies. They will be asked whether their anonymised samples can be used for future studies and whether their samples could be collated at a licensed biobank.

There is a potential risk of infection to the researcher. However, this study is being undertaken strictly in convalescent and asymptomatic participants. They will be asked when they make contact for the appointment whether they have any symptoms. Usual precautions as recommended by the current NHS policy will be adopted in terms of Personal Protective Equipment. Only medics or researchers who are trained in phlebotomy will be able to take blood tests.

8.0 Safety reporting

This is an observational study; we will record only serious adverse events that occur as a result of direct study involvement or death from any cause.

The Study Office will report all events assessed to be reportable as serious, unexpected and possibly related to the study procedures (refer to definition below) to the main Research Ethics Committee (REC), and Sponsor within 15 days of the Chief Investigator becoming aware of the event, in accordance with the Sponsor's safety reporting procedures.

Serious Adverse Event

The study acknowledges that multiple serious adverse events are likely to occur during the study due to the natural course of the participants' disease. These are expected events and will not be captured within the study. The study will record only serious adverse events that occur as a result of direct study involvement or death from any cause. Note that COVID infection and or hospitalisation for this infection is already captured as part of the study procedures.

- Related Event
    - An event which resulted from the administration of any of the study procedures.
- Unexpected Adverse Event (UAE)
    - The type of event that is not listed in the protocol as an expected occurrence.
- Unexpected and Related Event
    - An event which meets the definition of both an Unexpected Event and a Related Event.

Expected related events that **do not need to be reported** as an AE / SAE include:

1. Contact bleeding from the nose following a swab, that stops within 15 minutes
2. AEs are commonly encountered in participants having blood tests however blood testing is usually well tolerated. The most common adverse event is an individual feeling faint, during phlebotomy. Facilities, including a bed on which to lie, will be available to mitigate this if required. Sometimes there is bruising at the puncture site. This is a common adverse event and so will not be recorded or reported.

Reporting Procedure

Events defined as serious and related to the study or death from any cause require reporting as an SAE and should be reported on an online SAE Form. When completing the form, the Principal Investigator or named delegate will be asked to define the causality and the severity of the SAE. On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form.

A copy of the completed, signed and dated SAE form, will then be sent automatically to the Study Team via the REDCap database, for the attention of the Research Coordinator as soon as possible and no later than 24 hours after first becoming aware of the event:

CONTACT DETAILS FOR SAE REPORTING

Research Coordinator- Hollie Wagg
Study mailbox: STRAVINSKY@CONTACTS.BHAM.AC.UK
Study Contact number: 0121 3715339
Address: Institute of Translational Medicine, Heritage Building, Mindelsohn Way, Birmingham B15 2TH

On receipt, the Study Office will allocate each SAE a unique reference number. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE.
For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Study Team and a copy kept in the ISF. Investigators should also report SAEs to their own Trust in accordance with local practice.
Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form.
On receipt of an SAE Form relatedness and expectedness will be assessed by the Chief Investigator or named delegate. An SAE judged by the Chief Investigator to have a reasonable causal relationship with the study procedure will be regarded as a related SAE. If the event is unexpected (i.e. is not defined in the Protocol) it will be classified as an unexpected and related SAE.

9.0 Laboratory investigations, processing and procedures

The details of sample transfer, laboratory processing, sampling, and testing will be described in the laboratory manual. In short:

9.1 Anti-spike antibody testing

Antibodies will be tested using the Roche spike IgG quantitative assay (Birmingham). The assay detects anti-spike antibodies against the original Wuhan strain and so is suitable for detecting vaccine responses in a quantitative way. It will also detect antibodies following infection and cannot distinguish between these. It will be the primary platform to be used for all participants as it is already in widespread use by PHE and in the NHS. The Roche assay has been validated in Birmingham for DBS and shows excellent correlation and concordance with serum in providing a quantitative result. This remote sampling has been widely used for COVAD and other COVID-19 studies (PANORAMIC, COVIDENCE). To ensure applicability, the Roche assay performance will be compared with other platforms in use in the NHS using World Health Organisation (WHO) reference serum. This assay can be used to assess blood and mucosal samples.

9.2 Additional antibody testing

Although the primary test is the Roche assay we will also further characterise the antibody response in other exploratory assays. These may include examining nucleocapsid antibodies assay, which can detect antibodies against a protein found within the SARS-CoV-2 virus which enables detection of a response to infection rather than vaccination, antibody being against other variants of concern and neutralisation ability (Oxford) and binding avidity (Southampton). These tests may be applied to the mucosal samples as well as the blood samples.

9.3 Antigen specific T-cell response

Antigen-specific T-cell responses will be explored. Testing will include the key laboratory assay used is an established and standardised IFNγ ELISpot assay (Oxford, Southampton), and through other immunologic assays.

9.4 Sample Storage

Samples will be processed at Birmingham, Southampton, Oxford, and Imperial. To reduce transfer of samples they will remain within the processing laboratory according to the Health and Safety Executive (HES) license. Samples will be transferred between the laboratories for analysis during the study. The Clinical Immunology Service at the University of Birmingham is an ISO15189 UKAS accredited laboratory and will then centralise and store any remaining samples for the remainder of the study. Samples will be retained for 3years following completion of the study to enable repeat

testing or for other ethically approved studies. This includes acellular and cellular material. At the end of this time samples will be stored in a licensed tissue bank. Samples will be labelled with the participants unique study identification, year of birth and initials; laboratory staff will be unable to identify participants from this information. Only authorised personnel will have access to the REDCap.

Samples will be processed at Birmingham, Southampton, Oxford, and Imperial. To reduce transfer of samples they will remain within the processing laboratory according to the Health and Safety Executive (HES) license. Samples will be transferred between the laboratories for analysis during the study. Samples will be retained for 3 years following completion of the study to enable repeat testing or for other ethically approved studies. This includes acellular and cellular material. At the end of this time samples will be stored in a licensed tissue bank. Samples will be labelled with the participants unique study identification, year of birth and initials; laboratory staff will be unable to identify participants from this information. Only authorised personnel will have access to the REDCap.

All freezers used in this study will be monitored for temperature controlled. Freezers are in rooms that require passcard or passcode access which is only granted to relevant members of the team. Storage of the samples will be pseudo-anonymised using three identifiers: by trial sample number, initials, and year of birth. This record will be kept at each laboratory information management system. Samples will be identified by barcodes generated within the laboratory and linked to the pseudo-anonymised record. Samples will be stored for up to 10 years in the so that repeat or further testing can be performed.

Participants will be given the option whether their samples can then be used in the future, in an anonymous way, for other research projects. They will be specifically asked whether their anonymized data and samples can be used in other ethically approved research studies. We would also ask, when the study storage period ends, whether in the future the sample could be donated to other licensed biobanks for long term storage of samples to be used in future studies.

9.5 Adverse event planning in the laboratory

The majority of samples will be processed and tested in the Clinical Immunology Service (CIS) at the University of Birmingham. The CIS provides NHS services to the NHS and has been accredited by UKAS. The governance process used for research in the CIS conforms with UKAS standards. Adverse events in the laboratory will be addressed according to the quality manual and accredited standard operating procedures. A STRAVINSKY laboratory manual will be used to ensure standardised procedures across all 4 laboratories.

Loss or damage to sample or samples not provided with 3 identifiers will be rejected and reported as a study violation. As with an NHS sample, the clinician or the PI will be contacted and if appropriate (timing of sample may make repeat request inappropriate) the participant will be contacted to explain and offer another appointment if they would be prepared to offer a further sample.

10.0 Withdrawals and loss to follow-up

Participants will be aware when they consent to this study that they will be free to withdraw at any time. Participants will be encouraged to complete the study, but they do not need to offer a reason for the withdrawal. If participants are lost to follow up, their samples and data will be included in further analysis. If the participant withdraws, their samples which have already been collected will be included in the study unless it is specified by the participant that they would like their samples destroyed and data removed. If this is the case, there will be a note applied to the study file to confirm

the witnessed removal of these samples and data. In the consent form we have clarified that it may not be possible to remove anonymised data and samples once analysis has begun but we will endeavour to do this as far as possible if requested.

11.0 Statistics and analysis plan

Please see **APPENDIX 3** for the statistical analysis plan.

12.0 Data management and participant confidentiality

Personal data collected during the study will be handled and stored in accordance with the 2018 Data Protection Act.

All essential documentation and study records will be stored on the secure REDCap database by the Study Team in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel including sponsor representatives and regulatory authorities.

All samples will be pseudonymised and identifiable by study number, initial and date of collection to enable a 3-point identifier to ensure the correct sample is being used (standard good laboratory practice). When samples are transferred, they will be transferred in this pseudo anonymised way. Should the samples be used for other ethically approved studies, the link will be broken and will be transferred (with data if approved by ethics) in a fully anonymised way.

We acknowledge that sometimes electronic devices fail and so the study will also accept paper consent, clinical records, and registration to occur. These will be scanned, or the information uploaded to the REDCap database as soon as practicable. Once the records have been confirmed as uploaded the paper copies will be destroyed.

To safeguard rights, the study team will use the minimum personally identifiable information possible. If a participant withdraws from the study, we will keep the information about the participant that we have already obtained unless specifically asked to delete.

13.0 Study organisation

Leadership team: The study is co-led by Professor Alex Richter and Professor Sean Lim. In addition, the leadership study team includes Dr Michelle Willicombe, Professor Eleanor Barnes and Dr Beth Stuart (Statistician).

Together with the leadership team, the study will be managed by the Research First Team at the University of Birmingham Institute of Translational Medicine. The Leadership team and management team will hold study meetings will be held once a month to unite the laboratory and clinical research study members to ensure that the study is running smoothly. These meetings will also inform updates on participant recruitment, standard operating procedures (clinical and laboratory), as well as laboratory updates (sample turnover, etc.).

A Trial Steering Committee (TSC) which will include the leadership team, the Research First team, a patient representative, a representative from the British Society of Immunology (BSI) and at minimum, 3 participating site members. A TSC meeting will take place every 6 months.

The BSI will also manage the study Stakeholder Group. Membership will comprise key contacts from industry, policy, communications and professional and/or patient organisations. The PPI Panel will feed into and be represented on the stakeholder group. The Stakeholder Group will be responsible for providing independent advice to the study management team on the study's strategy and progress, monitoring emerging trends and assisting with information dissemination and links to key contacts in the related spheres. The Group would meet twice a year, one online and once in-person at the annual network meeting.

14.0 Ethical conduct

The study will be conducted in accordance with the principles of good clinical practice (GCP) that have their origin in the Declaration of Helsinki and are consistent with the UK Policy Framework for Health and Social Care Research. These principles protect and promote the interests of patients, service users and the public in health and social care research, by describing ethical conduct and proportionate, assurance-based management of health and social care research, to support and facilitate high-quality research in the UK that has the confidence of patients, service users and the public.

It is for organisations and individuals that have responsibilities for health and social care research. This includes funders, sponsors, researchers and their employers, research sites and care providers.
All investigators within the UK and trial site staff will comply with the requirements of the GDPR and Data protection Act 2018 with respect to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

The Chief Investigators or representative will send Annual Progress Reports to the Main REC and the Sponsor and report any serious breaches of the study protocol/research governance within 7 days. Any substantial amendments to the research will be submitted to the Main REC and the Sponsor before implementation and copied to the R&D, except in the case of urgent safety measures which may be taken without prior approval.

15.0 Indemnity and sponsorship

The study is being run by the University of Birmingham. The University of Birmingham will act as Sponsor.
The University of Birmingham has in place Clinical Trials indemnity coverage which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the study at Site and other clinical care of the patient, responsibility remains with the NHS organisation responsible for the clinical site and is therefore indemnified through NHS Resolution. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation. The NHS have a duty of care to participants whether or not the participant is taking part in research.

16.0 Research governance

Dr Birgit Whitman (Head of Research Governance and Ethics Manager) from the University of Birmingham will act as Sponsor Representative on behalf of The University of Birmingham (Sponsor).

16.1 End of Study

Participants will continue within the study until it formally closes and funding ends (currently April 2025), however, we will ask to contact participants to request their continuing enrolment should the study be extended.

It is anticipated that the study will need to remain open to complete analysis and to repeat testing where necessary for a year following this time and so the study end date is currently April 2027.

If a participant withdraws from study due to his/her own reasons, they will be asked if any samples collected up until can continue to be used as per the original consent for this current study and/or future research. It will be clarified whether the samples can be used for research purposes if the study period is extended and whether they would like to be contacted if this is the case.

The study will be stopped prematurely if:

- Mandated by the Ethics Committee
- Funding for the study ceases

The Ethics Committee and Sponsor will be notified in writing if the study has been concluded or terminated early.

16.2 Financial Support

The study is funded for 2 years from February 2023 by the NIHR Reference NIHR135830.

17.0 Patient and public involvement

The BSI will recruit a Patient and Public Involvement (PPI) panel comprising people with lived experience of different medical conditions that are defined by the participant eligibility criteria of the study. We will ensure the panel comprises diverse ages, ethnicities, a gender balance, represent different disease groups and fair geographical spread. This will be achieved by actively reaching out to patient community groups through supporting charities and networks to ask for expression of interest from people with lived experience. We already have expressions of interest from individuals that meet these criteria from when we set up the pre-grant focus group and are in close liaison with the patient group organisations linked to the conditions we are studying. Individuals who have expressed an interest have lived experience and also PPI experience working with a number of COVID-19 projects. These will include, but is not limited to, people with immunodeficiencies, blood cancer, taking immunosuppressant therapies, chronic organ damage, solid organ transplants and individuals with diabetes.

The PPI panel will meet virtually with the lead investigators right from the start of the project to provide feedback and input into the research protocol and priorities to ensure the voice of people with lived experience is included in all facets of the study. This was discussed in the original focus group and the preference would be to meet virtually as many patients are continuing to practice some form of social distancing and so travel and group meetings are not appealing. The panel will continue to meet regularly with the scientists involved in the study to provide their perspective on the ongoing research and outcomes and how to communicate results to the public.

19.0 Dissemination and publication

This urgent research is relevant to the general public and all health care professionals. We will aim to publish as soon as data is available due to urgent clinical and occupational need. Our engagement strategy is three pronged:

Patient engagement: This is a unique population where many are continuing to practice social distancing as highlighted by our grant focus group. We will make it a priority at the first PPI panel meeting to discuss this, particularly with those with lived experience, and how as a community we can best communicate and engage with the immune vulnerable cohorts. In addition, we are working with all the key patient groups and would hope to support or be part of any online or in-person events that they are arranging. Patients will be invited to our in-person stakeholder meetings but will be given the option to attend remotely as well. All the clinicians in this study support patient days and local engagement activities and will use these added value opportunities for STRAVINSKY engagement activities. We will hold in-person local events at the research sites (e.g., a public lecture in Birmingham) if our target audience show enthusiasm for this.

Stakeholder engagement: There will be 2 face-to-face stakeholder meetings that are being arranged by the BSI. These planned and costed events will enable patients, industry, government, and academics to meet in-person to set the agenda for this study and interpret and communicate its findings. In addition to this, the PIs already contribute to other national advisory groups and industry meetings and will therefore use these in-person opportunities to be ambassadors for STRAVINSKY. For wider engagement on the project, we will engage with news media, including TV, radio, and print. As well as utilising local university press offices and networks, we have particularly strong links to the national health news media through the British Society for Immunology and our links to the Science Media Centre. We will use their extensive experience of communication in this area to ensure we reach out through different media to communicate our message and our findings with diverse groups.

Clinician engagement: The leadership team for this study come from multiple specialties and attend a wide range of academic conferences. As a result, there will be face to face presentation of key academic outputs from STRAVINSKY to national and international meetings. These would be attended by the individual for their CPD and so have not been specifically costed into this study. Academic meetings also provide the opportunity to meet with industry and patient organisations in-person and we will use these opportunities to arrange specialty specific meetings.

20.0 References

1. Agrawal U, Bedston S, McCowan C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet* 2022; **400**(10360): 1305-20.
2. Whitaker HJ, Tsang RSM, Byford R, et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response amongst individuals in clinical risk groups. *J Infect* 2022; **84**(5): 675-83.
3. Lim SH, Stuart B, Joseph-Pietras D, et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UK PROSECO study. *Nat Cancer* 2022; **3**(5): 552-64.
4. Hippisley-Cox J, Khunti K, Sheikh A, Nguyen-Van-Tam JS, Coupland CA. QCovid 4 - Predicting risk of death or hospitalisation from COVID-19 in adults testing positive for SARS-CoV-2 infection during the Omicron wave in England. *medRxiv* 2022.
5. DHSC. Higher-risk patients eligible for COVID-19 treatments: independent advisory group report. 2022. https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report (accessed 20 December 2022 2022).

21.0 Appendix 1 Treatment categories

The following medications will be considered as B-cell depleting treatment (group 17) for the purpose of this study.

B-CELL DEPLETING TREATMENT
Any monoclonal antibody against CD20, e.g.
Rituximab
Obinutuzumab
Ocrelizumab
Ofatumumab
Any bispecific antibody against CD20, e.g.
Mosunetuzumab
Epcoritamab
Glofitamab
Odronextamab
Chimeric antigen receptor (CAR-T) therapy directed against CD19, CD20, e.g.
Tisagenlecleucel
Axicabtagene Ciloleucel
Others
Alemtuzumab
ATG

The following medications will be considered as either chemotherapy, immunotherapy, or immunosuppressive medication for the purpose of this study (groups 18 & 20).

MEDICATIONS	**CATEGORY OF MEDICATIONS**
6-Mercaptopurine (6-MP)	Anti-metabolites
Abatacept	Biologic - Immune checkpoint
Abemaciclib	Biologic therapy - Other (Protein Kinase Inhibitor)
Acalabrutinib	B-cell targeted (BTK inhibitors)
Adalimumab	Biologic - Anti TNF

Afatinib	Biologic therapy - Other (Protein Kinase inhibitor)
Apremilast	Biologic - Other (PDE4 Inhibitor)
Aromatase inhibitors	Hormonal therapies
Atezolizumab	Biologic therapy - Other (Checkpoint inhibitor)
ATG	Biologic - polyclonal antibody against immune cells
Azacitidine	Cytotoxic Chemotherapy
Azathioprine	Anti-metabolites
Baricitinib	JAK inhibitor
Beclomethasone	Corticosteroids
Betamethasone	Corticosteroids
Bortezomib	Biologic therapy other
Bosutinib	Biologic - Other (BCR-ABL inhibitor)
Brentuximab	Biologic - Other (Anti CD30)
Capecitabine	Cytotoxic chemotherapy
Carboplatin	Cytotoxic chemotherapy
Certolizumab	Biologic - Anti TNF
Cisplatin	Cytotoxic chemotherapy
Cortisone	Corticosteroids
Crenolanib	Biologic - Other
Cyclophosphamide	Cytotoxic chemotherapy
Cyclosporine	Calcineurin inhibitor
Cytarabine	Cytotoxic chemotherapy
Daratumumab	B-cell targeted (anti-CD38)
Dasatinib	Biologic - Other (BCR-ABL inhibitor)
Daunorubicin	Cytotoxic chemotherapy
Decitabine	Cytotoxic Chemotherapy
Dexamethasone	Corticosteroids
Docetaxel	Cytotoxic chemotherapy
Doxorubicin	Cytotoxic chemotherapy
Durvalumab	Biologic therapy - Other (Checkpoint inhibitor)
Elotuzumab	B-cell targeted (other)
Epirubicin	Cytotoxic chemotherapy
Etanercept	Biologic - Anti TNF
Etoposide	Cytotoxic chemotherapy
Everolimus	Biologic therapy other
Fludarabine	Cytotoxic chemotherapy
Fluorouracil	Cytotoxic chemotherapy
Fulvestrant	Hormonal therapies
Gefitinib	Biologic therapy - Other (Protein Kinase inhibitor)
Gemcitabine	Cytotoxic chemotherapy
Gemtuzumab ozogamicin	Biologic therapy other
Gilteritinib	Biologic - Other
Golimumab	Biologic - Anti TNF
Guselkumab	Biologic - Other (Anti IL23)
Hydrocortisone	Corticosteroids
Ibrutinib	B-cell targeted (BTK inhibitors)
Idarubicin	Cytotoxic chemotherapy
Imatinib	Biologic - Other (BCR-ABL inhibitor)
Infliximab	Biologic - Anti TNF

Isatuximab	B-cell targeted (anti-CD38)
Ixekizumab	Biologic - Other (Anti IL17A)
Leflunomide	DMARDs - Other
Lenalidomide	Cytotoxic chemotherapy
Lestaurtinib	Biologic - Other
Melphalan	Cytotoxic chemotherapy
Methotrexate	DMARDs - Methotrexate
Methotrexate	DMARDs - Methotrexate
Methylprednisolone	Corticosteroids
Midostaurin	Biologic - Other
Mitoxantrone	Cytotoxic chemotherapy
Mycophenolate mofetil	Anti-metabolites
Nab-paclitaxel	Cytotoxic chemotherapy
Neratinib	Biologic therapy - Other (Protein Kinase inhibitor)
Nilotinib	Biologic - Other (BCR-ABL inhibitor)
Olaparib	Cytotoxic chemotherapy
Paclitaxel	Cytotoxic chemotherapy
Palbociclib	Biologic therapy - Other (Protein Kinase Inhibitor)
Pembrolizumab	Biologic therapy - Other (Checkpoint inhibitor)
Pertuzumab	Biologic therapy - Other (Protein Kinase Inhibitor)
Pomalidomide	Biologic therapy other
Ponatinib	Biologic - Other (BCR-ABL inhibitor)
Prednisolone	Corticosteroids
Quizartinib	Biologic - Other
Ribociclib	Biologic therapy - Other (Protein Kinase Inhibitor)
Ruxolitinib	Biologic - JAK inhibitor
Sarilumab	Biologic - Other (Anti IL6)
Secukinumab	Biologic - Other (Anti IL17A)
Sirolimus	Biologic therapy other
Sorafinib	Biologic - Other
Sulphasalazine	Non-myelosuppressive therapy
Tacrolimus	Calcineurin inhibitor
Tamoxifen	Hormonal therapies
Thalidomide	Biologic therapy other
Tocilizumab	Biologic - Other (Anti IL6)
Tofacitinib	JAK inhibitor
Toremifene	Hormonal therapies
Trastuzumab	Biologic therapy - Other (Protein Kinase Inhibitor)
Triamcinolone	Corticosteroids
Upadacitinib	JAK inhibitor
Ustekinumab	Biologic - Anti IL23
Vedolizumab	Biologic - α4β7 inhibitor
Vemurafenib	Biologic therapy - Other (Protein Kinase Inhibitor)
Venetoclax	B-cell targeted (BTK inhibitors)
Vinblastine	Cytotoxic chemotherapy
Vincristine	Cytotoxic chemotherapy
Vinorelbine	Cytotoxic chemotherapy

22.0 Appendix 2 Visit Summary

Timing	VISIT	Checklist	Responsibility (Local Study Team (L) or Central Study Team (C) or Participant (P))	
			Remote Cohort	In-person cohort
	PARTICIPANT IDENTIFICATION	Offer PIS	**L**	**L**
	SCREENING*	1) Informed Consent	**P with L assistance if needed.**	**P with L assistance if needed.**
		2) Check and confirm eligibility	**P**	**P**
		3) Trial registration onto REDCap	**C / L**	**C / L**
		4) Supply participants with Central Study Team contact details	**C / L**	**C / L**
As soon as possible after consent	**VISIT 1**	1) Complete online CRF	**L**	**L**
		2) Blood sampling	**P**	**L**
		3) Nasal swab COVID-19 test kit	**Provided by C, returned by P**	**Provided by C, returned by P**
		4) Antibody or swab result reported to patient	**C**	**C**
Remote cohort: Ideally 1 week before booster vaccine In-person cohort: As above, but this visit can be omitted if it is less than 12 weeks after VISIT 1	**VISIT 2**	1) Complete online CRF	**P with L assistance if needed.**	**L**
		2) Blood sampling	**P**	**L**
4-10 weeks post booster vaccine	**VISIT 3**	1) Complete online CRF	**P with L assistance if needed.**	**L**
		2) Blood sampling	**P**	**L**
24-36 weeks post booster vaccine	**VISIT 4**	1) Complete online CRF	**P with L assistance if needed.**	**L**
		2) Blood sampling	**P**	**L**
Anytime during study	**ANYTIME**	1. Participant to inform Central Study	**P**	**P**

		Team if they have a COVID-19 infection 2. Return of nasal swab to be repeated 2 weekly till negative	**Provided by C, returned by P**	**Provided by C, returned by P**

*Individuals who self identifies for participation AND who are not registered with one of the participating sites will have their screening activities managed by the Central Study Team

23.0 Appendix 3 Statistical analysis plan

Sample size and randomisation

We have assumed that a sample size of 3000 is feasible and that this is likely to be distributed as 750 in the "low response/no response" group and 2250 in the "normal response" group. We might then wish to estimate what difference between these two groups we could detect with 90% power. We have good estimates from previous studies over time in vulnerable populations and have therefore considered a range of infection and hospitalisation rates that might be plausible for this group. We have also considered the statistically most conservative option by setting the proportion at 50%.

In all cases, we can detect an absolute difference between groups of less than 10% and often less than 5% even for the rarer outcome of hospitalisation. These are consistent with a standardised effect sizes ranging from 0.15 to 0.36 for infection, which are consistent with small to moderate effects. The effect size for hospitalisation is less certain and ranges from 0.24 consistent with a small effect through to 1.33, a very large effect.

We consider this reassuring as it indicates that for a wide range of scenarios, we should have adequate power in the whole cohort for our primary outcome of infection and we may have power to detect a moderate effect for the rarer secondary outcome of hospitalisation, depending on the prevailing population rates and the variant of interest.

We will monitor all the assumptions that underlie these calculations at least monthly and will discuss monthly at our Trial Meeting Groups, if there are any concerns about power for key analyses.

Randomisation procedure
This is an observational cohort and participants will not be randomised. The cohort may be used in future to recruit to randomised trials and the process for selection and randomisation would be described accordingly in the associated trial protocol.

Statistical analysis considerations

Definition of analysis populations
CV groups are defined below and are derived in part from the QCOVID4 risk groups.

The Healthy Control (HC) group represent a population sampled from the PITCH Study (Protective immunity from T-cells in healthcare workers).

Baseline characteristics
At baseline the following characteristics will be described for the study cohort:

- Demographics (Age, BMI, self-reported ethnicity, sex, Index of Multiple Deprivation)
- Occupation, nature of work and type of personal protective equipment used during that work
- Medical conditions (self- reported)
- Iatrogenic immunosuppression (or within 6 months of iatrogenic immunosuppression including chemotherapy)
- Vaccination history including COVID-19, influenza, and any test vaccines given
- Known prior infection

Behavioural variables

If the participant self-isolated as a result of an illness in a household contact, we will collect data on the nature of that illness (when was illness, symptoms, severity, duration) and how many other household contacts were unwell.

Serological response

Time points for serological measurements: Assessment at 4 timepoints (Visit 1: baseline visit, Visit 2: before next vaccine dose, visit 3: 4 weeks post vaccine dose and Visit 4: 24-36 weeks post vaccine).

ii) 'Low' antibody range: Antibody values which lie within the lower 10^{th} percentile of range of IgG antibody concentrations in HC following vaccine dose.

General analysis principles

- Summary statistics will include either mean, standard deviation, and/or median, interquartile range for continuous variables as appropriate to the distribution and n (%) for frequencies.
- The amount of missing data will be reported. Analysis will be of complete data and missing data will not be imputed.
- 5% two-sided level of statistical significance, with corresponding 95% confidence intervals presented where applicable.
- No adjustments for multiplicity are planned.

Planned analyses and reporting:

Primary Outcome

To assess the additive value of serological responses to CV status in predicting infection
The binary infection outcome will be captured by recording the timing and incidence rates of all infections from ≥14 days post vaccination given between Visit 2 until Visit 4 will be reported in the total combined CV groups, and by individual CV groups. We will describe the number and proportion of infections for each level of antibody response post-V3 (no, low, normal)

The primary analysis will be undertaken using a logistic regression model with infection as the outcome and antibody response post-V3 as a binary variable as the exposure. We will present odds ratios with 95% confidence intervals for the unadjusted model, as well as for a model adjusted for the baseline and behavioural variables as well as any COVID-19 therapy received in the community, pre-admission and in hospital (where data available).

Assuming serology is predictive of outcome, we will build a model to explore the predictive value of key patient data and the added value of serological results. We will explore the discrimination and calibration of a model only including baseline and behavioural variables compared to this model also including serological response. Discrimination will be determined by Harrell's C statistic and calibration will be determined by the predicted probabilities for infection. It is not possible to externally validate this model in this study; instead 1000 bootstrapped samples will be used in determining the 95% confidence intervals for the C statistic.

As a sensitivity analysis we will also consider serological response as a continuous variable. We will also consider time to first infection as a time to event outcome with death as a competing risk. This will be implemented in Stata using the *stcrreg* command. The same covariates will be included in the adjusted model as for the primary analysis. Unadjusted and adjusted analyses will present hazard ratios with 95% confidence intervals.

To assess the additive value of serological responses to CV status in predicting severe outcome
We will undertake an analysis using the same modelling approach as for the primary outcome but with a composite outcome of severe infection (infection, hospitalisation or death).

Secondary Outcomes

To evaluate the serological vaccine responses of CV patients to new vaccines
28-day post vaccine (Visit 3) IgG antibody levels (BAU/ml) will be reported in HC and CV individuals.
The proportion of combined and individual CV groups with no, low or normal Visit 3 antibody levels will be reported.
The median (IQR) of Visit 3 antibody levels in each CV group will be reported, alongside the values for HC.
Logistic regression models will be used to assess factors that contribute to serological response as a binary outcome with normal compared to lack of response (no/low). The model will include the baseline variables set out in **Section 5.2** and further variables may be added to the model if evidence emerges that such variable impacts on vaccine responses to vaccines. Univariable logistic regression will be used to explore the unadjusted relationship of each variable with the outcome and multivariable logistic regression will be used to explore the independent relationship of each variable with the outcome. We will report odds ratios and 95% confidence intervals for all models.

To assess serological responses, antibody boosting, antibody waning and correlation with infection

The above analyses focus primarily on Visit 3 (4 weeks post vaccine booster). Similar analysis will be performed from antibody status at time point Visit 1, with adjustment required for time post-vaccine to Visit 1, and also vaccine type pre-Visit 1 (Wuhan or bivalent vaccine). Infection outcomes will be described up until Visit 2. Assessment of waning (rate of antibody concentration decline) will also be described between Visit 1 and Visit 2. Assessing differences between HC versus CV group, but also individual groups. Similar waning analysis will be reported between Visit 3 and Visit 4.
Descriptive changes in antibody levels between Visit 3 and Visit 4 by CV groups will also be reported.

Antibody binding to VOC

This analysis will be focused on samples derived from Visit 1 and at subsequent follow up points, assuming this will capture most diversity in VOC during the study duration. Antibody binding to SARS-CoV-2 WT will be compared against binding to the dominant VOCs in participants with detectable antibodies and reported as fold-change (e.g. VOC/WT) and absolute change.

Subgroup analyses

We will present the number and proportion of patients with adequate and inadequate antibody response in each disease subgroup. We will also present the number and proportion in each of these groups with COVID-19 infection and COVID-19 related hospitalisation. Provided there are sufficient numbers in each group, we will undertake exploratory analyses using the same approach as for the analysis of the primary outcome in the full cohort.

Exploratory Analyses

Evaluation of QCOVID4 risk score

i) Is the QCOVID4 score associated severe COVID-19 in our cohort? (low/med/high and quantitative analysis)

For all participants, we will calculate the QCOVID risk score and explore whether this is associated with adverse outcome in this cohort. QCOVID was derived for hospitalisation and death as an outcome so we will explore this relationship in the first instance. However, we will also test whether QCOVID is valid for predicting our primary outcome of infection. The key outcomes in our cohort are binary so logistic regression will be used, with QCOVID risk score as the exposure variable. In line with the common protocol published for validation of the QCOVID algorithm (Kerr et al BMJ Open 2022) (but using the latest QCOVID4 score), Harrell's C statistic will be used to determine model discrimination and predicted probabilities of outcomes will be used to determine model calibration.

ii) Is the QCOVID4 score associated with anti-S titres in our cohort? (low/med/high and quantitative analysis)

We will quantify the relationship between QCOVID4 risk score and the anti-S titres using Pearson or Spearman's correlation, as appropriate to the distribution. We will also summarise the mean QCOVID score for each group of antibody results (none, low, normal) and use ANOVA to test for between group differences.

iii) Is the QCOVID4 score associated with T-cell responses in our cohort? (positive/negative and quantitative)

We will undertake the same analyses described in ii above for T-cell responses in relation to QCOVID4 risk score.

iv) Does the addition of serology measurements enhance QCOVID4 score?

If QCOVID4 score shows good model discrimination and calibration with respect to adverse outcome or infection in our cohort, we will explore whether serology measurements improve the model. Serology measurements will be added to the logistic regression model and model fit diagnostics produced as per the common protocol (see i above). We will test these nested models to determine whether serology measurements significantly improve the model.

B) Identify additional laboratory methods to predict COVID-19 infection/hospitalisation if antibody testing fails to predict relevant clinical outcomes

Peripheral blood (and mucosal) samples will be stored, so that alternative assays can be performed to look for correlates of protection should blood anti-S IgG fail to stratify for COVID-19 risk. These will include:□□□□□□□

i) Antigen-specific T-cell response e.g. through IFNγ ELISpot (Oxford, Southampton)
ii) Functional antibody assays e.g. live virus neutralisation and others (Oxford, Southampton)□□□
iii) Mucosal secretion serology on the MSD platform to monitor mucosal immunity (Birmingham)□□
IgG and IgA quantification on samples from Visit 2 and Visit 3. Logistic regression analysis will be used to study the association between mucosal antibody titres and serum/plasma antibody titres, infection episodes and hospitalisation.

Descriptive analysis of these assays will be performed, statistical assessment will include, but will not be limited, to the following analyses:

C) To evaluate cellular responses to new vaccines in CV patients
28-day post vaccine (Visit 3) T-cell responses will be reported in HC and 400 CV individuals, as a binary value of present or absent.
The proportion of combined total and individual CV groups with present or absent T-cell responses will be reported.
The median (IQR) of T-cell responses (per 10^6 PBMCs) will be reported in HC and 400 CV individuals.
Multiple regression models will be fit to assess response, the following variables have been highlighted for inclusion in the model, using in the variables described in the serological models.
Pearson's Correlation or Spearman's Rank, as appropriate to the distribution. will be used to quantify the correlation between serological and cellular responses, in individual CV groups and combined group.

D) To evaluate cellular responses to new VOCs in CV patients
IFN□ reactivity in T-cells to variant spike peptides and compare this against reactivity to WT spike and expressed as fold change and absolute values for 2 time points 12 months apart.

24.0 Appendix 4 Abbreviations

In full	Abbreviation
Adverse event	AE
Association of the British Pharmaceutical Industry	ABPI
British Society of Immunology	BSI
Case report form	CRF
Chronic Kidney Disease	CKD
Clinical Immunology Service	CIS
Coronavirus disease-2019	COVID-19
Clinically Vulnerable	CV
Dried Blood Spot	DBS
Estimated Glomerular Filtration rate	eGFR
Good Clinical Practice	GCP
Haematopoietic stem cell transplant	HSCT
Health care workers	HCW
Human Immunodeficiency Virus	HIV
Monoclonal gammopathy of undetermined significance	MGUS
Myelodysplastic syndrome	MDS
Myeloproliferative neoplasms	MPN
Nucleocapsid	N
Patient and Public Involvement	PPI
Research Ethics Committee	REC
Serious Adverse Events	SAEs
Severe acute respiratory syndrome coronavirus 2	SARS-CoV-2
Solid organ transplant	SOT
Spike	S
Trial Steering Committee	TSC
University of Birmingham	UoB
Variant of Concern	VOC

25.0 Appendix 5 Covid Severity Score

Patient Status	WHO	Proposed severity score for STRAVINKSY for infection out of hospital		Proposed severity sco acquired infection
	WHO description	STRAVINSKY description	Score	
Uninfected	Uninfected		0	0
Ambulatory mild disease	Asymptomatic, viral RNA detected	Asymptomatic	1	Asymptomatic
	Symptomatic independent	Mild symptoms, no need for bedrest or assistance	2	Mild symptoms, no as
	Symptomatic, assistance needed	Symptoms that require bedrest or assistance	3	Symptoms that requir oxygen
Hospitalised moderate disease	Hospitalised, no oxygen therapy	Hospitalised, admitted for COVID, no oxygen**	4	Symptoms that requir oxygen
	Hospitalised oxygen by mask or nasal prongs	Hospitalised, admitted for COVID and required oxygen	5	Oxygen required for s
Hospitalised severe disease	Hospitalised, oxygen by NIV or high flow	Hospitalised, admitted for COVID and required oxygen	5	Oxygen required for s
	Intubation and mechanical ventilation $pO_2/FI0^2$>150 or $SpO_2/FI0^2$>200	Hospitalised on ITU for COVID	6	Transferred to ITU fo
	mechanical ventilation $pO_2/FI0^2$<150 or $SpO_2/FI0^2$<200 or vasopressors	Hospitalised on ITU for COVID	6	Transferred to ITU fo
	mechanical ventilation $pO_2/FI0^2$<150 and vasopressors, dialysis or ECMO	Hospitalised on ITU for COVID	6	Transferred to ITU fo
Dead	Dead	Dead	7	Dead

WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Follow up STRAVINSKY- Remote Patients

With the autumn 2023 booster vaccinations underway, we anticipate patients recruited into the STRAVINSKY study will now fall into the 3 categories below. *This may change again, pending government decisions on vaccinations, all changes will be communicated to sites before they are implemented in the database.*

Recruitment PRIOR to autumn 2023 booster AND if a participant is going to have an autumn 2023 vaccine AND has not yet had Autumn 2023 booster

Click **"YES"** to planning to have autumn 2023 booster on REDCap

Central Team will send two DBS cards with instructions for patient to return the second DBS card 28 days after autumn vaccination.
Local team – please reiterate temporal instructions to return 2nd DBS 4-10 weeks post vaccination

All patients to have a 3rd DBS, 6 months after the autumn 2023 vaccine date (date from patient access form will be used)

Recruitment after participant has had the autumn 2023 booster

Recruited - central team will send one DBS.
Local team – please reiterate that this should be filled in as soon as possible but a minimum of 28 days and ideally between 4 and 10 weeks post autumn 2023 booster.

All patients to have a 3rd DBS, 6 months after the autumn 2023 vaccine date (date from COVID history form will be used)

Participant chooses not to take up autumn 2023 booster

The above notification is based on most recent vaccination prior to Autumn 2023 and ticks "NO" to planning to have Autumn 2023 booster

Recruited - central team will send one DBS

Central team to send a 2nd DBS, 6 months from recruitment date (date of completed registration form will be used)

Follow up STRAVINSKY- Face to Face Visits

All patient visits due will be set as a notification on the database. If your patient is due to be booked into a clinic, you will receive a reminder two weeks before the due date.

Recruitment PRIOR to autumn 2023 booster AND if a participant is going to have an autumn 2023 vaccine AND has not yet had Autumn 2023 booster.

The above notification is based on most recent vaccination prior to Autumn 2023 and ticks **"YES"** to planning to have Autumn 2023 booster.

Recruited - Study team to take bloods and other tests as per the protocol Visit 1

Study team to arrange another visit 28 day after Autumn vaccination if they have clicked "yes" to having booster in Autumn 2023 Visit 3

All patients to have a Visit 6 months post autumn 2023 vaccine date (from patient access form) Visit 4

Recruitment after participant has had the autumn 2023 booster

Recruited - study team to arrange Visit as soon as possible but a minimum of 28 days and ideally between 4 and 10 weeks post autumn 2023 booster Visit 1*

Visit to be arranged 6 months after autumn 2023 booster (date from COVID history form) Visit 4

Participant is choosing not to take up autumn 2023 booster

The above notification is based on most recent vaccination prior to Autumn 2023 and ticks "NO" to planning to have Autumn 2023 booster

Recruited - Study team to take bloods and other tests as per the protocol Visit 1

Visit to be arranged at 6 months from recruitment date (use date of completed registration form) Visit 4

* Please note that the blood tube requirements for Visit 1 are slightly different to other visits. Regardless of when the participant is recruited, their first attendance or first DBS is considered Visit 1. This will ensure the correct tubes are collected.