A Phase III, Multicentre, Randomised Trial Comparing SARS-CoV-2 Re-Boost Vaccine Strategies in Immunocompromised Patients

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OCTAVE-DUO Trial Protocol

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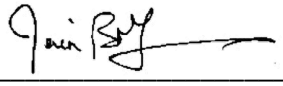
Signature:		Date:	17 / 05 / 2022

This protocol describes the OCTAVE-DUO trial and provides information about procedures for participants taking part in the trial.

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.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA-01	21-Jul-2021	3.0	Substantial	An error in the definition of antibody non-response and antibody low response was corrected.
SA-02	04-Oct-2021	4.0	Substantial	Inclusion of a paragraph to state participants should not receive an additional (third) primary dose if invites to do so by the NHS vaccination program.
SA-03		5.0	Substantial	Change to eligibility, for purpose of clarification. Limitation of pregnancy monitoring to participants taking part in the randomised sub-study only. Inclusion of an appendix of equivalent SARS-CoV-2 spike antibody assays measurements. Addition of a screening assessment for SAR-COV-2 spike antibody levels for some disease cohorts. Addition of a separate CAR-T Cell therapy disease cohort. Clarification of the randomisation pathway for lymphoid malignancy patients to make it clear participants can be included in the Main Study randomisation as well as the sub-study randomisation. Other non-substantial amendments including update to contact details, and correction of topographical errors.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA-04		6.0	Substantial	The addition of the Binding Site SAR-COV-2 spike antibody assay as a new approved assay for determining eligibility. The inclusion of justification for the definitions of antibody non-responder and antibody low responder for each CE marked SAR-COV-2 spike antibody approved by the Trial Management Group to determine eligibility. Addition of a clear statement in the protocol that patients can be re-randomised should the Novavax COVID-19 vaccine be unavailable. Non-substantial changes include: the addition of a further interim analysis; inclusion of wording regarding the power of the study if only 800 evaluable patients are recruited; inclusion of wording regarding the screening assessment for SAR-COV-2 spike antibody levels which was missed in error in the last amendment and an organisational name change.

TRIAL SYNOPSIS

Title	OCTAVE-DUO: A Phase III, Multicentre, Randomised Trial Comparing SARS-CoV-2 Re-Boost Vaccine Strategies in Immunocompromised Patients
Trial Design	Phase III, multi-centre, multi-disease, open-label, randomised trial to determine whether a re-boost vaccine strategy can induce an immune response in clinically vulnerable patients with proven inadequate response to SARS-CoV-2 vaccination
Aim	To determine whether a SARS-CoV-2 re-boost vaccination strategy can induce an adequate immune response in clinically vulnerable patient cohorts with proven inadequate response to 2 doses of SARS-CoV-2 vaccine.
Objectives	**Primary Objective** • To determine across a range of immune-mediated/immunosuppressive diseases whether re-vaccination with Pfizer or Moderna vaccines will increase the magnitude of SARS-CoV-2 immune responses in patients with no or low antibodies after two prior vaccine doses. **Secondary Objectives** • In a sub-set of participants with lymphoid malignancies, evaluate the immune response following re-vaccination with Pfizer, Moderna or Novavax vaccines in patients with no or low antibodies after two prior vaccine doses. • To compare the relative change in magnitude of immune responses arising following revaccination with Pfizer, Moderna and Novavax vaccines across different underlying disease states and therapeutic regimens. **Exploratory Objectives** • Evaluate the safety of re-boost with SARS-CoV-2 vaccines in immunocompromised cohorts. • Investigate the mechanistic pathways underpinning vaccine responsiveness in disease/drug clinical states. • To determine whether such immunologic pathway analysis can offer predictive markers of the magnitude or qualitative components of subsequent immune responses following vaccination.
Outcome Measures	**Primary Outcome** **Vaccine-specific Immunogenicity** • Anti-Spike SARS-CoV-2 antibody and T cell responses to SARS-CoV-2 peptides following Pfizer and Moderna re-boost vaccinations will be measured before the re-boost vaccination was given and will be compared with those achieved at day 21 post dose. **Secondary Outcomes** • In a sub-set of participants with lymphoid malignancies, we will measure the change in vaccine specific immunogenicity in response to vaccination (as defined for the primary outcome) with Pfizer, Moderna or Novavax vaccines. • In all patient groups, we will assess the capacity of re-boost vaccine induced SARS-CoV-2 antibodies to neutralise/block SARS-CoV-2 infection using IgG (pseudo)neutralisation assays.

	Exploratory Outcomes **Safety** • A descriptive analysis of the reported adverse events in the participants will be presented. **Cellular Immunogenicity** • The impact of revaccination on T cell subsets and their function across disease groups will be assessed using a range of assays.
Patient Population	Participants with: 1) solid cancer; 2) lymphoid malignancies; 3) immune-mediated rheumatic diseases; 4) end stage kidney disease; 5) chronic liver disease; 6) gastrointestinal disease on immune suppressive therapy; 7) haematopoietic stem cell transplant; 8) primary immunodeficiency; and 9) chimeric antigen receptor (CAR)-T cell therapy who have received the SARS-CoV-2 vaccine as part of the national vaccination programme but have proven inadequate response to SARS-CoV-2 vaccine. Initiation of recruitment into each cohort will be staggered with lymphoid malignancy, immune-mediated rheumatic diseases, end stage kidney, liver, and gastrointestinal disease on immunosuppressive therapy being prioritised in the initial recruitment phase of the trial.
Sample Size	**Total:** Up to 1200 (recruitment targets vary per disease cohort).
Inclusion Criteria	**Inclusion** • Aged ≥18 years. • Have an inadequate response to two doses of SARS-CoV-2 vaccine measured at least 14 days post second vaccine. • Anticipated life expectancy of 6 months or greater. • Fall into one (or more) of the patient cohorts specified above, and meet disease relevant classification, disease state, and staging according to established international standards. • Participant is willing and able to comply with trial requirements. • For the randomised sub-study only, female participants of childbearing potential must be willing to ensure that they or their partner use acceptable effective contraceptive methods until 3 months after re-vaccination. **Exclusion** • Receipt of any vaccine within 30 days before trial entry, with the exception of: a SARS-CoV-2 vaccine which is allowed ≥14 days prior; or a flu vaccination which is allowed ≥7 days prior. • For aggressive B-NHL or Hodgkin lymphoma only, participants on active systemic treatment or within 4 weeks of completion of systemic treatment. • Any known contraindications as specified in the applicable product information including but not limited to: o Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients. o History of anaphylaxis to prior COVID-19 vaccinations, or any component of the vaccine. • In the judgement of the Investigator, the patient is unsuitable to participate in the trial or is unlikely to comply with trial procedures.

	• For the randomised sub-study only, patients who are pregnant or lactating at trial entry or planning to become pregnant within 3 months after re-vaccination.
Blood Sample Collection	Whole blood, serum, plasma, and where possible peripheral blood mononuclear cells (PBMC) will be collected at the following time points: • Pre-re-boost vaccine (baseline) • 21 (+14) days post-booster
Trial Duration	Patients are expected to be recruited over 3 months and followed up for 3 months in accordance with standard clinical practice for the relevant disease cohort.
Contacts	**Sponsor:** University of Birmingham **Chief Investigator:** Professor Iain McInnes, University of Glasgow **OCTAVE-DUO Trial Office:** Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Edgbaston, Birmingham, B15 2TT ✉ OCTAVE-DUO@trials.bham.ac.uk

SCHEDULE OF EVENTS

	Screening	Trial Entry	Baseline *Prior to re-vaccination*	Re-vaccination[1]	Post-re-vaccination[2] *21 days post re-vaccination*	3-month follow-up *Seen in accordance with clinical practice*[3]
Eligibility assessment (including dip stick pregnancy test)	x					
Consent	x					
Measurement of SARS-CoV-2 spike antibody response	(x)[4]					
Randomisation		x				
Re-vaccination				x		
Data collection		x	x		x	x
Assessment of adverse events					x	
Research blood samples[5]			X[6]		x	
Participant Diary Booklet[7]			x		x	

Key

[1] At least 14 days after receipt of the second dose of vaccine

[2] Minimum 21 days + 14 days post re-boost vaccination

[3] Three months after re-vaccination, where possible data collected retrospectively from participants medical records, telephone follow-up permissible

[4] For the solid cancer, haematopoietic stem cell transplant and CAR-T cell therapy disease cohorts only: where a result is not available from a previous study or antibodies levels are not available from disease site specific clinics, SARS-CoV-2 spike antibody response can be measured as a screening assessment using one of the assays listed in Appendix 1

[5] Research blood samples include: Whole blood, serum, plasma, and where possible peripheral blood mononuclear cells (PBMC)

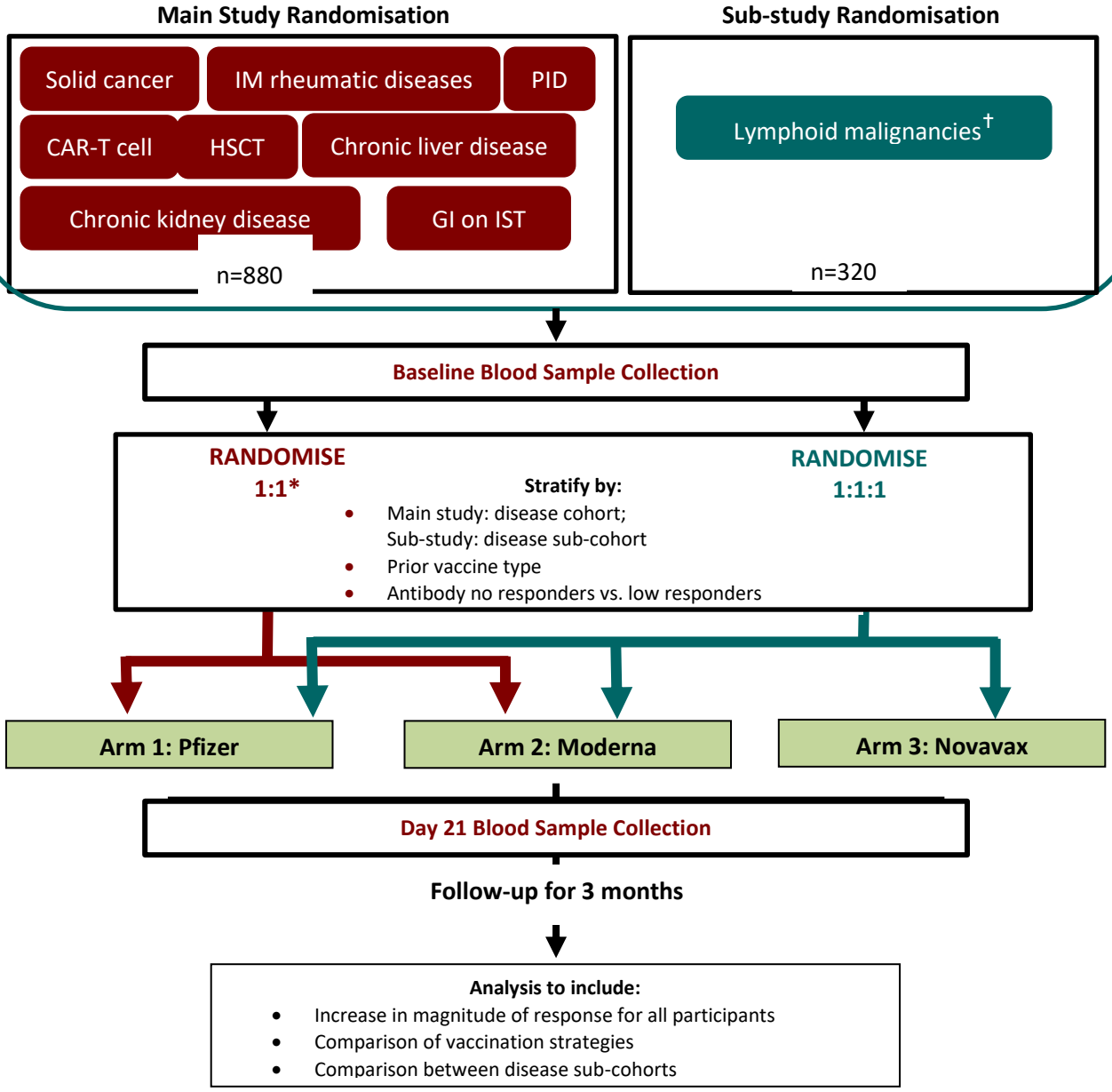
[6] Research blood sample to be collected -14 to 0 days before re-boost vaccination

[7] Participant Diary Booklet handed out at baseline and collected at post re-vaccination appointment to aid in collection of Adverse Event (AE) data

TRIAL DESIGN

Immunocompromised Patients

- Aged ≥18 years
- Have a suboptimal response to two doses of SARS-CoV-2 vaccine
- Anticipated life expectancy of 6 months or greater
- One (or more) of the patient cohorts specified below, and meet disease relevant classification, disease state, and staging according to established international standards
- For the randomised sub-study only, female participants of childbearing potential must be willing to ensure that they or their partner use acceptable effective contraceptive methods



† Note: lymphoid malignancy patients can be randomised to the Main Study randomised comparison only or the sub-study Sub-study participants randomised to Pfizer and Moderna arms will be included in the Main Study randomised comparisons also

Key
CAR-T = chimeric antigen receptor (CAR)T cell; GI = Gastrointestinal disease; HSCT = Haematopoietic stem cell transplant; IM = Immune mediated; IST = Immune suppressive therapy; PID = Primary immunodeficiency

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1 BACKGROUND AND RATIONALE

In the UK, the government's Vaccine Taskforce has secured early access to over 500 million doses of the most promising vaccine candidates, including: BioNTech/Pfizer, Oxford/AstraZeneca, Moderna, Janssen, Novavax, GSK/Sanofi, Valneva and CureVac. Four vaccines are already approved by the Medicines and Healthcare products and Regulatory Agency (MHRA); the COVID-19 mRNA Vaccine BNT162b2 (Pfizer/BioNTech), ChAdOx1 nCOV-19 Vaccine (AstraZeneca formerly AZD1222), the mRNA vaccine developed by Moderna (COVID-19 Vaccine Moderna), and the peptide vaccine developed by Janssen (COVID-19 Vaccine Janssen). To date, in the UK, over 75 million doses of SARS-CoV-2 vaccines have been given with nearly 32 million people, over 45% of the population, being fully vaccinated with 2 doses.

According to the COVID-19 vaccine surveillance report [1], vaccine efficacy trials conducted in the UK demonstrated that a single dose of vaccine infers a 55 to 70% efficacy against symptomatic disease, with rates as high as 90% in participants receiving their second dose [2]. However, phase III trials of COVID-19 vaccines have largely excluded clinically vulnerable patients with chronic disease and immune suppression. It is currently estimated that over 60% of people aged over 65 have one or more chronic disease [3]. Therefore, on-going trials including OCTAVE (https://www.birmingham.ac.uk/research/crctu/trials/octave/index.aspx), COVAD and PROSECO [4] are aiming to understand responses to COVID 19 vaccines in these patients and are specifically recruiting within these vulnerable clinical groups and are identifying patients with low or no T-cell and antibody response after the second homologous vaccine doses.

Preliminary data (e.g. from Imperial College Renal Group) emerging from studies in immunocompromised patients suggest that 30% of patients with immune-compromise are generating low or no detectable antibody or T-cell immune response after two homologous doses of the BNT162b2 (Pfizer/BioNTech) or the ChAdOx1 nCOV-19 vaccines. This raises the question of the potential benefit of a third (re-boost) SARS-CoV-2 vaccine dose in vulnerable patients with inadequate immune responses. The rationale for an additional dose is supported by evidence for enhanced immunogenicity of vaccination following natural infection and also the successful use of this strategy with other vaccines e.g. hepatitis B in haemodialysis patients. To date, data on a third dose of SARS-CoV 19 vaccines are limited and trials in healthy volunteers are ongoing (COV-BOOST) (https://www.covboost.org.uk/home). Case series reports are emerging suggesting a variable response to a third SARS-CoV-2 vaccine in patients with solid organ transplant [5, 6] but more robust evidence is needed to inform re-vaccination policies.

Participants in OCTAVE-DUO will represent patients who are clinically vulnerable to COVID-19 infection and have immune system status that could impair their response to SARS-CoV-2 vaccines, namely immune mediated inflammatory diseases, hepatic and intestinal disease, renal failure, breast cancers,

lymphoid malignancies, haematopoietic stem cell transplant and chimeric antigen receptor (CAR) T-cell therapy recipients and patients with primary immune deficiency. Their potential for altered immune responses to SARS-CoV-2 vaccines are either a function of their underlying disease and associated immune dysregulation or due to their requisite management with immune modifying medications, including cytotoxic chemotherapies biologics, disease-modifying anti-rheumatic drugs (DMARDs), broad spectrum immune suppressants and glucocorticoids. The OCTAVE-DUO trial will recruit patients with known inadequate SARS-CoV-2 vaccines responses and will determine whether a SARS-CoV-2 re-boost vaccination strategy can induce an adequate immune response and whether this is affected by disease phenotype.

The majority of SARS-CoV-2 vaccinations performed in the UK used the mRNA vaccine BNT162b2 (Pfizer/BioNTech) or chimpanzee adenovirus vector vaccine ChAdOx1-nCov19 (Astra Zeneca). It is not known whether re-vaccination with the same type of vaccine technology or an alternative vaccine technology is more likely to boost the immune response. There are trials ongoing examining these questions in healthy volunteers (the COM-COV trial, IRAS Project ID: 291055 EudraCT Number: 2020-005085-33 and COV-BOOST IRAS Project ID: 299180 EudraCT Number: 2021-002175-19).

Preliminary data from the COM-COV trial suggests that healthy participants that have received either ChAdOx1 nCOV-19 vaccine or mRNA vaccine BNT162b2, who then subsequently receive a dose of BNT162b2 generate a superior immunological response compared to those who received a dose of ChAdOx1 nCOV-19 vaccine [personal communication]. However, it should be appreciated that ChAdOx1 nCOV-19 vaccine followed by ChAdOx1 nCOV-19 vaccine does generate an effective immune response in healthy individuals. Given the scale of the increased response with BNT162b2 boost (approximately 5 times higher) and the fact that we need to sufficiently enhance the sub-optimal immunological response in clinically vulnerable patients, the decision was made to include BNT162b2 as one of the vaccines for the OCTAVE DUO study. The second vaccine chosen is the Moderna mRNA vaccine. In a sub-set of patients, the Novavax nano-particle vaccine will also be evaluated. The rationale for inclusion of the Novavax nano-particle vaccine is based on the unique formulation compared to the ChAdOx1 and mRNA vaccines. It is important that we determine whether this type of vaccine formulation will provide added benefits in clinically vulnerable patients. Finally, the use of the Novavax nano-particle vaccine aligns with the COM-COV2 trial, which is comparing boosting of healthy individuals that have received either ChAdOx1 nCOV-19 vaccine or mRNA vaccine BNT162b2 with a dose of an mRNA vaccine (BNT162b2 or COVID-19 Vaccine Moderna) or the Novavax nano-particle vaccine.

OCTAVE-DUO will address the re-boost question in the immunocompromised patient and evaluate whether the third vaccine immune response can be induced by the mRNA vaccines Pfizer BNT162b2 or Moderna. In a sub-set of patients, immune response will also be evaluated using the unlicensed nano-particle vaccine Novavax. The comparative response between participants receiving 3 doses of BNT162b2, 2 doses of ChAdOx1-nCov19 and a booster with BNT162b2 or Moderna, (and in a sub-set

Novavax) will be investigated. State-of-the-art immune technologies on common assay platforms will be used, so that vaccine responsiveness between different disease cohorts can be directly assessed. This knowledge is urgently required to guide re-vaccination strategies and to inform government policies in the UK and globally.

1.1.1 OCTAVE-DUO Trial Hypotheses

The specific hypotheses are:

- Patients with no detectable SARS-CoV-2 specific immunoglobulin (Ig) antibodies after two doses of vaccines have failed to prime SARS-CoV-2 humoral responses and will not respond to an additional booster vaccine, whereas patients with low but detectable SARS-CoV-2 Ig responses have successfully primed responses and are likely to benefit from an additional re-boost vaccination.
- The absence/presence of SARS-CoV-2 specific T-cells in patients with no/low SARS-CoV-2 specific Ig antibodies after two vaccines may identify patients who will respond to re-boost strategies.
- Patients with unified clinical phenotypes (e.g., same underlying primary disease, or common immune suppressive drugs in different disease states) will respond similarly to re-boost vaccinations.

The OCTAVE DUO trial represents the most extensive study of sub-optimal vaccine responses in chronic disease.

2 AIM, OBJECTIVES AND OUTCOME MEASURES

The aim of this trial is to assess whether a SARS-CoV-2 re-boost vaccine strategy can induce an adequate immune response in clinically vulnerable patient cohorts with proven inadequate response to two doses of SARS-CoV-2 vaccine.

2.1.1 Primary Objective

- To determine across a range of immune-mediated/immunosuppressive diseases whether re-vaccination with Pfizer or Moderna vaccines will increase the magnitude of SARS-CoV-2 immune responses in patients with no or low antibodies after two prior vaccine doses.

2.1.2 Secondary Objective

- In a sub-set of participants with lymphoid malignancies, to evaluate the immune response following re-vaccination with Pfizer, Moderna or Novavax vaccines in patients with no or low antibodies after two prior vaccine doses.

- To compare the relative change in magnitude of immune responses arising following revaccination with Pfizer, Moderna and Novavax vaccines across different underlying disease states and therapeutic regimens.

2.1.3 Exploratory Objective

- To evaluate the safety of re-boost with SARS-CoV-2 vaccines in these immunocompromised disease cohorts.
- Investigate the mechanistic pathways underpinning vaccine responsiveness in disease/drug clinical states.
- To determine whether such immunologic pathway analysis can offer predictive markers of the magnitude or qualitative components of subsequent immune responses following vaccination.

2.2 Outcome Measures

2.2.1 Primary Outcome

2.2.1.1 Vaccine-specific immunogenicity:

- Anti-spike SARS-CoV-2 antibody and T cell responses to SARS-CoV-2 peptides following Pfizer and Moderna re-boost vaccinations will be measured before the re-boost vaccination was given and will be compared with those achieved at day 21 post dose.

  Anti-spike SARS-CoV-2 antibodies following re-boost vaccination will be measured using the Roche platforms by the UK Health Security Agency formerly known as Public Health England (PHE) Laboratories at Porton Down. The Roche assays will measure the presence and amount of serum antibodies to both the spike (S) and the nucleocapsid (N) antigens of SARS-CoV-2. This assay will enable the discrimination of antibody responses to SARS-CoV-2 that results from vaccination and/or SARS-CoV-2 infection.

  T cell responses to SARS-CoV-2 peptides following re-boost vaccination will be measured using the Oxford Immunotec modified T-spot discovery SARS-CoV-2 assay. This IFNγ ELISpot assay will provide insights into the participants' reactivity to SARS-CoV-2 s1, s2, nucleocapsid and membrane peptides.

2.2.2 Secondary Outcomes

- In a sub-set of participants with lymphoid malignancies, measure the change in vaccine specific immunogenicity in response to vaccination (as defined for the primary outcome) with Pfizer, Moderna or Novavax vaccines.

- In all patient groups, we will assess the capacity of re-boost vaccine induced SARS-CoV-2 antibodies to neutralise/block SARS-CoV-2 infection using IgG (pseudo)neutralisation assays.

2.2.3 Exploratory Outcomes

2.2.3.1 Safety

A descriptive analysis of the reported Adverse Events (AEs) in the participants will be presented.

2.2.3.2 Cellular Immunogenicity

Additional assays relevant to immune state and response may also be undertaken pending further funding applications, but express consent for their conduct will be sought at this time:

The impact of revaccination on T cell subsets and their function across disease groups will be assessed using a range of assays including those outlined below:

- Intracellular cytokine flow cytometric analysis (ICCS) – (established at Oxford University laboratories [7])
- Proliferation assays (CTV assay) will evaluate the recall potential of SARS-CoV-2 memory T cells at later (6 month) time points (established at Oxford University laboratories [8])
- Serum antibodies (IgG/IgM/IgA) to important SARS-CoV-2 antigens and SARS-CoV-2 related antigens (including but not limited to SARS, MERS and circulating seasonal coronaviruses: CoV-2 S, NL63 S, CoV-2 N, CoV-1 S, MERS S, HKU1 S, OC43 S, 229E S, CoV-2 RBD) will be measured in an MSD assay or bespoke ELISA established at University of Glasgow laboratories (MRC-CVR)
- Deep immune phenotyping using flow cytometric characterisation of the circulating immune compartment (e.g. T cells and B cells) will be undertaken in various participant centres
- T cell and B cell specific responses to defined peptides/stimuli will be undertaken using established ELISpot assays, at Imperial College London and Oxford University laboratories

Furthermore, other assays may be added as data emerges from other SARS-CoV-2 vaccine studies.

3 TRIAL DESIGN AND RECRUITMENT TARGETS

3.1 Trial Design

OCTAVE-DUO is a phase III, multi-centre, multi-disease, open-label, randomised trial to determine whether a re-boost vaccine strategy can induce an immune response in clinically vulnerable patients with proven inadequate response to SARS-CoV-2 vaccine. Patients with 1) solid cancer; 2) lymphoid malignancies; 3) immune-mediated rheumatic diseases; 4) end stage kidney disease; 5) chronic liver

disease; 6) gastrointestinal disease on immune suppressive therapy; 7) haematopoietic stem cell transplant; 8) primary immunodeficiency; and 9) CAR-T cell therapy who have received two doses of SARS-CoV-2 vaccine but have proven inadequate response to SARS-CoV-2 vaccine attending specialist clinics across the UK will be recruited.

Patients will be randomly allocated to receive either Pfizer or Moderna (or for a sub-set of patients Pfizer or Moderna or Novavax) SARS-CoV-2 re-boost vaccine and their immunogenic responses analysed.

If the Novavax vaccine is not available and patients have already been randomised to this arm they will be re-randomised to the Main Study randomisation (Pfizer vs. Moderna).

3.2 Recruitment Targets

Up to 1200 participants will be recruited from the 8 different disease cohorts. The numbers recruited per cohort will vary as indicated below.

Initiation of recruitment into each cohort will be staggered with lymphoid malignancy, immune-mediated rheumatic diseases, end stage kidney, chronic liver disease, and gastrointestinal disease on immunosuppressive therapy and patients being prioritised in the initial recruitment phase of the trial.

The target recruitment for the study components (see Section 12.2.6 for power calculations) are:

- Main study - minimum of 1100 participants will contribute to the analysis
- Randomised sub-study – minimum of 300 participants will contribute to the analysis

3.2.1 Anticipated Recruitment by Disease Cohort

3.2.1.1 Solid Cancer

Target 80 participants

3.2.1.2 Lymphoid Malignancies

Target 320 participants. Target recruitment per disease cohort sub-type:

- Aggressive B-Non Hodgkin Lymphoma (NHL) - 40 participants
- Chronic lymphocytic leukaemia (CLL) - 80 participants
- Hodgkin Lymphoma - 40 participants
- Indolent B NHL (except CLL and small lymphocytic lymphoma (SLL)) - 80 participants
- Myeloma - 80 participants

3.2.1.3 Immune-mediated Rheumatic Diseases

Target 160 participants.

3.2.1.4 End Stage Kidney Disease

Target 160 participants.

3.2.1.5 Chronic Liver Disease

Target 80 participants.

3.2.1.6 Gastrointestinal Disease on Immune Suppressive Therapy

Target 80 participants.

3.2.1.7 Haematopoietic Stem Cell Transplant

Target 80 participants.

3.2.1.8 Primary Immunodeficiency

Target 160 participants.

3.2.1.9 CAR-T Cell Therapy

Target 80 participants.

4 ELIGIBILITY

The eligibility criteria for OCTAVE-DUO aim to allow inclusion of patients with a range of conditions that impact on their immune status. The study aims to reflect the patient population who may be eligible for a third dose of vaccine in the future and therefore the study exclusion criteria are limited to those that would preclude administration of SARS-CoV-2 vaccines in the normal population, in accordance with the vaccines' applicable product information (see Section 7.1).

Patients meeting the criteria below are eligible to participate in the trial.

4.1 Inclusion Criteria

1. Aged ≥18 years.
2. Have an inadequate response to two doses of SARS-CoV-2 vaccine measured at least 14 days after receipt of the second vaccine, defined by SARS-CoV-2 spike antibody response.

An inadequate response is defined as:

i) ***Antibody non-response***: SARS-CoV-2 anti-spike antibodies below the level of detection using the PHE Roche platform [or equivalent assay, see Appendix 1] <0.8 Arbitrary Units (AU)/ml; or

ii) ***Antibody low-response***[†]: SARS-CoV-2 anti-spike antibodies ≥0.8 and <400 AU/mL using the Roche platform [or equivalent assay, see Appendix 1]).

[†] *There is no agreed international/WHO cut off for titres of AU following vaccination and serologic assessment. As such, the low responder status for OCTAVE-DUO eligibility is by definition arbitrary. We have examined the serology levels obtained in the OCTAVE study, compared with PITCH (health care workers without vulnerable conditions) and elected to choose a titre that equates to approximately 30% of the OCTAVE population – this equates to approx. 400 AU hence this selection for this part of the eligibility criteria. Since in practice all vulnerable groups will receive a re-boost in due course, by choosing the lowest tertile for evaluation of enhancement of response, we are maximising the pragmatic value of the study in terms of policy advice, and determination of magnitude of immune response, representing our primary outcome. Moreover, we are thereby ensuring rapid and representative recruitment from the variety of vulnerable patient groups in the study protocol.*

3. Anticipated life expectancy of 6 months or greater.
4. Fall into one (or more) of the following patient cohorts who will meet disease relevant classification, disease state, and staging according to established international standards:

   - **Diagnosed with any of the following solid cancers:**
     - Breast
     - Lung
   - **Diagnosed with any of the following lymphoid malignancy categories:**
     - Aggressive B-NHL
     - CLL
     - Hodgkin Lymphoma
     - Indolent B NHL (except CLL and SLL)
     - Myeloma
   - **Diagnosed with the following rheumatic/inflammatory conditions:**
     - Rheumatoid Arthritis
     - Psoriatic Arthritis
     - Seronegative Arthritis
     - Spondyloarthritis
     - Anti-neutrophil cytoplasm antibodies (ANCA) -associated Vasculitis
     - Systemic Lupus Erythematosus (SLE)
     - Psoriasis

- Crohn's disease / Ulcerative colitis
- Autoimmune hepatitis

- **Diagnosed with the following chronic renal conditions:**
  - End stage kidney disease secondary to any cause
  - Renal transplant following end stage kidney disease
- **Diagnosed with the following chronic liver conditions:**
  - Liver cirrhosis
  - Liver transplantation
  - Chronic liver disease (of any stage) on immune suppressive therapy

- Diagnosed with gastrointestinal disease and on immune suppressive therapy
- **Diagnosed with primary antibody deficiency:**
  - Defined as any patient who is on immunoglobulin replacement therapy or any patient with an IgG <4g/l and on prophylactic antibiotics.
- **Haematopoietic stem cell transplant†:**
  - Previously treated with autologous or allogeneic haematopoietic stem cell transplant for any indication and with any conditioning regimens and intensities, who have not relapsed post-transplant
- **CAR-T Cell therapy†:**
  - Previously treated with CAR-T cell therapies for any indication, irrespective of remission status

5. Participant is willing and able to comply with trial requirements.
6. For the randomised sub-study only, female participants of childbearing potential* must be willing to ensure that they or their partner use acceptable effective contraceptive methods until 3 months after the re-boost immunisation. See Section 7.4 and definition of acceptable effective contraceptive methods.

   ** Defined as a fertile woman, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal is defined as no menses for 12 months without an alternative medical cause.*

   † Note: HSCT and CAR-T recipients who have received any SARS-CoV-2 vaccine pre-procedure and are receiving a re-vaccination course post HSCT/CAR-T are eligible for recruitment

4.2 Exclusion Criteria

1. Receipt of any vaccine within 30 days before trial entry, with the exception of: a SARS-CoV-2 vaccine which is allowed ≥14 days prior; or a flu vaccination which is allowed ≥7 days prior.
2. For aggressive B-NHL or Hodgkin lymphoma only, participants on active systemic treatment or within 4 weeks of completion of systemic treatment.
3. Any known contraindications as specified in the applicable product information (see Section 7.1) including but not limited to:
   - Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients; and
   - History of anaphylaxis to prior COVID-19 vaccinations, or any component of the vaccine.
4. In the judgement of the Investigator, the patient is unsuitable to participate in the trial or is unlikely to comply with trial procedures.
5. For the randomised sub-study only, patients who are pregnant or lactating at trial entry or planning to become pregnant within 3 months after re-vaccination.

5 SCREENING AND CONSENT

5.1 Screening

Participants with an inadequate response to COVID-19 vaccination will be identified from participation in OCTAVE or other aligned SARS-CoV-2 vaccine studies (e.g. COVAD and PROSECO); or if SARS-CoV-2 anti-spike antibodies levels are available from disease site specific clinics; or for the solid cancer, haematopoietic stem cell transplant and CAR-T cell therapy disease cohorts only, a SARS-CoV-2 spike antibody response can be measured as a screening assessment using one of the assays listed in Appendix 1.

Those participants identified from pre-existing studies may receive a phone call or a letter of invitation (ethically approved template provided) from the Site Research Team.

Patients will be recruited at the clinical site by members of the clinical team who have been delegated this responsibility on the Site Signature and Delegation Log by the Principal Investigator.

An Eligibility Checklist should be completed prior to randomisation by the Investigator or designee. A copy should be returned to the Trial Office and the original filed in the Investigator Site File.

For the randomised sub-study only, women who are of child-bearing potential, a negative urine dipstick pregnancy test will be required prior to vaccination.

5.2 Informed Consent

It is the responsibility of the investigator or designee (e.g., registrars, Research Nurses if local practice allows and this responsibility has been delegated by the Principal Investigator) to obtain written informed consent for each participant before any trial related procedures. A Participant Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim of the trial and what the trial would involve for the participant.

The Joint Committee on Vaccination and Immunisation (JCVI) recommended on 01-Sep-2021 that a third primary dose be offered to individuals with severe immunosuppression in proximity to their first or second COVID-19 vaccine doses as part of their primary vaccination schedule (see https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice). Invitations for this additional third primary vaccination were subsequently sent to patients who fall within this group. However, patients taking part in OCTAVE-DUO have already had this additional vaccine and should be advised at the point of consent not to take up this invitation.

The investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (ideally 24 hours) to read the Participant Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

The informed consent process is expected to involve an interview between member(s) of the investigator team and the patient which should facilitate two-way communication. It is possible for this interview to be conducted remotely. Where this occurs, the patient can be sent the Participant Information Sheet in advance in the post or electronically. If the patient agrees to participate in the trial, they should be asked to sign and date the latest version of the Informed Consent Form. The Informed Consent Form should either be wet-ink signed by the patient and the investigator (or designee) or signed electronically using software which allows signature authentication (e.g., DocuSign). If wet-ink signed the Informed Consent Form can be returned when the patient attends for their first clinic appointment or it can be returned in the post, but it must be signed by both parties prior to the patient's entry into the trial.

Once the patient is entered into the trial, the participant's trial number should be entered on the Informed Consent Form. A copy of the Informed Consent Form should be given to the participant, a copy should be filed in the hospital notes, a copy sent to the Trial Office and the original placed in the Investigator Site File. Details of the informed consent discussions should be recorded in the patient's medical notes; including date of, and information regarding the initial discussion, the date consent was

given, with the name of the trial and the version numbers of the Participant Information Sheet and Informed Consent Form.

Throughout the trial the participant should have the opportunity to ask questions about the trial and any new information that may be relevant to the participant's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the participant, in which case the process above should be followed and the participant's right to withdraw from the trial respected. Participants are permitted to re-consent at the same visit that new information is provided if they wish to do so. Details of these discussions (as specified above) should also be recorded in the patient's medical notes.

Electronic copies of the Participant Information Sheet and Informed Consent Form are available from the Trial Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded electronically on the Patient Screening/Enrolment Log.

The patient's General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter template is provided electronically for this purpose.

6 TRIAL ENTRY

After screening, the following will be checked prior to recruitment:

- Participant has provided consent and;
- Confirmation that the eligibility criteria have been met.

If eligibility is confirmed, the patient can be randomised into the trial.

6.1 Randomisation

As soon as the patient is considered eligible the Investigator should enter the patient into the trial by completing the Randomisation Form on the electronic Remote Data Capture (eRDC) system below.

https://www.cancertrials.bham.ac.uk

Investigators must be registered with the Trial Office before they are permitted to enter patients into the trial.

The site is asked to confirm the patient's eligibility, and provide the following information:

- Name of the investigator responsible for the care of the randomised patient
- Patient's initials and date of birth

- Date of consent
- Disease cohort (or sub-cohort for the lymphoid malignancies)
- Type of SARS-CoV-2 vaccine previously received
- SARS-CoV-2 anti-spike antibody test performed and level (AU/ml)
- Whether the patient participated in a prior SARS-CoV-2 vaccine immune response study (including study acronym and unique subject identifier)

6.1.1 Main Study Randomisation

For the main study randomised comparison, patients will be randomised in a 1:1 ratio using a minimisation program (developed by the CRCTU) with the following stratification variables:

- Disease cohort: solid cancer; lymphoid malignancies; immune-mediated rheumatic diseases; end stage kidney disease; chronic liver disease; gastrointestinal disease on immune suppressive therapy; haematopoietic stem cell transplant; primary immunodeficiency; and CAR-T Cell therapy
- Prior SARS-CoV-2 vaccine type: AstraZeneca; Pfizer; Moderna; Other
- SARS-CoV-2 vaccine response: antibody non-responders or antibody low-responders defined as:
  - Antibody non-responders: Defined as SARS-CoV-2 anti-spike antibodies below the level of detection using the PHE Roche platform <0.8 AU/ml [or equivalent]); and
  - Antibody low-responders: Defined as SARS-CoV-2 anti-spike antibodies ≥0.8 and <400 AU/mL using the PHE Roche platform [or equivalent].

Patients will be randomised to receive:

- Arm 1: Pfizer SARS-CoV-2 Vaccine; or
- Arm 2: Moderna SARS-CoV-2 Vaccine.

6.1.2 Sub-study Randomisation

For the sub-study randomised comparison, patients will be randomised in a 1:1:1 ratio using a minimisation program with the following stratification variables:

- Lymphoid malignancies sub-cohort diseases:
  - Aggressive B-NHL
  - CLL
  - Hodgkin Lymphoma

- Indolent B NHL
- Myeloma

- Prior SARS-CoV-2 vaccine type: AstraZeneca; Pfizer; Moderna; Other
- SARS-CoV-2 vaccine response: antibody non-responders or antibody low-responders as defined above.

Patients will be randomised to receive:

- Arm 1: Pfizer SARS-CoV-2 Vaccine; or
- Arm 2: Moderna SARS-CoV-2 Vaccine; or
- Arm 3: Novavax SARS-CoV-2 Vaccine.

6.1.3 Following Randomisation

The randomisations are not blinded and, therefore, both participants and the Site Research Team will know which treatment has been allocated to the patient.

At the end of the randomisation procedure, the participant will be allocated to the appropriate arm and given a unique trial number.

Where applicable the Responsible Pharmacist (e.g. where the participant is randomised to Novavax) will be notified by a member of the site research team that a patient has been entered onto the trial.

The Baseline Form* should be completed on the eRDC system.

A copy of the Randomisation Confirmation Report, signed Informed Consent Form, and Eligibility Checklist should be filed within the Investigator Site File.

* *Where the participant took part in OCTAVE, completion of the Baseline Form will not be required for some disease cohorts as data will be obtained from the OCTAVE database and the OCTAVE Case Report Form (CRF) used for monitoring purposes*

7 TRIAL TREATMENT

7.1 Investigational Medicinal Products

The following SARS-CoV-2 vaccines are regarded as Investigational Medicinal Products (IMPs) for this trial:

- Pfizer SARS-CoV-2 vaccine
- Moderna SARS-CoV-2 vaccine

- Novavax SARS-CoV-2 vaccine

7.1.1 Pfizer SARS-CoV-2 Vaccine

The SARS-CoV-2 vaccine BNT162b2, manufactured by Pfizer, is an mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. mRNA vaccines exploit the host's cells to make the target protein.

BNT162b2 is approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.

Vaccine should be ordered from PHE using IMMFORM. It will not be labelled as IMP for this trial and the product will be used as supplied by the manufacturer (as for national supply). Vaccine accountability will be in accordance with local Trust policy.

Each pack of the Pfizer vaccine contains 195 vials which after dilution contain 6 doses per vial.

Vaccine should be stored and prepared as specified in the Information for UK Healthcare Professionals.

See the OCTAVE-DUO Pharmacy Manual for additional information.

7.1.2 Moderna SARS-CoV-2 Vaccine

The Moderna SARS-CoV-2 vaccine, manufactured by Moderna Biotech, is an mRNA vaccine which encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein.

Moderna SARS-CoV-2 vaccine has been authorised by MHRA in Great Britain (consisting of England, Scotland and Wales).

Vaccine should be ordered from PHE using IMMFORM. It will not be labelled as IMP for this trial and the product will be used as supplied by the manufacturer (as for national supply). Vaccine accountability will be in accordance with local Trust policy.

The vaccine is supplied in multidose vials which contain 10 doses of 0.5 mL.

Vaccine should be stored and prepared as specified in the Summary of Product Characteristics (SmPC).

See the OCTAVE-DUO Pharmacy Manual for additional information.

7.1.3 Novavax COVID-19 Vaccine

The SARS-CoV-2 vaccine NVX-CoV2373, manufactured by Novavax, was constructed from the full-length wild-type pre-fusion trimers of SARS-CoV-2 spike glycoprotein.

NVX-CoV2373 is currently unlicenced in the UK. It will be supplied pre-labelled as clinical trial supplies by Novavax. See the OCTAVE-DUO Pharmacy Manual for details of accountability arrangements.

Vaccine will be supplied labelled as clinical trials supplies by Novavax. Ordering procedures are described in the Pharmacy Manual.

The vaccine is supplied in 10 dose vials. Vaccine should be stored and prepared as specified in the Investigator Brochure (IB).

7.2 Administration of Investigational Medicinal Products

Participants should receive their re-boost vaccine a minimum of 14 days after their second booster.

The administration of the Pfizer and Moderna SARS-CoV-2 vaccines should be postponed in individuals suffering from acute severe febrile illness. The presence of a minor infection and/or low-grade fever should not delay vaccination.

7.2.1 Pfizer SARS-CoV-2 Vaccine

The dose of Pfizer vaccine is 30µg contained in 0.3ml of the diluted vaccine (standard dose) given intramuscularly.

Vaccine should be prepared and administered in accordance with the Information for UK Healthcare Professionals.

Participants should be observed for 15 minutes following vaccination.

7.2.2 Moderna SARS-CoV-2 Vaccine

The dose of Moderna vaccine is 0.5ml, containing 100 µg of messenger RNA (mRNA), given intramuscularly.

Vaccine should be prepared and administered in accordance with the SmPC.

Participants should be observed for 15 minutes following vaccination.

7.2.3 Novavax SARS-CoV-2 Vaccine

A dose of 5 µg recombinant spike protein with 50 µg Matrix-M1 adjuvant (0.5ml) will be given intramuscularly.

Participants should be observed for 15 minutes following vaccination.

7.3 Assessments

Assessments should be carried out as detailed below.

7.3.1 Screening

For the randomised sub-study only, a negative urine dipstick pregnancy test should be performed to confirm eligibility at screening for women of child-bearing potential.

For the solid cancer, haematopoietic stem cell transplant and CAR-T cell therapy disease cohorts only, a SARS-CoV-2 spike antibody response can be measured as a screening assessment using one of the

assays listed in Appendix 1, or another assay with the prior agreement of the Trial Management Group (TMG).

7.3.2 Baseline

Participants will be required to attend clinic for the collection of the baseline research sample which must be collected prior to re-vaccination (see Section 7.5 for details of sample collection). Samples can be collected on the day of vaccination as long as this is prior to the re-boost vaccination or up to 2 weeks (14 days) in advance.

The participant should be given a Participant Diary Booklet and instructed on how to complete the diary sheets. Participants should be advised to complete one column per day for 3 weeks. They should be asked to return the Booklet at the day 21 visit.

Data (including medical history, disease history and treatment, prior COVID-19 infection and vaccination history) will be collected on the Baseline Form. These data may be collected retrospectively from the participants' medical records. Where the participant took part in the OCTAVE trial these data will be obtained from the OCTAVE trial database and this information does not need to be provided by the site.

A Research Blood Sample Collection Form should also be completed.

7.3.3 Re-Boost vaccination

Participants will be required to attend clinic for re-boost vaccination (see Section 7.3.3).

The following forms should be completed at this time point:

- Treatment Form (documenting disease specific treatment)
- Vaccination Form

7.3.4 Post Re-boost vaccination

Participants will be required to attend clinic for the collection of the post re-boost vaccination research blood sample which must be collected on day 21 (as a minimum) or within an additional 14 days (by day 35). See Section 7.5 for details of research blood sample collection.

Participant Diaries should be collected from the participant and used as a guide to complete the Adverse Event Form.

The following forms should be completed at this time point:

- Adverse Event Form
- Research Blood Sample Collection Form

7.3.5 Three Month Follow-up

Where possible participants will be followed up in accordance with standard clinical practice for the relevant disease cohort and data will be collected retrospectively from clinic records 3 months after re-boost vaccination. Where participants do not attend for a routine clinic visit, data may be collected following an additional telephone follow-up call.

A Follow-up Form should be completed.

7.4 Contraception and Pregnancy for Participants in Randomised Sub-study

There is no evidence from animal studies that the SARS-CoV-2 vaccines used in this trial cause direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development for any of the COVID-19 vaccines included in this trial. However there is limited experience using SARS-CoV-2 vaccines in pregnant women and particularly with regard to Novavax. Therefore female participants of childbearing potential taking part in the randomised sub-study are required to ensure that they or their partner use acceptable effective contraceptive methods until 3 months after the re-boost immunisation.

Acceptable birth control methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

7.5 Sample Collection and Analysis

7.5.1 Collection

Sites will be provided with kits for the collection of the research blood samples.

Up to 55 ml of blood will be collected from participants at any one visit comprising whole blood, serum plasma, and peripheral blood mononuclear cells (PBMC) where possible. Samples will be collected at the following time points:

- Pre-vaccine (baseline) -14 to day 0 (but must be given prior to re-vaccination)
- 21 (+14) days post-re-boost vaccination

See Table 1 for further details on samples types collected and storage conditions.

Samples must be received by Oxford Immunotec within 32h of collection. The remaining samples will be shipped in batches to the relevant coordinating laboratory. Sites will be provided with details of which laboratory to send the samples to at the time of shipment. Full details of the sample collection and processing procedure are included in the Laboratory Manual.

Table 1: Details of Sample Collection and Storage

Sample Type	Collection Tube	Volume	Laboratory Analysis	Aliquots	Sample Storage
Whole Blood	Tempus RNA	3ml	RNA	None	-80°C
Whole Blood	EDTA	9ml x minimum of 2 (maximum of 3)	Cellular immunoassays & DNA	4 x 500ul (as PBMCs) † 5 x 700ul (as Plasma)	-80°C for Plasma (long-term) and PBMCs (short-term), then liquid nitrogen or -150 °C; depends on site (long-term)
Serum	Serum separator tubes (SST)	5ml x 2	Immunoassay; ELISA and virus neutralisation assays	10 x 400ul	-80°C
Whole Blood	Lithium Heparin*	6ml x 2	ELISpot assay	None	None

** Two 6ml lithium heparin tubes will be shipped to Oxford Immunotec at ambient temperature*

† PBMCs will be collected where possible but are not mandated

7.5.2 Analysis

Laboratory analysis to be conducted on the samples will include:

- Assessment of quantitative antibody responses to SARS-CoV-2 spike and nucleocapsid antigens will be undertaken by the UK Health Security Agency Laboratories at Porton Down.
- Assessment of IFN-g T cell responses to SARS-CoV-2 antigens in an ex vivo ELISpot assay, to be undertaken by Oxford Immunotec.
- Assessment of neutralising antibody responses to SARS-CoV-2 antigens be undertaken at the laboratories at the University of Glasgow.
- Assessment of fine specificity of T cell (ELISpot and Flow cytometric assays) will be performed by laboratories at the University of Oxford and Imperial College London.
- Assessment of IgG/IgM/IgA responses to SARS-CoV-2 antigens and other relevant season antigens will be undertaken by the laboratories at the University of Glasgow.

This is not an all-inclusive list, additional assays will be included as more information becomes available about the immune response elicited by SARS-CoV-2 vaccination.

Principal Investigators will be provided with the results of their patients' assessment of immune response to at the end of the trial. Participants should be provided with the results on request.

7.5.3 Future Research and Biobanking

Any samples remaining at the end of the trial will be banked in a Human Tissue Authority (HTA) licenced biobank. The samples and data will be made available for future research in other ethically approved studies (see Section 13.3 and Section 18 for further details).

7.6 Data Linkage

The participant's NHS number or CHI number will be collected to allow linkage with national data registries such as NHS Digital, UK Health Security Agency, the Information Services Division (part of NHS Scotland), or the electronic Data Research and Innovation Service (eDRIS). For the haematopoietic stem cell transplant cohort the British Society of Blood and Marrow Transplantation (BSBMT) registry identification (PROMISE ID) will also be collected, where participants have also consented to collection of data within this registry, to allow for data linkage. Data linkage will allow for long-term follow-up data to be collected and it will provide a more complete profile of the participants' health and disease without increased data collection burden to the NHS.

7.7 Participant Withdrawal

Participants may withdraw consent at any time during the trial. For the purposes of this trial two types of withdrawal are defined:

- The participant would like to withdraw from the trial but is willing to be followed up as standard (i.e., the patient has agreed that data can be collected at disease cohort specific clinic visits and used in the analyses); or
- The participant would like to withdraw from the trial entirely and is not willing to be followed up for the purposes of the trial (i.e., only data and blood samples collected prior to the withdrawal of consent can be used in the trial analysis) – withdrawal of consent.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data. A Withdrawal of Consent Form should be completed to notify the Trial Office of the participant's withdrawal from the trial.

8 ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 2. The seriousness and causality (relatedness) of all AEs experienced by the participant should be assessed with reference to the relevant IMP information as specified in Section 7.1.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE should be reported, with the exception of abnormal laboratory findings which should only be reported if they are CTCAE grade 3 or above.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE.

Pre-existing conditions should only be reported if the condition worsens by at least one CTCAE grade.

Participants will be provided with a Diary Booklet to aid in the capture of AEs. If the participant does not return the Booklet, they should be asked to provide details of any AEs they experienced. Details of AEs recorded by the participant or noted by the Research Team will be captured on an AE Form.

8.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE and are not excluded from the reporting process as described in Section 8.1.2.1. These events should be reported on an SAE Form after first becoming aware of the event as described in Section 8.3.1.2.

8.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Disease treatment
  - Receipt of supportive care for disease treatment related toxicities (e.g. neutropenic sepsis, vomiting for cancer participants)
  - Disease progression (unless there is concern this has been exacerbated by vaccination)
  - Pre-planned elective procedures unless the condition worsens

8.1.3 Monitoring Pregnancies for Potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

For those participants taking part in the randomised sub-study only, in the event that a female participant of child-bearing potential becomes pregnant during the SAE reporting period, please complete a Pregnancy Notification Form (providing the patient's details) as soon as possible. Provide outcome data on the Pregnancy Notification Form once this is available. If appropriate also complete an SAE Form as detailed in Section 8.3.1.2.

8.2 Reporting Period

The screening procedures for this trial are limited to a review of hospital records, for women of child-bearing potential in the lymphoid cohort who are participating in the sub-study randomisation, a urine dip stick pregnancy test and SAR-CoV-2 antibody level screening for HSCT and CAR-T cell patients only. For all other cohorts SAR-CoV-2 antibody levels have already been assessed outside the study. Hence details of AEs will be documented and reported from the date of re-boost vaccination until 21 days after the administration of the SARS-CoV-2 re-boost vaccination.

SAEs will be captured from consent until 28 days post re- boost vaccination.

SAEs that are judged to be at least possibly related to the IMP and are unexpected must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.3 Reporting Procedure

8.3.1 Site

8.3.1.1 Adverse Events

For more detailed instructions on AE reporting refer to the CRF Completion Guidelines contained in the Investigator Site File.

Participants will be provided with a Participant Diary Booklet to aid in the documentation of AEs for up to 21 days post vaccination. The Booklet should be returned at the re-vaccination visit and can be used to facilitate the completion of the Adverse Event Form.

AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (see Appendix 3).

Any AEs experienced by the participant but not included in the CTCAE should be graded by an investigator and recorded using a scale of (1) mild, (2) moderate or (3) severe.

For each AE, the highest grade should be recorded.

8.3.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the Investigator Site File.

AEs defined as serious that require reporting as an SAE should be reported on an SAE Form. When completing the form, the investigator will be asked to define the causality and the severity of the AE which should be documented using CTCAE version 5.0.

The form should be emailed to the Trial Office as soon as possible and no later than 24 hours after first becoming aware of the event:

Send SAEs to:

Reg@trials.bham.ac.uk

Cc OCTAVE-DUO@trials.bham.ac.uk

Include "OCTAVE-DUO SAE" in the subject line

On receipt, the Trial Office will allocate each SAE a unique reference number. The site will be informed of the SAE reference number in an email acknowledging receipt of the event. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The email from the Trial Office acknowledging receipt should be filed with the SAE Form in the Investigator Site File.

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 Trial Office and a copy kept in the Investigator Site File.

Investigators should also report SAEs to their own Trust or Health Board in accordance with local policy.

Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.3.2 OCTAVE-DUO Trial Office

On receipt of an SAE Form, causality and expectedness will be determined by a Clinical Coordinator. An SAE judged by the investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). If the event meets the definition of a SAR that is unexpected (i.e., is not listed in the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.3.3 Reporting to the Competent Authority and Research Ethics Committee

8.3.3.1 Suspected Unexpected Serious Adverse Reactions

The Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA and REC within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

8.3.3.2 Serious Adverse Reactions

The Trial Office will report details of all SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation (CTA), in the form of a Development Safety Update Report (DSUR).

8.3.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.3.3.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

8.3.3.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

8.3.3.6 Manufacturer of Investigational Medicinal Product

All SAEs which occur for participant who received the Novavax SARS-CoV-2 vaccine will be reported to the manufacture, Novavax, within 7 days of receipt by the Trial Office.

9 DATA COLLECTION

The CRF will be comprised of the forms listed in Table 2.

Table 2: OCTAVE-DUO Trial Case Report Form

Form	Summary of Data Recorded*	Schedule for Submission to Trial Office
Eligibility Checklist	Confirmation that eligibility criteria are met	Complete at trial entry
Randomisation	Minimal identifiers (initials and date of birth), and stratification factors	Complete at trial entry
Baseline	NHS/CHI/ PROMISE registry ID, hospital number, demographic data (sex, ethnicity), World Health Organisation (WHO) performance status (Appendix 4), body mass index, medical history including comorbidities, disease group specific information (including disease status), and details of prior COVID-19 infection	Within 2 weeks of trial entry
Treatment	Details of rituximab, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) and other disease cohort specific treatments	As soon as possible after re-boost vaccination and no later than 2 weeks after trial entry
Vaccination	Date of re-boost vaccination, type of vaccination, batch number (if known)	As soon as possible after re-boost vaccination and no later than 2 weeks after re-boost vaccination
Adverse Event	Details of AEs including date of on-set and grade	No later than 2 weeks after re-boost vaccination
Research Blood Sample Collection	Confirmation of collection of research blood samples in accordance with the protocol	As soon as possible on collection of research blood samples

Form	Summary of Data Recorded*	Schedule for Submission to Trial Office
Follow-up	Survival data, COVID-19 infection data, WHO performance status, disease site specific follow-up information where relevant	Three months post re-vaccination
Death	Date and cause of death	As soon as possible upon notification of participant's death
Withdrawal of Consent	Used to notify the Trial Office of the participant's withdrawal from the trial	As soon as possible upon participant withdrawal
Deviation	Details on deviations from the protocol not captured elsewhere on the CRF	As soon as possible upon discovery of a deviation
Serious Adverse Event	Details of any SAE meeting the definition of an SAE (see Section 8.1.2)	No later than 24h after becoming aware of the event
Pregnancy Notification	Details of any pregnancy which occurs within 3 months of re-vaccination	No later than 24h after becoming aware of the event

This trial will use an eRDC system to capture the CRF data, the only exception to this will be the Eligibility Checklist and SAE Form which will be completed on paper and emailed to the Trial Office.

Access to the eRDC system will be granted to site research staff by the Trial Office.

https://www.cancertrials.bham.ac.uk

The investigator and site staff will ensure all data is promptly entered into the eRDC system in accordance with the trial specific User Manual and CRF Completion Guidelines. The CRF must be completed by the investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log).

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on the CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The CRF may be amended from time to time by the Trial Office throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRF must be implemented by participating sites immediately on receipt.

9.1 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g., signed Informed Consent Forms, Investigator Site Files, participants' hospital notes, etc.) at their site are securely retained for at least 10 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Archivist.

10 QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

All sites will be required to sign a model Clinical Trials Agreement (mNCA) prior to participation. In addition, all participating investigators will be asked to sign the necessary agreements e.g., Registration Forms and supply a current *curriculum vitae* (CV) to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. A light touch initiation process will be conducted for sites participating in the OCTAVE trial which utilises nearly identical procedures. For all other sites initiation meetings will be held on request. Where these are held, key members of the site research team will be invited to attend a teleconference covering aspects of the trial design, protocol procedures, collection and reporting of data and record keeping. Sites will be provided with the documentation for an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the OCTAVE-DUO Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the OCTAVE-DUO trial staff access to source documents as requested.

10.3 Central Monitoring

The Trial Office will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial staff will check incoming CRF for compliance with the protocol, data consistency, missing data and timing. Sites will be sent queries through the eRDC system requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or Good Clinical Practice (GCP). Any major problems identified during monitoring may be reported to the TMG and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC (see Section 10.5 for further details).

10.4 Audit and Inspection

The investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are requested to notify the Trial Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11 END OF TRIAL DEFINITION

The end of trial will be 18 months after the last participants' last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input, and sample analyses. The Trial Office will notify the MHRA and REC that the trial has ended and will provide them with a summary of the trial report within 12 months of the end of trial.

12 STATISTICAL CONSIDERATIONS

12.1 Definition of Outcome Measures

12.1.1 Primary Outcome Measures

The primary outcome measure is defined in Section 2.2.1.

12.1.2 Secondary Outcome Measures

Secondary outcome measures are defined in Section 2.2.2.

12.2 Analysis of Outcome Measures

Full details will be specified in a Statistical Analysis Plan (SAP) but an outline of the analysis methodologies of the primary and secondary outcome measures are provided here.

Statistical analyses will be performed using appropriate statistical software (e.g. Stata, Stata Inc, Texas, USA).

12.2.1 Primary Outcome Measures

The primary outcome assessment will be based on the immune response observed in the total combined participants recruited to both the Pfizer and Moderna vaccine arms (n=1160). Analysis will be based on the difference in immune response measured using the specified assays at baseline (pre-third vaccination booster) and then at Day 21 post-third vaccination booster using a paired T-Test analysis method.

12.2.2 Secondary Outcome Measures

Assay data from the subset of lymphoid malignancies, randomised into one of either Pfizer, Moderna or Novavax vaccine arms, will be analysed using repeated measure analysis of variance (ANOVA) with a Tukey's post-hoc test to detect differences in groups if any significant differences are detected.

Analysis of the IgG (pseudo) neutralisation assay data will be analysed using repeated measure ANOVA with a Tukey's post-hoc test to detect differences between groups if any significant differences are detected.

12.2.3 Planned Subgroup Analyses

Subgroup analyses will be carried out in order to investigate immune responses in disease-specific cohorts. Comparisons of vaccine performance within specific diseases will be examined.

12.2.4 Exploratory Analyses

A descriptive analysis of the reported adverse events in the participants will be presented.

The exploratory analyses will utilise the methods to analyse data as described in Section 12.2.2 where appropriate.

12.2.5 Interim Analyses

An interim analysis will be undertaken on the first 160 patients (combining all disease groups, including participants in the main randomisation and sub-study randomisation). This will be a descriptive analysis of the magnitude of the anti-spike and anti-nucleocapsid Ig response, the Menarini Diagnostics surrogate neutralisation antibody response and the T cell responses as measured by the Oxford Immunotec modified T-SPOT Discovery SARS-CoV-2 assay. A further interim analysis will be conducted as the results may be relevant to the public's interest. The analysis will be conducted as specified in the SAP.

12.2.6 Sample Size Justification

12.2.6.1 Primary outcome sample size justification

A power calculation based on a paired T-Test was performed using Stata version 17.0 (Stata Corps, USA) to estimate the detectable effect size based on a proposed recruitment of 1100 participants (this reduction of 60 participants allows for withdrawal or loss to follow-up). It was found that with 1100 pairs using 90% power and significance (alpha) set to 5%, a very small effect size of 0.0978 would be detectable. For 800 evaluable patients with a significance (alpha) set at 5% an effect size of 0.0978 would be detectable with 79% power.

12.2.6.2 Secondary outcome sample size justification for sub-study randomisation

There is a potential for 320 participants to be recruited to the sub-study, however, in order to allow for drop out or recruitment failures, a total number of 300 recruits has been used in the power calculation. A power calculation based on an ANOVA statistical test was carried out using Stata version 17.0 (Stata Corps, USA) to estimate the detectable effect size based on total sample size number of 300 participants, recruited into one of three treatment arms (Pfizer, Moderna or Novavax, n=100 in each arm). Using power of 80%, significance (alpha) set at 5%, an effect size of 0.1801 would be detected.

These power calculations will be revised should the recruitment numbers differ from those predicted.

13 TRIAL ORGANISATIONAL STRUCTURE

This is a collaborative trial being conducted by the University of Glasgow, University of Birmingham, University of Oxford and Imperial College London. Additional sites will participate in the study.

13.1 Sponsor

The trial is being sponsored by the University of Birmingham.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the CRCTU, University of Birmingham according to their local procedures.

13.3 Access Committee

An Access Committee has been established to ensure the appropriate governance of the research samples. Samples will be made available to academic researchers for ethically approved studies, subject to the approval of the Access Committee.

13.4 Trial Management Group

The Chief Investigator, Deputy Chief Investigator, cohort leads, co-investigators, trial statisticians, Patient and Public Involvement and Engagement (PPIE) representatives, Trial Management Team Leader and Trial Coordinator will form the TMG. The TMG will be responsible for the day-to-day conduct of the trial. They will be responsible for the clinical set-up, promotion, ongoing management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

The TMG will meet formally (virtually) weekly during the recruitment phase of the trial. Thereafter the formal TMG meetings may be replaced by a regular progress report.

The membership of the OCTAVE-DUO TMG is almost identical to the OCTAVE TMG hence it is anticipated joint meetings will be held whenever possible.

13.5 Trial Steering Committee

The TSC will be set up to oversee the trial. Membership will be composed of independent clinicians and at least one patient advocate. Members of the TMG will report to the TSC. The TSC will meet three monthly once the trial opens to recruitment, they will supervise the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial.

13.6 Data Monitoring Committee

Data analyses pertaining to trial conduct, data quality and patient safety will be supplied in confidence to an independent DMC, which will be asked to advise on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further

patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet following the interim analysis and then 3 monthly during recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.

13.7 Finance

This is an investigator-initiated and investigator-led trial funded by UK Research and Innovation (UKRI) in accordance with Medical Research Council grant terms and conditions**.** The trial has been adopted on to the NIHR CRN Portfolio.

Individual per patient payment will be made to NHS Trusts to cover the NHS Research costs.

Participants will be able to claim travel expenses for extra clinic visits but no other payments will be made for taking part in the trial.

Novavax SARS-CoV-2 vaccine is provided free of charge by the biotechnology company Novavax LTD.

Pfizer and Moderna SARS-CoV-2 vaccines will be supplied by PHE via the normal clinical supply route.

14 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (Appendix 5).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments; the General Data Protection Regulation 2018; and Data Protection Act 2018; and Human Tissue Act 2004 or Human Tissue (Scotland) Act 2006 and GCP.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC and Health Research Authority prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain formal confirmation of capacity and capability from their local R&D Department and provide evidence of this to the Trial Office. Sites will not be permitted to enrol patients until this has been obtained.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15 CONFIDENTIALITY AND DATA PROTECTION

The University of Birmingham is the Data Controller for this trial. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation 2018 and the Data Protection Act 2018. Data will be processed under Article 6 (i) (performance of a task carried out in the public interest) and Article 9 (j) (necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1)). Information about how information is handled can be found in the CRCTU and University of Birmingham's privacy policies:

https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/crctu-privacy-notice.aspx

The participant's initials, date of birth, NHS/CHI Number and hospital number will be collected at trial entry to aid in identification and matching with other data sources where appropriate for the purposes of further analysis. Patients will be identified using only their unique trial number and initials on the CRF and correspondence between the Trial Office and the participating site.

The investigator must maintain documents not for submission to the Trial Office in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Representatives of the CRCTU may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

The Trial Office will maintain the confidentiality of all participants' data and will not disclose information by which participant may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given consent for data transfer. Anonymised participant level data and research samples may be shared in accordance with the CRCTU Data Sharing Policy (see Section 18 for further details).

16 INSURANCE AND INDEMNITY

The University of Birmingham has in place indemnity 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 trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at site and other clinical care of the participant, responsibility remains with the NHS organisation responsible for the clinical site and is therefore indemnified through the NHS Litigation Authority.

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.

17 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscripts will be prepared by the TMG and authorship will be on behalf of the collaborative group in accordance with the trial Publication Policy.

Any secondary publications and presentations prepared by investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham and all funding bodies must be appropriately acknowledged in accordance with the funder's terms and conditions. Intellectual property rights will be addressed in the agreements between sponsor, collaborators and the sites.

The results of the trial will be made available on ISRCTN and provided to participants in the form of a lay summary on the trial website.

18 DATA SHARING

The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of trial participants. Data anonymised in compliance with the Information Commissioners Office requirements, using a procedure based on guidelines from the MRC Methodology Hubs, will be available for sharing with researchers outside of the trials team within 6 months of the primary publication.

More detailed information on the CRCTU's Data Sharing Policy and the mechanism for obtaining data can be found on the CRCTU website:
https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/index.aspx.

19 REFERENCE LIST

1. *Public Health England Report: COVID-19 vaccine surveillance report - Week 24* 2021.
2. Lopez Bernal, J., et al., *Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study.* Bmj, 2021. **373**: p. n1088.
3. *Office of National Statistics Report: Living longer: how our population is changing and why it matters* 2018.
4. Lim, S.H., et al., *Antibody Responses after SARS-CoV-2 Vaccination in Lymphoma.* Lancet Haematology, 2021. **In press**.
5. Kamar, N., et al., *Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients.* New England Journal of Medicine, 2021. **Letter**.
6. Werbel, W.A., et al., *Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series.* Annals of Internal Medicine, 2021. **Letters**.
7. Peng, Y., et al., *Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19.* Nature Immunology, 2020. **21**(11): p. 1336-1345.
8. Ogbe, A., et al., *T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral responses.* Nature Communications, 2021. **12**(1): p. 2055.

APPENDIX 1 - SARS-COV-2 SPIKE ANTIBODY ASSAYS - DEFINITION OF INADEQUATE RESPONSE

Assay	Antibody non responder (AU/ml)	Antibody low responder (AU/ml)
Abbott	<50	≥ 50 but <700
Diasorin	Either <33.8 AU/ml for Trimeric S or 15 AU/ml for S1/S2.	For Trimeric S: equal to or >33.8 AU/ml and <400; or For SI/S2: >15 AU/ml and <400 Please Note: if results are available by both methods, both need to be <400
Roche	<0.8	≥ 0.8 and <400
SIEMENS*	0.0	N/A
The Binding Site	<0.04	0.04 and 3.14

***** The SIEMENS assay has a binary response (negative or positive). All patients are randomised as non-responders.

Note: Other assays with a relative relevant mark of conformity (e.g. UKCA, CE or CE UKNI) may be added following discussion with, and approval by, the Trial Management Group.

Justification for Definitions of Antibody Non-responder and Anti-body Low Responder

Abbot Assay

The justification for the cut off for the antibody non-responder and the low responder for the CE marked Abbot SARS-CoV-2 IgG II Quant antibody test (see https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2- and https://abbott.mediaroom.com/2020-12-15-Abbott-Receives-CE-Mark-for-its-COVID-19-IgG-Quantitative-Antibody-Blood-Test) was determined in 356 samples using both the Roche and Abbot assays.

The 356 paired results were plotted and the IgG Abbot value corresponding to the set Roche cut-offs for enrolment in OCTAVE DUO determined.

The commercially defined cut off for positivity on the Abbot assay is a value equal to > 50. Anything below this is, by definition, negative.

The equivalent Abbot value for low response is between 50 and 700.

The equivalent Abbot value for non-response is <50.

Diasorin Assay

The justification for the cut off for the antibody non-responder and the low responder for the CE marked LIAISON SARS-CoV-2 S1/S2 IgG assay and CE marked LIAISON SARS-CoV-2 TrimericS IgG assay produced by Diasorin (see https://www.diasorin.com/sites/default/files/allegati/liaisonr_sars-cov-2_s1s2_igg_brochure.pdf) or https://www.diasorin.com/sites/default/files/allegati_prodotti/liaisonr_sars-cov-2_trimerics_igg_assay_m0870004408_a_lr_0.pdf) was based on published data (https://journals.asm.org/doi/10.1128/Spectrum.00247-21, https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30634-4/fulltext).

The commercially defined cut off for positivity on the Diasorin assay is equal to >33.8 AU/ml for Trimeric S or is equal to >15 AU/ml for S1/S2. Anything below this is, by definition, negative.

The equivalent Diasorin assay value for low response is between 33.8 AU/ml and 400 for the Trimeric S assay; or 15 AU/ml and 400 for the SI/S2 assay.

The equivalent Diasorin assay value for non-response is <33.8 AU/ml for Trimeric S or <15 AU/ml for S1/S2.

Roche

The justification for the cut off for the antibody non-responder and the low responder for the CE marked Roche Elecsys Anti-SARS-CoV-2 S assay (see https://diagnostics.roche.com/in/en_gb/news-listing/2021/RocheReceivesApprovalforLaboratoryBasedElecsysSARS-CoV-2AntigenTest.html) is included on page 8 of the protocol.

SIEMENS Assay

The SIEMENS SARS-CoV-2 Total (COV2T) CE marked assay (see https://www.fda.gov/media/138442/download) reports results as Nonreactive (< 1.00 Index) and Reactive (≥ 1.00 Index).

The commercially defined cut off for positivity on the Diasorin assay is equal to > 1.00. Anything below this is, by definition, negative.

There is no equivalent Siemens assay value for low response, and therefore this assay cannot be used to define low responders.

The equivalent Siemens assay value for non-response is <1.

The Binding Site Assay

In order to generate the ranges used to define enrolment to the OCTAVE DUO study for participants with previous serological results run on the Binding Site (TBS) Human Anti-IgG/A/M SARS-CoV-2 ELISA (MK654, CE Marked assay, https://www.bindingsite.com/en/our-products/covid-19), anti-spike antibody concentrations were determined in 253 samples using both the Roche and TBS assays.

Results were aligned in rank order and trimmed using Healey's method to remove outlier results generated on either platform. The remaining 211 paired results were plotted and the IgGAM TBS Ratio corresponding to the set Roche cut-offs for enrolment in OCTAVE DUO determined.

The commercially defined cut off for positivity on the TBS assay is a ratio of 1.0. Anything below this is, by definition, negative.

The equivalent TBS ratio for low response is between 0.04 and 3.14.

The equivalent TBS ratio for non response is <0.04.

APPENDIX 2 - DEFINITION OF ADVERSE EVENTS

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an IMP whether or not related to the IMP.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting investigator or sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction (SAR)

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction (UAR)

An AR, the nature or severity of which is not consistent with the Reference Safety Information.

When the outcome of an AR is not consistent with the Reference Safety Information, the AR should be considered unexpected.

APPENDIX 3 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved: https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX 4 – WORLD HEALTH ORGANISATION (WHO) PERFORMANCE STATUS

Grade	WHO Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 5 - WMA DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human patients

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly, Somerset West, Republic of South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human patients must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human patients.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human patients. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

a. Biomedical research involving human patients must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

b. The design and performance of each experimental procedure involving human patients should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

c. Biomedical research involving human patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given his or her consent.

d. Biomedical research involving human patients cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the patient.

e. Every biomedical research project involving human patients should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the patient or to others. Concern for the interests of the patient must always prevail over the interests of science and society.

f. The right of the research patient to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the patient and to minimize the impact of the study on the patient's physical and mental integrity and on the personality of the patient.

g. Physicians should abstain from engaging in research projects involving human patients unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

h. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

i. In any research on human beings, each potential patient must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the patient's freely-given informed consent, preferably in writing.

j. When obtaining informed consent for the research project the physician should be particularly cautious if the patient is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

k. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the patient is a minor, permission from the responsible relative replaces that of the patient in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

l. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The patient should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the patient.

NOTES

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Trial Database

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Serious Adverse Event Reporting

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Include "OCTAVE-DUO SAE" in the subject line