Observational Cohort Trial-T-cells Antibodies and Vaccine Efficacy in SARS-CoV-2

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OCTAVE Trial Protocol

This protocol has been approved by:

Name: IAIN MCNNOY **Trial Role:** Chief Investigator

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This protocol describes the OCTAVE 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
SAM01	24-Feb-2021	V 2.0	Substantial	Change to eligibility criteria to allow the Deep Immunophenotyping Group participants to enter the trial after receiving the first vaccination and Serology Group prior to post-booster time point. Clarification of sample collection requirement. Other non-substantial changes including addition of Trial Summary
SA_04	12-Apr-2021	V 3.0	Substantial	Removed reference to the Green Book and added that vaccines should be administered in accordance with national guidelines and current versions of the applicable information for healthcare professionals.
NSA_01	22-Apr-2021	V 4.0	Non-Substantial	Change in eligibility criteria to add recruitment of participants with systemic lupus erythematosus (SLE) and treatment with IL-12/23 inhibitors and IL-23 inhibitors Clarification of sample collection time points and Other non-substantial changes, including: change of term boost to booster to refer to second dose of the vaccine; changes to CRF Forms table; inclusion on on-site monitoring section.
SA_05	24-Jun-2021	V 5.0	Substantial	Clarification of sample collection time points Change of sample size Clarification eligibility criteria for HSCT patients
NSA_04	14-Jul-2021	V 6.0	Non-Substantial	Addition of provision to Principal Investigators with the results of their patients' assessment of immune response and that participants should be provided with the results on request.

TRIAL SYNOPSIS

Title	**OCTAVE**: Observational Cohort Trial -T-cells Antibodies and Vaccine Efficacy in SARS-CoV-2
Trial Design	Multi-centre, multi-disease, prospective observational cohort trial of the immune response to SARS-CoV-2 vaccination.
Aim	To evaluate the immune response to SARS-CoV-2 vaccination in clinically vulnerable groups across the UK.
Objectives	**Primary Objective** • To determine the magnitude of the humoral and T cell immunogenicity of SARS-CoV-2 vaccines in participants with chronic diseases and/or secondary immunodeficiency. **Secondary Objectives** • To determine phenotype and function of SARS-CoV-2 vaccine induced immune responses in participants with chronic diseases and/or secondary immunodeficiency, compared to each other and healthy controls in parallel studies. • To evaluate the impact of distinct immune therapeutic drug classes on the development of humoral and cellular immune responses to SARS-CoV-2 following vaccination.
Outcome Measures	**Primary Outcomes** Vaccine Specific Immunogenicity: • To measure the presence and amount of serum antibodies to discriminate IgG responses to SARS-CoV-2 from vaccination and/or infection. • To measure T cell responses to SARS-CoV-2 peptides following vaccination. **Secondary Outcomes** Clinical Protection • The first symptomatic PCR-proven COVID-19 occurrence from 14 days after first dose of vaccine in participants without evidence of prior infection with SARS-CoV-2. **Exploratory Outcomes** Humoral Immunogenicity • To assess the capacity of vaccine induced SARS-CoV-2 antibodies to neutralise/block SARS-CoV-2 infection. Cellular Immunogenicity • To assess the relative contribution of T cell subsets and T cell function and the recall potential of SARS-CoV-2 memory T cells at later time points.
Patient Population	Participants with end stage kidney disease, liver disease or gastrointestinal disease on immune suppressive therapy, cancer, immune-mediated rheumatic diseases and haematopoietic stem cell transplant recipients who are receiving the SARS-CoV-2 as part of the national vaccination programme.

Sample Size	**Deep Immunophenotyping Group:** between 100 and 200 participants depending on disease cohort will be recruited for full immune response analysis. **Serology Group:** between 150 and 850 participants depending on disease cohort, for serology analysis **Total:** Up to 3250participants

Inclusion Criteria	• Eligible for vaccination by one of the SARS-CoV-2 approved vaccines and:
	  ○ For the Deep Immunophenotyping Group, have not received the second dose of vaccine (booster)
	  ○ For the Serology Group, have not passed 28 days post booster (within -7/+56 days)
	  ○ Anticipated life expectancy of ≥ 6 months
	• Fall into one (or more) of the five disease cohorts who will meet disease relevant classification, disease state, and staging according to established international standards (refer to protocol for details)

Sample Collection	**Deep Immunophenotyping Group:** whole blood, peripheral blood mononuclear cells (PBMC), serum, plasma and saliva will be collected at the following time points: • Pre-vaccine, baseline (optional) – may have been collected prior to recruitment to OCTAVE • 1 day after first vaccination (optional) – tempus and EDTA sample only • Pre-booster • 28 days post-booster (ideally within +/- 3 days) • 6 months post-booster (as close to time point as possible) • 12 months after first vaccine dose or prior to third vaccine dose (if applicable), whichever is earlier **Serology Group:** serum (as a minimum) collected at the following time points: • Pre-vaccine, baseline (optional) – may have been collected prior to recruitment to OCTAVE • Pre-booster (optional) – any time after first vaccination and before booster • 28 days post-booster (within -7/+ 56 days)
Trial Duration	Patients will be recruited over a 6 month period and followed up for 12 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 Trial Office:** Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Edgbaston, Birmingham, B15 2TT ✉ OCTAVE@trials.bham.ac.uk

SCHEDULE OF EVENTS

		Screening	Trial Entry	Baseline[1] *Prior to vaccination Optional*	Day 1 After First Vaccination[2] *Optional*	Pre-Booster	Post-Booster[3] *28 days post 2nd vaccination*	6 Months Post Booster[4]	6 Month Follow-up *Seen in accordance with clinical practice*[5]	12 Months[6]
Eligibility assessment		x								
Consent		x								
Trial entry			x							
Research samples	Deep immunophenotyping Group[7]			x	x	x	x	x		x
	Serology Group[8]			x		x[9]	x			
Data collection				x			x		x	x

Key

[1] Optional sample. Baseline research samples may also be collected prior to recruitment to OCTAVE as part of another Research Ethics Committee (REC) approved study

[2] Optional sample. To include 3ml tempus sample and 2-3 x 9ml EDTA samples only

[3] +/- 3 days for the Deep Immunophenotyping Group and -7/+ 56 days for the Serology Group

[4] Six months after booster, as close to time point as possible

[5] Six months after booster, data collected retrospectively from participants medical records

[6] Twelve months after first vaccine dose or prior third vaccine dose (if applicable), whichever is earlier

[7] Research samples include: whole blood, peripheral blood mononuclear cells (PBMC), serum, plasma and saliva

[8] Research samples include: serum as a minimum, whole blood, peripheral blood mononuclear cells (PBMC), and plasma where possible

[9] Optional sample. Any time after first vaccination but before booster

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1. BACKGROUND AND RATIONALE

1.1 SARS-CoV-2 Vaccines

The rapid development and subsequent authorisation of vaccines against SARS-CoV-2 has been a major step forward for medical science. In the UK, three vaccines are already approved by the Medicines and Healthcare products and Regulatory Agency (MHRA), the COVID-19 mRNA Vaccine BNT162b2 (Pfizer/BioNTech), COVID-19 Vaccine AstraZeneca (formerly AZD1222), and the mRNA vaccine developed by Moderna (COVID-19 Vaccine Moderna). It is likely that further vaccines will become available in the coming months. National vaccination programmes have been initiated in the UK for Pfizer-BioNtech and the Astra-Zeneca vaccines. The populations evaluated in the trials of these vaccines were generally healthy volunteers. Therefore questions remain as to the level of protection these vaccines will afford patient populations with chronic illnesses who may have primary or secondary immune deficiencies and, therefore, may not generate the same protective responses observed in healthy volunteers.

This prospective observational trial will investigate the immune responses and protective value of approved SARS-CoV-2 vaccines as they are implemented in the national vaccination programme in patient cohorts with a range of chronic diseases that intrinsically, or as a result of the associated therapies, have impaired immunity. The effectiveness of the immune response and its durability will be assessed.

1.1.1 Justification for the Trial and Participant Population

The differential impact of COVID-19 infection in multiple disease groups has been extensively reported over the last 12 months. In particular, patient disease cohorts with end stage kidney disease, liver disease, cancer, immune-mediated rheumatic diseases, and transplant recipients are likely to exhibit altered immune responses to SARS-CoV-2 vaccines either as a function of their underlying disease and associated immune dysregulation or due to their requisite management with immune modifying medications, including biologics, disease-modifying anti-rheumatic drugs (DMARDs), broad spectrum immune suppressants and glucocorticoids.

1.1.1.1 Cancer

In the field of oncology, there are reports to suggest that some patients with cancer are more likely to be infected by SARS-CoV-2, develop a severe COVID-19 infection and more likely to die as a result of COVID-19. There is wide heterogeneity of this patient population, including the disease type, stage, nature of the (multi-modality) treatment, age and co-morbidities. Multiple prospective cohort studies have identified consistent patterns of groups of patients at risk of more severe outcomes, including patients with lung cancer, haematological malignancies and advanced or active cancers. There is a notable difference between the impact on patients with solid tumours compared to haematological malignancies, especially multiple myeloma (MM) where disease and treatment related immune dysfunction combines with the advanced age to result in significant mortality risk [1-3]. The UK Coronavirus Cancer Monitoring project [4, 5] recently updated its analyses and compared patients who

died of COVID-19, rather than of all causes. This revealed that patients with MM (N=108; OR 1.99; 1.18-3.34; p=0.010), leukaemia (N=139; OR 2.07; 1.24-3.44; p=0.005), as well as lung cancer (N=201; OR 1.61; 1.02-2.56; p=0.041) were at significantly increased risk of death (Middleton, manuscript in preparation). The impact of systemic anti-cancer chemotherapy *per se* is less clear but factors associated with adverse outcome in the general population, including male sex, increasing age, comorbidities, poor performance status, and smoking are also negative risk factors in the cancer patients.

There is clear vulnerability of patients with cancer to COVID-19, which therefore increases the importance of vaccination to this patient group. However, their reduced immune-competence may also compromise their response to SARS-CoV-2 immunisation. Indeed, the same factors that increase risk of COVID-19 in these patients may also reduce their immune response to SARs-Cov-2 vaccines. Studies have demonstrated that the immunogenicity of influenza vaccines is lower in patients with cancer compared to healthy individuals [6]. Population studies demonstrate that influenza vaccine effectiveness is only 25% in patients with solid tumours and only 8% in patients with haematological malignancies. The humoral immunogenicity of influenza vaccination was less in patients receiving cytotoxic chemotherapy compared to those receiving immune checkpoint inhibitors [5].

Solid Tumours

Breast Cancer

Breast cancer is the commonest cancer in women, affecting up to 1 in 7 women with 55,000 new cases per year in the UK and causing 11,000 deaths per year [7]. Treatment for both early and advanced disease is complex and multimodal involving surgery, radiotherapy, chemotherapy and targeted therapies including endocrine therapy, anti HER-2 therapies, immunotherapy and other treatments such as CDK inhibitors and m-TOR inhibitors. Treatment for early disease is often protracted with immunosuppressive treatments for up to 6 months and many adjuvant therapies extending over many years. In advanced disease, patients can be on myelosuppressive treatment for very protracted periods often extending over several years. Understanding the effectiveness of the SARS-CoV-2 vaccine in breast cancer patients undergoing treatment in both early and advanced disease settings is of great importance.

Lung Cancer

There are nearly 48,000 new cases of lung cancer per annum in the UK making it the second most common cancer in both women and men. The incidence is highest in the 85-89 age group, a demographic highly associated with poor outcomes following COVID infection [5] and 44% are diagnosed in those aged 75 or above. Although the outcome for the majority of patients with advanced inoperable disease used to be uniformly poor, both targeted therapy and immunotherapy have transformed the outcome for numerous patients with the prospect of long-term survival for many. COVID-19 represents a particularly ominous threat to patients with lung cancer and they are a cancer group that arguably more than any other might benefit from vaccination to protect against COVID infection. The UK Coronavirus Cancer Monitoring project compared the case fatality rate of patients with different solid cancers and demonstrated that patients at significantly increased risk of death as

a result of COVID infection were those with lung cancer (n=227; OR 1.62; 95% CI 1.07-,2.46; p=0.023) compared to digestive tract cancer patients. Of the 227 lung cancer patients with valid outcome, age, gender and comorbidities, there were 113 patients who received no treatment, 45 patients who received chemotherapy, 34 patients who received immunotherapy, and 32 patients who received radiotherapy in the 4 weeks before a COVID-19 diagnosis. Multivariate analysis adjusted for age, gender and comorbidities, revealed lung cancer patients who received immunotherapy in the 4 weeks before a COVID-19 diagnosis had a significantly lower risk of death than those who did not receive immunotherapy (N=34; OR 0.40; 0.18-0.89; p=0.025). On the other hand, lung cancer patients who received chemotherapy in the 4 weeks before a COVID-19 diagnosis had no significantly different outcome compared to those patients who did not receive chemotherapy (N=45; OR 0.698; 0.35-1.37; p=0.290). Similarly, lung cancer patients who received radiotherapy in the 4 weeks before a COVID-19 diagnosis did not have a significantly different outcome compared to those patients who did not receive radiotherapy (N=32; OR 1.03; 0.48-2.23; p=0.942).

In a study of outcomes of unplanned hospital admissions of patients with non-small-cell lung carcinoma (NSCLC), 36% were a direct result of pneumonia with an in-patient mortality of 43.9% compared with 13.1% for all other causes [8]. Crucially, a positive 5-year pneumovax status was protective with an odds ratio of 0.16. In the pneumonia cohort, pneumovax status also significantly reduced mortality with the odds ration being 0.269 in multivariable analysis. For patients admitted to hospital with pneumonia without previous pneumovax vaccination in the past 5 years the odds of death were almost 60-fold higher compared with those that had been vaccinated.

In summary lung cancer, the second commonest cancer in men and women, is associated with significantly increased risk of death after COVID infection which does not appear to be related to chronic obstructive pulmonary disease, smoking or treatment. The protective benefit of pneumovax vaccination strongly supports a programme of prophylactic COVID vaccination in these patients but the efficacy of such vaccination in engendering an immune response against the virus, will be explored in the OCTAVE trial.

Malignant Haematology

In a systematic review of the outcome of blood cancer patients with COVID-19, hospitalised patients have a high risk of death (pooled risk estimate 36%). Older patients experience higher mortality, and paediatric patients appear to be relatively spared [1]. All subgroups of haematological malignancies had high risks of overall mortality: acquired bone marrow dysfunction syndromes 57% (95% CI 42-72, 11 studies, 42 patients); leukaemias 44% (95% CI 31-58, 15 studies, 159 patients), MM 38% (95% CI 29-47, 18 studies, 387 patients); lymphomas (including chronic lymphocytic leukaemia (CLL)) 32% (95% CI 26-38, 16 studies, 696 patients); lymphomas (excluding CLL) 32% (95% CI 18-48, 11 studies, 156 patients); CLL 31% (95% CI 24-39, 13 studies, 457 patients) and myeloproliferative neoplasms 37% (95% CI 25-49, 9 studies, 62 patients). Importantly, based on the observational data available to date, recent cancer treatment does not appear to significantly increase the risk of dying. These data highlight the need for robust strategies to prevent patients with hematologic malignancy from contracting COVID-19.

Multiple Myeloma

Patients with MM, a malignancy of terminally differentiated B-cells, may be at particularly high risk from COVID-19 owing to the significant disease and treatment-related immune dysfunction present throughout the disease course. This disordered immunity is multifactorial and progressive with advancing disease, affecting innate and humoral compartments [9-13]. Occurring in a predominantly elderly population, often with multiple co-morbidities, this MM-associated immune dysfunction is additive to a background of age-related immunodeficiency and immunosenescence [14]. This is further compounded by the immunosuppressive and immunomodulatory impact of therapy, particularly autologous haemopoietic stem cell transplant (ASCT). Despite marked improvements in MM outcomes in the last 20 years, infection remains a leading cause of death, with MM patients rendered particularly susceptible to adverse outcome from both bacterial and viral respiratory tract infections [15, 16]. Responses to vaccination are frequently inadequate or short-lived. Whilst data regarding novel coronavirus vaccines in MM patients are lacking, it is likely that the impact of COVID-19 on patient management will continue until there is a significant background level of vaccination-mediated herd immunity.

Published studies on outcome in MM patients with COVID-19 are limited and drawn from early experience in the pandemic. The Spanish Myeloma Collaborative Group have reported the largest cohort to date (167 inpatients from 67 centres), though this was from early in the first wave (patients experiencing COVID-19 from 1st of March to 30th of April 2020). Mortality was 34% in MM patients, compared to 23% in non-cancer patients, rising to 42% in those >65 years and 49% for those with active or progressive disease [17]. Datasets from New York indicated a mortality rate of 30% for patients requiring in-hospital management. Interim analysis of the UK early first wave experience was published in June 2020, where the highest reported mortality of 55% was seen, rising to 71% in those >80 years [3].

Acute Myeloid Leukaemia

Acute myeloid leukaemia (AML) is the second commonest adult haematological malignancy and its incidence rises to more than 30 per 100,000 in patients over 70 years of age. In fit adults under the age of 75 intensive chemotherapy, consolidated by allogeneic hematopoietic stem cell transplant (allo-HSCT), represents an important curative strategy [18]. In older patients, venetoclax, in combination with azacitidine has emerged as the new standard of care [19]. In both populations, standard treatment options including potently myelosuppressive and immunosuppressive drug therapies are compounded in many patients by the additive immuno-paretic effects of the allo-HSCT. It is, therefore, no surprise that registry-based studies have identified an increased rate of both COVID-19 infection and mortality in adults with AML [20, 21]. Further prospective studies examining both the clinical course of COVID-19 infection and its immunological sequelae in adults with AML are required and Birmingham's CRCTU Trials Acceleration Programme has already recruited 193 patients to a national prospective non-interventional study (PACE) addressing this issue. Given the prolonged courses of therapy mandated for both younger and older adults with AML, it is vital that COVID-19 vaccination strategies are optimised with specific reference to timing in relation to chemotherapy, impact of specific chemotherapy regimens, including venetoclax based regimens in older patients. Vaccine

efficacy also needs to be studied in the sizeable population of patients with AML who subsequently undergo allo-HSCT.

1.1.1.2 Rheumatic and Inflammatory Diseases

Patients with immune-mediated rheumatic diseases require a range of long-term systemic immunosuppressive therapies to control their inflammatory diseases and are at increased risk of infections in general, which is increased further by these therapies [22-25]. This established vulnerability is now being realised in the context of COVID-19. These patients are at greater risk of infection, hospitalisation and death, with their therapies frequently predicting severe outcome [26-28]. Furthermore, many of these therapies are known to be associated with attenuated responses to influenza and other existing vaccines [29-31] and such patients were excluded from the existing studies of SARS-CoV-2 vaccines. Therefore, both the diseases and the therapies used to treat them may impact on response and require evaluation in this setting.

The immune-mediated rheumatic diseases are a heterogeneous group of conditions treated with a range of broad and targeted immunosuppressive therapies, which are likely to have differing impacts on SARS-CoV-2 infection and vaccination. It is not possible to study in detail all therapies or conditions, individually or in combination. Therefore, this trial will use a two-tiered approach in order to address the key research questions in detail for the most clinically relevant therapies and also to obtain information to understand the effects on the wider community of patients with immune-mediated inflammatory disorders (IMID) in a real-world setting.

The rheumatic and IMID component of the trial will recruit patients with inflammatory arthritis including rheumatoid arthritis (RA), seronegative and psoriatic arthritis (PsA) treated with methotrexate or tumour necrosis factor (TNF) inhibitors and patients with anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitis (AAV) treated with rituximab. Methotrexate and TNF inhibitors are the most widely prescribed conventional synthetic and biologic DMARDs in clinical practice in the UK and globally for inflammatory arthritis and a range of non-rheumatic IMID. Both therapies have been reported to be associated with reduced responses to existing vaccines [29, 30]. In order to minimise variability, these therapies will be evaluated in the context of inflammatory arthritis. Rituximab (anti-CD20 monoclonal antibody) is widely used for inflammatory rheumatic conditions, particularly in AAV where it is established as induction and maintenance therapy. Rituximab is of particular importance for SARS-CoV-2 vaccines in light of its B cell depletion and previous evidence of reduced humoral response to influenza vaccines [31, 32].

In addition, a wider clinical cohort of patients with rheumatic and inflammatory diseases who are being treated with these and other immunomodulatory therapies will be included for investigation of their serological response to the SARS-CoV-2 vaccines.

1.1.1.3 Chronic Renal Diseases

End-stage kidney disease (ESKD) is one of the strongest risk factors for severe COVID-19 (estimated hazard ratio for death 3.69) [33], and ESKD patients hospitalised with COVID-19 have a mortality of approximately 30% [34-37]. The UK renal registry and NHS Blood and Transplant have reported UK

national mortality rates of 19% in haemodialysis (HD) patients, and over 25% in renal transplant patients with COVID-19 [28, 38].

ESKD patients have a high prevalence of vascular and cardiometabolic disease (e.g. hypertension, ischaemic heart disease, diabetes), either as a result of the underlying cause of their renal disease and/or as a consequence of renal failure. In addition, ESKD results in both relative immunosuppression and chronic low-grade inflammation [39-44], which may impact viral defence and the host inflammatory response. As well as being enriched for cardio-metabolic risk factors, the ESKD group being studied at Imperial College NHS Trust also has a high proportion of Black, Asian, Minority Ethnic (BAME) origin patients. Of the patients sampled in this on-going study, 72% are non-white, including 17% of African or Afro-Caribbean origin and 42% of South Asian origin. Patients in these subgroups are at higher risk of death from COVID-19 pneumonia.

Poor seroconversion is well-documented following standard vaccinations amongst haemodialysis patients [33] and we have observed a high rate of recurrent SARS-CoV-2 infection in haemodialysis (HD) patients. Current medications have not improved SARS-CoV-2 -related mortality in these cohorts [38], and HD patients cannot easily socially distance when required to attend dialysis units several times per week [45].

1.1.1.4 Chronic Liver Diseases or with Gastrointestinal Disease on Immune Suppressive Therapy

Patients with chronic liver disease (CLD) and especially with cirrhosis have multiple mechanisms of immune dysfunction that can lead to increased susceptibility to infections and an increased inflammatory response during infection. Collectively known as cirrhosis associated immune dysfunction (CAID), there are alterations in the complement system, macrophage, lymphocyte and neutrophil activity, altered toll like receptors, and increases in intestinal dysbiosis [33, 35]. A recent international observational study (covid-hep.net) recruited >1200 patients with chronic liver disease and showed that baseline liver disease stage and alcoholic liver disease are independent risk factor for death from COVID-19 compared to age matched controls patients. [46]. Additional studies have shown that liver transplant recipients are more likely to require Intensive Care Unit admissions following SARS-CoV-2 infection. [45,[47] Patients with cirrhosis also have been shown to have an attenuated response to existing vaccines.[48, 49], however, patients with significant liver disease largely not been included in existing studies of SARS-CoV-2 vaccines.

Patients with inflammatory bowel disease may show an attenuated response to vaccination as disease control often requires prolonged therapy with immune suppressive and biological therapies. Evidence exists mostly on influenza vaccination which suggests a lower serological response in patients on Infliximab (anti-TNF) therapies. Evidence addressing other types of vaccines and therapies such as vedolizumab and ustekinumab is scarce.

1.1.1.5 Haematopoietic Stem Cell Transplant Recipients

Haematopoietic stem cell transplant (HSCT) is a potentially curative treatment for a range of malignant and non-malignant haematological conditions. Autologous (auto-) HSCT may induce periods of long-term remission in refractory autoimmune conditions. Reported outcomes of COVID-19 in patients treated with HSCT are limited to case series, but this group appears to be highly susceptible with

mortality up to 30% [50, 51]. Autologous (ASCT) and allo-HSCT recipients are immunocompromised for months to a year or more following the procedure, with quantitative and qualitative defects in the innate and adaptive immune response. In the pre-COVID-19 pandemic era, infections accounted for up to 10% of all-cause mortality following allo-HSCT [52]. Measures to reduce infection post-HSCT include physical infection control procedures, prophylactic antimicrobials and immunisation against vaccine preventable diseases. Antibody and T-cell responses to a range of vaccines are reported from 3 months post-HSCT respectively [53, 54], however the corresponding level of clinical protection against most vaccine preventable diseases in this population is unclear. The immunogenicity of the SARS-CoV-2 vaccine technologies in HSCT recipients is unknown, therefore prospective evaluation of vaccine immunogenicity and exploration of the patient, transplant and donor characteristics that impact this will inform optimisation of SARS-CoV-2 vaccine timing post-HSCT.

2. AIM, OBJECTIVES AND OUTCOME MEASURES

The aim of this trial is to evaluate the immune response to SARS-CoV-2 vaccination in clinically vulnerable groups across the UK.

2.1 Objectives

2.1.1 Primary Objective

- To determine the magnitude of the immune response to SARS-CoV-2 vaccines in participants with chronic diseases and/or secondary immunodeficiency

2.1.2 Secondary Objectives

- To determine phenotype and function of SARS-CoV-2 vaccine induced immune responses in participants with chronic diseases and/or secondary immunodeficiency, compared to each other and healthy controls in parallel studies
- To evaluate the impact of distinct immune therapeutic drug classes on the development of humoral and cellular immune responses to SARS-CoV-2 following vaccination

2.2 Outcome Measures

2.2.1 Primary Outcomes

2.2.1.1 Vaccine specific Immunogenicity:

- Anti-SARS-CoV-2 IgG Abs following vaccination will be measured using the Roche platforms by the Public Health England Laboratories at Porton Down. The Roche assay measures 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 IgG responses to SARS-CoV-2 that results from vaccination and/or SARS-CoV-2 infection.

- T cell responses to SARS-CoV-2 peptides following vaccination will be measured using the Oxford Immunotec modified T-SPOT Discovery SARS-CoV-2 assay. This IFNg ELISpot assay will provide insights into the participants' reactivity to SARS-CoV-2 S1, S2, Nucleocapsid and membrane peptides.

2.2.2 Secondary Outcome

2.2.2.1 Clinical protection

- First symptomatic, PCR-proven COVID-19 occurrence from 14 days after first dose of SARS-CoV-2 vaccine in participants without evidence of prior infection with SARS-CoV-2

2.2.3 Exploratory Outcomes

2.2.3.1 Humoral Immunogenicity

- SARS-CoV-2 IgG (pseudo)neutralisation assays to assess the capacity of vaccine induced SARS-CoV-2 Abs to neutralise/block SARS-CoV-2 infection

2.2.3.2 Cellular Immunogenicity

- The relative contribution of T cell subsets and T cell function will be assessed using intracellular cytokine analysis and flow cytometry (ICCS) - established at Oxford University laboratories (https://www.biorxiv.org/content/10.1101/2020.06.05.134551v1)
- 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 https://www.biorxiv.org/content/10.1101/2020.06.05.134551v1)

Additional assays relevant to immune state and response may be undertaken:

- 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
- Saliva antibodies (IgG/IgA) to both the spike (S) and the nucleocapsid (N) antigens of SARS-CoV-2 will be measured using an optimised saliva ELISA developed by the University of Bristol
- Flow cytometric characterisation of the circulating immune compartment (e.g. T cells and B cells) will be undertaken
- 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 OCTAVE and other related studies.

OCTAVE will include an optional additional blood sample 1-day post-vaccine that can be requested from trial participants primarily for next generation sequencing approaches (e.g., RNA sequencing) to evaluate in detail early innate responses at this time point.

TRIAL DESIGN

The OCTAVE trial is a multi-centre, multi-disease, prospective observational cohort trial of the immune response to SARS-CoV-2 vaccination. We will evaluate immunity arising from receipt of the COVID-19 Vaccine AstraZeneca, COVID-19 mRNA Vaccine BNT162b2 and COVID-19 Vaccine Moderna or other MHRA approved SARS-CoV-2 vaccines implemented in the UK. Participants with end stage kidney disease, liver disease, cancer, immune-mediated rheumatic diseases, and transplant recipients attending specialist clinics across the UK will be recruited. If funding permits additional disease cohorts may also be added by protocol amendment if scientifically and clinically relevant to the objectives of the trial.

Cohorts of approximately 100 to 200 participants depending on disease group will be recruited for full immune response analysis ("Deep Immunophenotyping Group"). Additional participants will be recruited, between 150 and 850 depending on disease group, for serology analysis ("Serology Group"). Up to 3250 participants will be recruited in total.

Additional vaccine response studies are ongoing across the UK, including Department of Health and Social Care funded analyses of responses in health care workers, care homes, and in BAME groups. Through use of common immune assay platforms, our data will be directly comparable with these emerging datasets allowing comparison with matched controls.

3. ELIGIBILITY

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

3.1 Inclusion Criteria

1. Are eligible for vaccination by one of the SARS-CoV-2 vaccines approved by the MHRA administered in accordance with national guidelines and current versions of the applicable information for healthcare professionals (see Section 7.1) and:
    - For the Deep Immunotherapy Group only, have not received the second dose of the vaccine (booster)
    - For the Serology Group only, have not passed the 28 days post booster (-7/+56 days)
2. Anticipated life expectancy of 6 months or greater
3. 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 malignancies**:
        - Breast
        - Lung
        - Acute Myeloid Leukaemia
        - Multiple Myeloma
    - **Diagnosed with the following rheumatic/inflammatory conditions:**
        - Specialist diagnosis of relevant condition

- Established on relevant therapy for ≥ 30 days
- Meet the definitions in any of the following cohorts:
  - Deep Immunophenotyping Group::
    - Methotrexate plus inflammatory arthritis (to include RA, PsA, seronegative arthritis, and spondyloarthritis)
    - TNF inhibitors (any) plus inflammatory arthritis (to include RA, PsA, seronegative arthritis, spondyloarthritis)
    - Rituximab in patients with AAV
  - Serology Group:
    - Methotrexate plus:
      - inflammatory arthritis (RA, seronegative arthritis and PsA)
      - psoriasis
    - TNF inhibitors (any) plus:
      - inflammatory arthritis (RA, seronegative arthritis, axSpA and PsA)
      - psoriasis
      - Crohn's disease
    - IL-17 inhibitors (any), IL-12/23 inhibitors and IL-23 inhibitors plus:
      - seronegative arthritis (PsA and axSpA)
      - psoriasis
    - IL-6 inhibitors (any) with RA
    - JAK inhibitors (any) with RA
    - Rituximab with RA or AAV
    - Any immune modifying treatment with Systemic Lupus Erythematosus (SLE)

- **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), or gastrointestinal disease on immune suppressive therapy

- **Haematopoietic stem cell transplant patients:**

- Previously treated with autologous or allo-HSCT for any indication and with any conditioning regimens and intensities
- Previously treated with CAR-T cell therapies

Note: HSCT and CAR-T recipients who have received one or two doses of a SARS-CoV-2 vaccine pre-procedure and are receiving re-vaccination post HSCT / CART-T are eligible for recruitment at:-

- Baseline (prior to re-vaccination dose 1) to either Deep Immunophenotyping Group or Serology Group
- For the Deep Immunophenotyping Group, before they received the second re-vaccination dose
- For the Serology Group, up to 28 (-7 /+ 56) days post second re-vaccination only if 2 doses have been administered post-HSCT / CAR-T procedure.

4. SCREENING AND CONSENT

4.1 Screening

Participants will be identified from existing clinical databases or via specialist clinics. They 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.

4.2 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 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.

5. TRIAL ENTRY

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

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

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

Registration will be conducted by completing the password protected site specific trial entry spreadsheet which should be emailed to the trial mailbox, preferably at the end of each day a participant is recruited. A unique Trial Number will be allocated to each participant, this number should be included on all samples, forms, and correspondence relevant to that participant.

The Trial Office will enter the participants' details onto the trial electronic Remote Data Capture (eRDC) database.

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

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

- Details of person registering the patient
- Patient's initials and date of birth

- Date of consent

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

Once a participant has been entered into the trial their name and contact details should be added to the Participant Identification Log and a copy of the signed Informed Consent Form should be sent in the post to the Trial Office for internal review.

6. TRIAL REQUIREMENTS

6.1 Investigational Medicinal Products

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

- COVID-19 mRNA Vaccine BNT162b2, manufactured by Pfizer.

  Information for healthcare professionals can be found at: https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine

- COVID-19 Vaccine AstraZeneca, manufactured by AstraZeneca.

  Information for healthcare professionals can be found at: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca

- COVID-19 Vaccine Moderna, manufactured by Moderna.

  Information for healthcare professionals can be found at: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna

6.1.1 Pharmacy Requirements

The vaccines will be administered in accordance with its temporary authorisation and national guidelines. Hence there are no trial specific pharmacy requirements. IMP labelling and accountability will not be required for this low risk trial. The batch number (where this is known) of IMP administered to the participant will be collected on the Vaccination Form.

6.2 Vaccination

Vaccine will be administered in line with its temporary authorisation under Regulation 174 of the Human Medicines Regulations 2012, the national recommendations, and guidance of the Joint Committee on Vaccination and Immunisation (JCVI) and current standard NHS practice.

The trial will have no influence on the type of vaccine given to the participant but the type of vaccine and the batch number used will be recorded in the Case Report Form (CRF) where possible.

6.2.1 First Vaccination

Participants enrolled in this trial will be signposted to, or assisted where necessary, in obtaining an appointment for delivery of their first vaccination according to local NHS COVID-19 vaccine delivery options. Participants who are sent unsolicited appointments or make their own independent arrangements for vaccination are still able to participate but sites will endeavour to make their involvement in this trial and the administration of the SARS-CoV-2 vaccine as straight forward as possible, minimising any visits to hospitals or vaccination centres. The operational details for this assistance will be determined at each site.

Once the first vaccination has been delivered, the intended appointment and location for the booster will be recorded and sampling around the second vaccination can be planned.

6.2.2 Second Vaccination (Booster)

The trial will have no influence on the timing of the delivery of the booster but it is expected that the second dose will be delivered in accordance with national recommendations and the guidance of the JCVI.

6.3 Assessments

Assessments should be carried out in accordance with the Schedule of Events.

6.4 Sample Collection and Analysis

6.4.1 Collection

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

For the **Deep Immunophenotyping Group** up to 55ml of blood will be collected from participants at any one visit comprising whole blood, peripheral blood mononuclear cells (PBMC), serum and plasma. Saliva samples will also be collected. Samples will be collected at the following time points:

- Pre-vaccine (baseline) – this is an optional time point, samples may have been collected prior to recruitment to OCTAVE
- 1 day after first vaccination – this is an optional time point*
- Pre-booster
- 28 days post-booster (within +/- 3 days)
- 6 months post booster (as close to time point as possible)
- 12 months after first vaccine dose or prior to third vaccine dose (if applicable), whichever earlier**

* 3ml Tempus sample and 2-3 x 9ml EDTA samples required at this time point

** 2 x 5ml SST samples required at this time point

For the **Serology Group** as a minimum 10ml of serum will be collected, but where possible whole blood, PBMC, and plasma will also be collected, from participants at the following time points:

- Pre-vaccine (baseline) – this is an optional time point, samples may have been collected prior to recruitment to OCTAVE
- Pre-booster – this is an optional time point, any time after the first vaccination but before booster
- 28 days post-booster (-7/+56 days)

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

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	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
Saliva †	Saliva collection funnel and 10ml collection tube	1 spit up to 1ml mark on collection tube	Immunoassay	1	-80°C

*Two 6ml lithium heparin tubes will be shipped to Oxford Immunotec at ambient temperature. Samples must be received by Oxford Immunotec within 32h of collection (see Laboratory Manual for further details).

† Samples should be kept at 4°C until processing and freezing at -80°C or immediate shipment.

Some participants will already have the appropriate baseline samples in storage under other sampling arrangements such as tissue banks or other observational Research Ethics Committee (REC) approved studies. Where these samples are available they can be used for this trial.

The remaining samples will be shipped in batches to the relevant coordinating laboratory. Site will be provided with details of which laboratory to send the samples to at the time of shipment.

6.4.2 Analysis

6.4.2.1 Deep Immunophenotyping Group

Laboratory analysis to be conducted on the Deep Immunophenotyping Group samples will include:

- 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 fine specificity of T cell and B cell responses (ELISpot and Flow cytometric) will be performed by laboratories at the University of Oxford and Imperial College London

This is not an all-inclusive list; additional assays will be included as more information becomes available about the immune response.

6.4.2.2 Serology Group

Laboratory analysis to be conducted on the Serology Group samples are expected to include:

- Assessment of quantitative IgG responses to SARS-CoV-2 spike and nucleocapsid antigens will be undertaken by the Public Health England Laboratories at Porton Down
- Assessment of neutralising antibody responses to SARS-CoV-2 antigens be undertaken at both the laboratories at the University of Glasgow and the Public Health England Laboratories at Porton Down
- 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
- Assessment of IgG/IgA responses to SARS-CoV-2 spike and nucleocapsid antigens will be undertaken by laboratories at the University of Bristol

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

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

6.4.3 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).

6.5 Participant Follow-Up

Participants will be followed up in accordance with standard clinical practice for the relevant disease cohort.

Data will be collected retrospectively from clinic records 6 months after the second vaccination and 12 months after first vaccination or at the time or 3rd vaccination (whichever is earlier). Data collected from face-to-face consultations or telephone follow-up calls are acceptable.

6.6 Data Linkage

The participant's NHS number or CHI number will be collected to allow future linkage with national data registries such as NHS Digital, Public Health England, the Information Services Division (part of NHS Scotland), or the electronic Data Research and Innovation Service (eDRIS). For the HSCT participant group 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 provide a more complete profile of the participants' health and disease without increased data collection burden to the NHS.

6.7 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 participants would like to withdraw from further sample collection but is willing to be followed up as standard (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the analyses)
- The participants 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 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.

7. 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 1. The seriousness and causality (relatedness) of all AEs experienced by the participant should be assessed with reference to the relevant information for healthcare professionals (see Section 7.1).

7.1 Reporting Requirements

7.1.1 Adverse Events

AEs are commonly encountered by participants with the chronic healthcare conditions being studied in this trial. Hence only Adverse Reactions (ARs) thought to be related to the administration of the SARS-CoV-2 vaccines will be collected.

7.1.2 Serious Adverse Events

Investigators should only report AEs that meet the definition of an SAE and which are thought to be related to the administration of the SARS-CoV-2 vaccine. These events should be reported on a SAE Form as described in Section 8.3.1.2.

7.2 Reporting Period

Details of AEs will be documented and reported from the date of recruitment into the OCTAVE trial and only after the initial vaccination of SARS-CoV-2 vaccine until 28 days after the administration of the booster.

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.

7.3 Reporting Procedure

7.3.1 Site

7.3.1.1 Adverse Events

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

ARs experienced following vaccination should be recorded on the Vaccination Form.

ARs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (see Appendix 2).

Any ARs 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 AR, the highest grade should be recorded.

7.3.1.2 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 which are thought to be related to SARS-CoV-2 vaccination and which 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 4.03.

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@trials.bham.ac.uk
Include "OCTAVE SAE" in the subject line

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).

7.3.2 OCTAVE 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).

7.3.3 Reporting to the Competent Authority and Research Ethics Committee

7.3.3.1 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.

7.3.3.2 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).

7.3.3.3 Adverse Events

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

7.3.3.4 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.

9. DATA COLLECTION

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

Table 2: OCTAVE Trial Case Report Form

Form		Summary of Data Recorded*	Schedule for Submission to Trial Office
Registration		Minimal identifiers (initials and date of birth)	Complete at trial entry
Baseline		NHS/CHI/ BSBMT registry ID, hospital number, demographic data (sex, ethnicity), World Health Organisation (WHO) performance status (Appendix 3), body mass index, medical history including comorbidities, disease group specific information (including disease status), details of prior COVID-19 infection, collection of baseline research samples	Within 1 month of trial entry
Treatment Form	First vaccination	Details of rituximab, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) and other disease cohort specific treatments	As soon as possible after relevant vaccination
	Second vaccination		
Vaccination form	First vaccination	Date of vaccination Type of vaccination Batch number (if known) Planned date of booster (if known)	As soon as possible after relevant vaccination
	Second vaccination	Date of booster Type of vaccination Batch number (if known)	
Vaccination Adverse Reaction Form	First vaccination	Details of ARs thought to be related to SARS-CoV-2 vaccination	As soon as possible after relevant vaccination
	Second vaccination		
Research Sample Collection Form		Confirmation of collection of research samples in accordance with the protocol	As soon as possible on collection of research samples
Follow-up		Survival data, COVID-19 infection data, WHO performance status, disease site specific	Six months post second vaccination (booster) and 12 months post first vaccine or third vaccination

Form	Summary of Data Recorded*	Schedule for Submission to Trial Office
Death	Date and cause of death	Immediately upon notification of participant's death
Withdrawal of Consent	Used to notify the Trial Office of the participant's withdrawal from the trial	Immediately upon patient withdrawal
Deviation Form	Details on deviations from the protocol not captured elsewhere on the CRF	Immediately upon discovery of a deviation
Serious Adverse Event	Details of any SAE thought to be related to SARS-CoV-2 vaccination	No later than 24h after becoming aware of the event

* It is anticipated data will collected retrospectively from the participants medical records.

This trial will use an eRDC system to capture the CRF data, the only exception to this will be the registration data which will be captured in an Excel workbook (a paper version of the Registration Form is also available) and the SAE Form which will be completed on paper.

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

https://crctu.redcap.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.

7.4 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.

8. QUALITY MANAGEMENT

8.1 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. Site 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.

8.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the OCTAVE 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 trial staff access to source documents as requested.

8.3 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 REDCap 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 Trial Management Group (TMG) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC (see Section 9.5 for further details).

8.4 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.

8.5 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.

9. 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 REC and MHRA that the trial has ended and will provide them with a summary of the trial report within 12 months of the end of trial.

10.STATISTICAL CONSIDERATIONS

10.1 Definition of Outcome Measures

10.1.1 Primary Outcome Measures

The primary outcome measure is defined in Section 2.2.1.

10.1.2 Secondary Outcome Measures

Secondary outcome measures are defined in Section 2.2.2.

10.2 Analysis of Outcome Measures

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

OCTAVE is a multicentre, prospective observational trial, examining humoral immunogenicity in multiple prospective cohorts of patients with end stage kidney disease, liver disease, cancer, immune-mediated rheumatic diseases, and transplant recipients. Joint analysis may be held with other disease datasets as the trial evolves.

Two different groups of research samples are being assessed during the trial: Deep Immunophenotyping Group - each disease cohort will include between 100 and 200 participants; and the Serology Group – each disease cohort will include between 150 and 850 participants. Up to 3,250 participants in total. Samples are being collected following vaccination at 4-6 time points for the Deep Immunophenotyping Group and 1-3 time points for the Serology Group (further details can be found in the Schedule of Events).

The primary and secondary outcomes will be assessed using assays and methods proven to give reliable and reproducible results, allowing for direct comparison of participants data, and removing measurement bias.

Vaccination responses will be assessed against a matched control group of vaccinated healthy participants from the health care workers, care homes, and BAME groups. Matching will be performed using the following factors: age, sex, Body Mass Index and ethnicity (details of the matching methodology can be found in the Statistical Analysis Plan).

Missing data will be presented and appropriate sensitivity analysis will be considered including per protocol analysis and multiple imputation.

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

10.2.1 Primary Outcome Measures

Continuous measures will be summarised via means, medians, standard deviations and ranges. Categorical measures will be summarised with number and proportion in each category. To determine the magnitude of the humoral and T cell immunogenicity, the longitudinal assay data will be analysed using linear mixed effects modelling (parametric and more flexible models may be considered), giving estimates of rate of response (slope) and at specific time points. Time-to-event data will be analysed using Kaplan-Meier methodology and Cox Proportional-Hazards models where appropriate. Comparisons to look at differences in IgG response from vaccination and/or infection across disease groups at specific time points will be carried out using two-sample t-tests. Appropriate data plots will be produced where applicable. Response comparisons will be made comparing disease-to-disease and disease-to-control groups (where appropriate healthy control data is available).

Once data collection of the Oxford Immunotec modified T-SPOT Discovery SARS-CoV-2 assay has been completed, an interim assessment of this data will be performed. A comparison of results with a

control group is not planned to be performed and included in the interim analyses. This interim analysis is to be completed within 1 year of OCTAVE being opened.

10.2.2 Secondary Outcome Measures

Appropriate summary statistics will be produced (continuous measures via means, medians, standard deviations and ranges, categorical measures with number and proportion in each category). Longitudinal assay data will be analysed using linear mixed effects modelling (parametric and more flexible models may be considered), giving estimates of rate of response (slope) and time point specific estimates. Response estimates (absolute changes) at specific time points will be compared between groups (disease-to-disease and disease-to-control) using two-sample t-tests. Time-to-event data will be analysed using Kaplan-Meier methodology and Cox Proportional-Hazards models where appropriate. Contingency tables, Fisher's Exact and Chi-Square testing will be used to investigate categorical data where applicable. Appropriate data plots will be produced where applicable.

10.2.3 Planned Subgroup Analyses

These analyses are not powered and as such are for exploratory information. Statistical analyses methods given in Section 11.2.2 will be utilised where appropriate.

- Vaccination response in disease-specific subgroups and comparison to control groups
- Vaccine specific response comparisons in disease and control groups
- The effect of disease-specific medications on vaccination response

10.2.4 Exploratory Analyses

For brevity, the exploratory analyses will utilise the methods to analyse data as described in Section 11.2.2 where appropriate.

10.2.5 Sample Size Justification

OCTAVE is an observational trial and as such no formal sample size calculations were feasible. However the numbers of participants for the Deep Immunophenotyping and Serology Groups have been selected based on the availability of potential participants who have the underlying diseases in the investigated populations to recruit from within the specified time and funding. It is felt that the sample sizes are large enough to adequately investigate the trial's objectives.

11.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 may also choose to take part.

11.1 Sponsor

The trial is being sponsored by the University of Birmingham.

11.2 Coordinating Centre

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

11.3 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.

11.4 Trial Management Group

The 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, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

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

11.5 Independent Oversight Committees

No independent oversight committees have been established for this low risk cohort trial.

11.6 Finance

This is an investigator-initiated and investigator-led trial funded by the Medical Research Council.

The collaborating institutions will receive payment from the funder to pay for participant recruitment. Additional NHS sites will receive payments to cover any 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.

12. 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 4).

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.

13.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).

14.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.

15.PUBLICATION POLICY

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

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.

16.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.

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APPENDIX 1 - 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 2 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. 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_4.03_2010-06-14_quickreference_5x7.pdf

APPENDIX 3 – 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 4 - 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.

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Trial Database

https://crctu.redcap.bham.ac.uk/

Serious Adverse Event Reporting

Reg@trials.bham.ac.uk

CC OCTAVE@trials.bham.ac.uk

Include "OCTAVE SAE" in the subject line