Study Title: A single-blind, randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules

Short Title: Comparing COVID-19 Vaccine Schedule Combinations (Com-COV)

Ethics Ref: 21/SC/0022

IRAS Project ID: 291055

ISRCTN: 69254139

EudraCT Number: 2020-005085-33

OVG Study Number: OVG 2020/03

Date and Version No: V3.1 29-Mar-2021

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Sponsor: University of Oxford

Funder: UK Vaccine Task Force and National Institute Health Research (NIHR)

Chief Investigator Signature:

Xinxue Liu, Oxford

Statistician Signature:

Nick Andrews, PHE

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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator	Signature	Site name or ID number	Date

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2 KEY TRIAL CONTACTS

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Funder(s)	National Institute for Health Research & UK Vaccine Task Force
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Statisticians	**Xinxue Liu** Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), University of Oxford, Churchill Hospital, Oxford, OX3 7LE, xinxue.liu@paediatrics.ox.ac.uk **Nick Andrews** Public Health England 61 Colindale Ave, London NW9 5EQ nick.andrews@phe.gov.uk
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3 CONFLICT OF INTEREST DECLARATION

The ChAdOx1 nCOV-19 vaccine was developed as a partnership between the University of Oxford, who are sponsoring and coordinating this study, and AstraZeneca. The University of Oxford and AstraZeneca have committed to making the vaccine available on a 'not for profit' basis for the duration of the current pandemic. Both parties could potentially profit from this vaccine in the future.

M. Snape is an investigator on the Cov001 and Cov002 studies evaluating ChAdOx1 nCOV19, these studies are funded by NIHR and receive logistical support from AstraZeneca. M Snape is currently, or has recently been, an investigator on studies funded +/- sponsored by vaccine manufacturers including Pfizer, GlaxoSmithKline, Janssen, MCM vaccines, Novavax and Medimmune. He receives no personal financial benefit for this work.

4 LAY SUMMARY

On the 2nd December 2020 the MHRA granted emergency authorisation for a vaccine against COVID-19, 'COVID-19 mRNA Vaccine BNT162b2', the European Medicines Agency then granted conditional authorisation on 21st December 2020. This was followed by emergency authorisation of the Oxford/AstraZeneca ChAdOx1 nCOV-19 vaccine on the 29th December 2020 by the UK MHRA. The MHRA then similarly granted emergency authorisation for the mRNA COVID-19 Vaccine Moderna on 8th January 2021. The adjuvanted protein COVID-19 vaccine from Novavax, NVX-CoV2373, is under rolling review of the MHRA at the time of writing. All of these vaccines were originally developed for use as homologous two-dose regimens. There are likely to be significant logistical challenges immunising large portions of the population. There would be significant advantages to having flexible immunisation programmes whereby the second vaccine dose is not necessarily the same as the first dose. Accordingly, this study will determine the safety as well as the immune responses to a variety of combinations of prime/boost schedules for candidate COVID-19 vaccines that are potentially to be deployed in the UK. The vaccines to be studied in this protocol will primarily be determined by those made available to the Department of Health and Social Care (DHSC) for population use.

5 SYNOPSIS

Trial Title	A single-blind, randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules
Internal ref. no. (or short title)	Comparing COVID-19 Vaccine Schedule Combinations (Com-COV)
Trial registration	EudraCT 2020-005085-33 ISRCTN: 69254139
Sponsor	University of Oxford Clinical Trials and Research Governance Joint Research Office Boundary Brook House Churchill Drive Headington Oxford OX3 7GB United Kingdom
Funder	National Institute for Health Research & UK Vaccine Task Force
Clinical Phase	Phase II
Trial Design	Single-blind, randomised prime-boost vaccine administration study
Trial Participants	Adults aged 50 years and above
Sample Size	A total of 820 participants, consisting of an Immunology cohort receiving their booster vaccine dose after 28 days (n=100) and a General cohort (n=720). Half of the general cohort participants (n=360) will receive their booster vaccine after 28 days, and half will receive their booster vaccine after 84 days. • Within the immunology cohort participants will be randomised 1:1:1:1 to the following arms receiving their booster vaccine dose after 28 days: Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19 • Prime ChAdOx1 nCOV-19, Boost BNT162b2

<table>
<tr><td></td><td colspan="3">

Prime BNT162b2, Boost BNT162b2
Prime BNT162b2, Boost ChAdOx1 nCOV-19

Within the general cohort participants will be randomised 1:1:1:1:1:1:1:1 to the following arms:

Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19 28 day boost
Prime ChAdOx1 nCOV-19, Boost BNT162b2 28 day boost
Prime BNT162b2, Boost BNT162b2 28 day boost
Prime BNT162b2, Boost ChAdOx1 nCOV-19 28 day boost
Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19 84 day boost
Prime ChAdOx1 nCOV-19, Boost BNT162b2 84 day boost
Prime BNT162b2, Boost BNT162b2 84 day boost
Prime BNT162b2, Boost ChAdOx1 nCOV-19 84 day boost

There will therefore be a sum total of 205 participants receiving each different permutation of vaccine, 25 of whom will be in the Immunology cohort with booster vaccine dose after 28 days, 90 in the General Cohort with booster vaccine dose after 28 days and 90 in the General Cohort with booster vaccine dose after 84 days.
</td></tr>
<tr><td>Planned Trial Period</td><td colspan="3">12 months per participant (following on from the first vaccination)
Total trial period 1 year, 9 months</td></tr>
<tr><td></td><td>Objectives</td><td>Outcome Measures</td><td>Timepoint(s)</td></tr>
<tr><td>Primary</td><td>To determine whether the immune response in COVID seronegative participants to immunisation with heterologous prime/boost COVID-19 vaccines regimens (boosted at D28) is non-inferior to that observed following immunisation with approved homologous prime-boost regimens (boosted at D28).</td><td>Immunogenicity: Anti-spike immunoglobulins</td><td>Day 56</td></tr>
<tr><td>Secondary</td><td>To determine whether the immune response in COVID seronegative participants to immunisation with heterologous prime/boost COVID-19 vaccines regimens across all dosing intervals is non-inferior to that</td><td>Immunogenicity: Anti-spike immunoglobulins</td><td>4 weeks post boost (D56 for 28 day boost cohort, D112 for the 84 day boost cohort)</td></tr>
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	observed following immunisation with approved homologous prime-boost regimens		
	To assess safety of heterologous prime-boost COVID-19 vaccines	Serious adverse events Adverse events of special interest	Throughout the study
	Further characterisation of immunogenicity of heterologous & homologous prime/boost schedules*	Anti-spike immunoglobulins	D0, 7, 14, 28, 35, 84, 112, 182, 364
		Neutralising antibodies against SARS-CoV-2	D0, 14, 28, 56, 84, 112, 182, 364
		Anti-nucleocapsid immunoglobulins	D0, 28, 56, 84, 112, 182, 364
		Pseudo neutralising antibodies	D0, 14, 28, 56, 84, 112, 182, 364
		Cellular immune responses by ELISpot	D0, 14, 28, 42, 56, 84, 112, 182, 364
		Cellular immune responses by ICS (Th1/Th2)	D0, 14, 42
	*D7, 14, 35 and 42 analysis only for immunology cohort (n=100) D28 analysis only for the immunology (n=100) and general cohorts boosted at 28 days (n=360) D84 analysis only for the general cohorts boosted at 84 days (n=360) D112 analysis for the general cohorts boosted at 84 days (n=360) and the immunology cohort (n=100)		
	Reactogenicity and safety of heterologous & homologous prime/boost schedules of COVID-19 vaccines	Solicited local reactions	7 days after each immunisation
		Solicited systemic reactions	7 days after each immunisation

		Unsolicited reactions	28 days after each immunisation
		Medically attended adverse events	Up to 3 months post booster dose
		Changes from baseline in laboratory safety measures	D0, 28, 35, 56 , 84, 112**
	**D35 safety bloods only for immunology cohort (n=100) D28 safety bloods only for the immunology (n=100) and general cohorts boosted at 28 days (n=360) D84, 112 safety bloods only for the general cohorts boosted at 84 days (n=360)		
	Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 IgG at baseline	Immunogenicity, safety & reactogenicity endpoints as outlined above	Timepoints as outlined above
Exploratory	To characterise COVID-19 infections experienced following administration of vaccination and the immune response to those infections	Anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot Genome sequencing of SARS-CoV-2 viruses isolated from infected participants	From prime dose, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
	To characterise and compare the mucosal immune response to immunisation with homologous and heterologous COVID-19 vaccines in the immunology cohort and from 100 participants in the general cohort who are boosted at 84 days using both nasal fluid samples	IgA & IgG ELISA and exploratory immunological assays	D0, 7, 14, 28, 35, 42, 56, 84, 112, 182, 364 (Saliva sampling only from D28)

<table>
<tr><td></td><td>(collected via SAM-strip) and saliva samples</td><td></td><td></td></tr>
<tr><td></td><td>To further characterise the blood antibody response in the immunology cohort and from 100 participants in the general cohort who are boosted at 84 days</td><td>Functional antibody assays</td><td>D0, 7, 14, 28, 35, 42, 56, 84, 112, 182, 364</td></tr>
<tr><td>Intervention(s)
• IMP(s)</td><td colspan="3"><table>
<tr><th>Vaccine</th><th>Dose</th><th>Route of administration</th></tr>
<tr><td>AstraZeneca COVID-19 vaccine AZD1222 (ChAdOx1 nCOV-19)</td><td>$5x10^{10}$vp (0.5ml)</td><td>Intramuscular</td></tr>
<tr><td>Pfizer BioNTech (BNT162b2)</td><td>30 µg (0.3ml)</td><td>Intramuscular</td></tr>
</table></td></tr>
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6 ABBREVIATIONS

ADE	Antibody Dependant Enhancement
AE	Adverse event
AESI	Adverse Event of Special Interest
Anti-N IgG	Anti-nucleocapsid Immunoglobulin G
Anti-S IgG	Anti-spike Immunoglobulin G
AR	Adverse reaction
C-19P	COVID-19 Pathway
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine, Oxford
ChAdOx1	Chimpanzee adenovirus 1
ChAdOx1-nCoV-19	Oxford/AstraZeneca COVID-19 vaccine
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EDC	Electronic Data Capture
ELISPOT	Enzyme-linked Immunospot
FBC	Full blood count
GCP	Good Clinical Practice

GMT	Geometric Mean Titre
GP	General Practitioner
HIV	Human Immunodeficiency virus
HRA	Health Research Authority
IB	Investigators Brochure
ICS	Intracellular Cytokine Staining
ICF	Informed Consent Form
IM	Intramuscular
IMP	Investigational Medicinal Product
IV	Intravenous
JCVI	Joint Committee on Vaccines and Immunisation
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribo-nucleic-acid
NHS	National Health Service
NIHR	National Institute for Health Research
NISEC	National Immunisation Schedule Evaluation Consortium
Novavax, NVX-CoV2373	Novavax COVID-19 vaccine
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
Pfizer BNT162b2	Pfizer COVID-19 vaccine
qPCR	Quantitative polymerase chain reaction
RES	Research Ethics Service
PB	Post-booster
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
REC	Research Ethics Committee
RSI	Reference Safety Information

SAE	Serious Adverse Event
SAM-strips	Synthetic absorbable matrix strips
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Trials Safety Group
µg	Microgram
Vp	Viral particle
VTF	Vaccine Task Force
WHO	World Health Organisation

7 BACKGROUND AND RATIONALE

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV(Zhu et al. 2020). The virus was subsequently renamed to SARS-CoV2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus(Lu et al. 2020). COVID-19 is the infectious disease caused by SARS-CoV-2. By January 2020 there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARSCoV-2 rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020. Globally, as of 25th February 2021, there have been 112,209,815 confirmed cases of COVID-19, including 2,490,776 deaths, reported to the WHO.

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs

infection via different receptors(Li 2016). SARS-CoV-2 belongs to the phylogenetic lineage B of the genus Betacoronavirus and it recognises the angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Zhou et al. 2020). It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

Many social measures have been undertaken in countries across the world in order to limit the spread of the virus(UK Department of Health and Social Care 2020a). These have included social distancing, lockdown and mask-wearing. Currently there is no definitive treatment for COVID-19. Dexamethasone has been shown to improve mortality in those with confirmed disease and an Oxygen requirement(The Recovery Collaborative Group 2020). Remdesivir, a direct anti-viral, has also been shown to reduce duration of symptoms in those who have only mild disease (Patterson et al. 2020).

Many countries have already experienced 'second, third waves' of infection. On the 2nd December 2020 the MHRA granted emergency authorisation for a vaccine against COVID-19, 'COVID-19 mRNA Vaccine BNT162b2'(UK Department of Health and Social Care 2020b), the European Medicines Agency then granted conditional authorisation on 21st December 2020. This was followed by emergency authorisation of the Oxford/AstraZeneca ChAdOx1 nCOV-19 vaccine on the 29th December 2020 by the UK MHRA. The MHRA then similarly granted emergency authorisation for the mRNA COVID-19 Vaccine Moderna on 8th January 2021. The adjuvanted protein COVID-19 vaccine from Novavax, NVX-CoV2373, is under rolling review of the MHRA at the time of writing. All of these vaccines were developed for use as homologous two-dose regimens. Further vaccines using different platforms are expected to be approved for use against COVID-19 during 2021. All of these are expected to be approved as two dose, homologous prime/boost schedules.

Given the anticipated programmatic challenges of immunising large proportions of the population, there would be advantages to having flexible immunisation programmes where the second dose is not necessarily the same as the first dose, i.e. a permissive approach to using heterologous prime/boost schedules. Accordingly, this study will determine the reactogenicity and immunogenicity of unapproved heterologous prime/boost schedules for candidate COVID-19 vaccines that are potentially to be deployed in the UK, for which safety and clinical efficacy data are not known. The vaccines to be studied in this protocol will primarily be determined by those made available to the Department of Health & Social Care (DHSC) for population use.

Furthermore, given the UK introduction of COVID-19 vaccines has utilised an extended (up to 12 week) interval between the first and second dose of vaccine, this study will evaluate combinations of vaccines with a 12 week, as well as 4 week, dosing interval.

As further vaccines get their licensure in the UK, they can be added to the trial, increasing the number of prime-boost vaccine permutations. The population to be studied will be adults 50 years and over; including those with comorbidities classified as mild/moderate/well controlled. The reason for this is that this will most

likely include the target population for vaccination, as these are the population who are most at risk of severe disease.

Table 1. Investigational medicinal product(s), summary of relevant studies

Country	Trial	Phase	Trials registration	Vaccine	Route	Dose	Age cohorts (years)	Number of participants
ChAdOx1 nCoV-19								
UK	COV001	Phase 1/2 efficacy, safety & immunogenicity	EudraCT 2020-001072-15	ChAdOx1 nCoV-19	IM	$5x10^{10}$ vp	18-55	1077
UK	COV002	Phase 2/3	EudraCT 2020-001228-32	ChAdOx1 nCoV-19	IM	2.5 - $5x10^{10}$ vp	18-64 >65	10,200
Brazil	COV003	Phase 3	NCT04536051	ChAdOx1 nCoV-19	IM	$5x10^{10}$ vp	>18	10,300
South Africa	COV005	Adaptive Phase 1/2	NCT04444674		IM	$5x10^{10}$ vp	18-65	2,130
BNT162b2								
Germany	BioNTech	Phase I/II, 2-Part, Dose-Escalation Trial	EudraCT 2020-001038-36	BNT162a1 BNT162b1 BNT162b2 BNT162c2	IM	10 µg 30 µg 100 µg (phase 1) 10 µg, 20 µg and 30 µg (phase 2)	18-55 56-85	486 132
Argentina Brazil, Germany South Africa Turkey United States	BioNTech & Pfizer	A phase 1/2/3, observer-blind, dose-finding study	EudraCT 2020-002641-42	BNT162b2	IM	30ug	12-17 18-64 >65	2500 31000 10498

7.1 Potential benefits

Participants in this study receiving an approved, homologous, prime boost schedule of a COVID-19 vaccine should have a lower risk of COVID-19 disease than unimmunised individuals. Although the heterologous prime/boost schedules have not been tested or approved as yet, the UK 'Green Book' guide to immunisation notes that, 'as both the vaccines are based on the spike protein, it is likely the second dose will help to boost the response to the first dose', therefore it is expected that those in the heterologous group will receive some protection(Public Health England 2020a). Participants may benefit from early receipt of an approved vaccine, should their age/risk group not be eligible for routine vaccination before the start of the trial.

It is hoped that the information gained from this study will contribute to the development of a safe, effective and versatile vaccine programme against COVID-19.

7.2 Potential risks

7.2.1 Associated with phlebotomy

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as AEs if they occur. The total volume of blood drawn over a 12 month period

will be up to 271-528ml (+ up to 57-77ml per COVID-19 visit if required, and/or up to 7ml per additional set of safety bloods) (blood volumes may vary slightly for participants at different investigator sites due to use of different volume vacutainers, following local Trust SOPs). This should not compromise these otherwise healthy volunteers, as these volumes are within the limits of 470mL every 3 – 4 months for blood donations to the National Blood Transfusion Service. Participants will be asked to refrain from blood donation for the duration of their involvement in the trial.

7.2.2 Associated with saliva sampling

Participants may find the saliva collection process unsavoury as it is involves drooling and spitting.

7.2.3 Associated with nasal fluid sampling

Localised discomfort can occur in the nostril. Infrequently, this can result in a small amount of epistaxis, which can be controlled with pressure to the affected area.

7.2.4 Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (about 1 in 1,000,000 vaccine doses) but can occur in response to any vaccine or medication(Public Health England 2020b).

7.2.5 Behaviour change

Participants might feel they can modify their COVID-19 risk behaviours on the assumption that they are protected once vaccinated. Participants will be extensively counselled that they should continue to follow all up to date government advice in relation to COVID-19 precautions during the trial.

7.2.6 Specific risk from vaccines

Please refer to Section 13.8 for full details.

7.2.7 Antibody Dependant Enhancement and Immunopathology

Safety concerns around the use of some viral antigens as a vaccine antigen have been raised following historical and limited reports of immunopathology and antibody dependant enhancement (ADE) reported in vitro and post SARS-CoV challenge in mice, ferrets and non-human primates immunised with whole SARS-CoV inactivated or full-length S protein based vaccines, including a study using Modified Vaccinia Ankara as a vector(T. et al. 2012; Dick et al. 2004; Perlman et al. 2019). To date, there has been one report of lung immunopathology following MERS-CoV challenge in mice immunised with an inactivated MERS-CoV candidate vaccine(S. et al. 2016).However, in preclinical studies of ChAdOx1 immunisation and MERS-CoV

challenge, no ADE was observed in hDPP4 transgenic mice, dromedary camels or non-human primates(J. et al. 2017; Abu-Obaidah et al. 2019)

The COVID-19 vaccines to be used in this study will have proven effectiveness, and recipients will have been monitored for any suggestion of ADE. The possibility of ADE have also been evaluated in pre-clinical studies. Nevertheless, this risk will not have been assessed for heterologous prime/boost schedules. Participants will be made aware of this theoretical risk.

7.2.8 Unwanted media attention

Trial participants can be subjected to unwanted attention from the media. They will therefore be provided with access to a document outlining some suggested media guidance.

8 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s)
Primary		
To determine whether the immune response in COVID seronegative participants to immunisation with heterologous prime/boost COVID-19 vaccines regimens (boosted at D28) is non-inferior to that observed following immunisation with approved homologous prime-boost regimens (boosted at D28).	Anti-spike immunoglobulins	Day 56
Secondary		
To assess safety of heterologous prime-boost COVID-19 vaccines	Serious adverse events and adverse events of special interest	Throughout the study
To determine whether the immune response in COVID seronegative participants to immunisation with heterologous prime/boost COVID-19 vaccines regimens across all dosing intervals is non-inferior to that observed following immunisation with approved homologous prime-boost regimens	Immunogenicity: Anti-spike immunoglobulins	4 weeks post boost (D56 for 28 day boost cohort, D112 for the 84 day boost cohort)

Further characterisation of immunogenicity of heterologous & homologous prime/boost schedules*	Anti-spike immunoglobulins	D0, 7, 14, 28, 35, 84, 112, 182, 364
	Neutralising antibodies against SARS-CoV-2	D0, 14, 28, 56, 84, 112, 182, 364
	Anti-nucleocapsid immunoglobulins	D0, 14, 28, 56, 84, 112, 182, 364
	Pseudo neutralising antibodies	D0, 14, 28, 56, 84, 112, 182, 364
	Cellular immune responses by ELISpot	D0, 14, 28, 42, 56, 84, 112, 182, 364
	Cellular immune responses by ICS (Th1/Th2)	D0, 14, 42
**D7, 14, 35 and 42 analysis only for immunology cohort (n=100) D28 analysis only for the immunology (n=100) and general cohorts boosted at 28 days (n=360) D84 analysis only for the general cohorts boosted at 84 days (n=360) D112 analysis only for the immunology (n=100) and general cohorts boosted at 84 days (n=360)		
Reactogenicity and safety of heterologous & homologous prime/boost schedules of COVID-19 vaccines	Solicited local reactions	7 days after each immunisation
	Solicited systemic reactions	7 days after each immunisation
	Unsolicited reactions	28 days after each immunisation
	Medically attended adverse reactions	Up to 3 months post booster
	Changes from baseline in laboratory safety measures	D0, 28, 35, 56 , 84, 112**
**D35 safety bloods only for immunology cohort (n=100) D28 safety bloods only for the immunology (n=100) and general cohorts boosted at 28 days (n=360) D84, 112 safety bloods only for the general cohorts boosted at 84 days (n=360)		
Evaluation of immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 IgG at baseline	Immunogenicity, reactogenicity and safety endpoints as outlined above	Timepoints as outlined above

To characterise COVID-19 infections experienced following administration of vaccination and the immune response to those infections	Anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot Genome sequencing of SARS-CoV-2 viruses isolated from infected participants	From prime dose, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
Exploratory		
To characterise COVID-19 infections experienced following completion of immunisation schedule and the immune response to those infections	Anti-spike and anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot Genome sequencing of SARS-CoV-2 viruses isolated from infected participants	From post-boost and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing.
To characterise and compare the mucosal immune response to immunisation with homologous and heterologous COVID-19 vaccines in the immunology cohort and from 100 participants in the general cohort who are boosted at 84 days, using both nasal fluid (collected via SAM-strips) as well as saliva samples	IgA & IgG ELISA and exploratory immunological assays	D0, 7, 14, 28, 35, 42, 56, 84, 112, 182, 364 (Saliva samples only from D28)
To further characterise the blood antibody response in the immunology cohort and from 100 participants in the general cohort who are boosted at 84 days	Functional antibody assays	D0, 7, 14, 28, 35, 42, 56, 84, 112, 182, 364

9 TRIAL DESIGN

A single-blind, randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules.

9.1 Setting

Multicentre study conducted through academic and NHS clinical trials sites.

9.2 Trial duration

Total duration of each participant will be 12 months from the administration of the first vaccine dose. The total trial period will be approximately 1 year, 9 months

9.3 Study groups

The study will initially consist of 2 cohorts, one for more detailed immunological assessment (immunology cohort, n=100, 25 per arm) boosted at Day 28 (randomised 1:1:1:1), one for main immunology endpoints for participants boosted at Day 28 and at Day 84 (general cohort n=720, 90 per arm) (randomised 1:1:1:1:1:1:1:1)

The study will be single-blind.

Cohort	Group	Arm	Prime (Day 0)	Boost (Day 28)	Boost (Day 84)	Visits
Immunology (n=100)	A - ChAdOx1 nCOV-19 (n=50)	IA1 (n=25)	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19	-	Day 0, 7, 14, 28, 35, 42, 56, 182, 364
		IA2 (n=25)	ChAdOx1 nCOV-19	BNT162b2	-	
	B - BNT162b2 (n=50)	IB1 (n=25)	BNT162b2	BNT162b2	-	
		IB2 (n=25)	BNT162b2	ChAdOx1 nCOV-19	-	
General (n=720)	A - ChAdOx1 nCOV-19 (n=180)	GA1-28 (n=90)	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19	-	Day 0, 28, 56, 182, 364
		GA2-28 (n=90)	ChAdOx1 nCOV-19	BNT162b2	-	
	B - BNT162b2 (n=180)	GB1-28 (n=90)	BNT162b2	BNT162b2	-	
		GB2 -28 (n=90)	BNT162b2	ChAdOx1 nCOV-19	-	
	A - ChAdOx1 nCOV-19 (n=180)	GA1-84 (n=90)	ChAdOx1 nCOV-19	-	ChAdOx1 nCOV-19	Day 0, 56, 84, 112, 182, 364
		GA2-84 (n=90)	ChAdOx1 nCOV-19	-	BNT162b2	
	B - BNT162b2 (n=180)	GB1-84 (n=90)	BNT162b2	-	BNT162b2	
		GB2-84 (n=90)	BNT162b2	-	ChAdOx1 nCOV-19	

The randomisation will be stratified by the study cohorts, i.e. immunology cohort and general cohort, and by study sites:

Immunology cohort (boosted 28 days) will have visits: 0, 7, 14, 28, 35, 42, 56, 112 (optional), 182, 364

General cohort (boosted 28 days) will have visits: 0, 28, 56, 182, 364

General cohort (boosted 84 days) will have visits: 0, 56, 84, 112, 182, 364

The study will be single-blind, i.e. while staff involved in study delivery will be aware of what vaccine schedule the participant is receiving, the participant themselves will remain blinded to their vaccine schedule (they will be informed their timing for boost). This blind will be maintained by applying a masking tape over the vaccine syringe. Laboratory staff will also be blinded to the vaccine schedule received.

Participants who acquire new infection with SARS-CoV-2 will have an additional study visit for clinical assessment, to take blood tests for immunological assessment and to take a sample for isolation of virus. They may also have nasal fluid and saliva samples taken.

Of note is that the interval between the BNT162b2 vaccines will be 28 days or 84 days. This is consistent with this vaccine's Summary of Product Characteristics, which specifies that the interval be 'at least 21 days'. For the shorter interval, the 28 day interval (rather than 21 day) has been chosen to ensure that participants remain blinded to the vaccines received, given the minimum interval for the ChAdOx1 nCoV-19 vaccine is 28 days.

On 10th February 2021 the WHO issued revised recommendations that the AstaZeneca/Oxford ChAdOx1-nCoV-19 vaccine be given at an 8-12 week boost interval in light of evidence that suggests longer prime-boost intervals may provide superior efficacy. However, the 4 week interval schedule for the homologous AstaZeneca/Oxford ChAdOx1-nCoV-19 vaccine is still an approved schedule and will continue to be used in this trial to maintain the scientific integrity of the study.

APPENDIX A: SCHEDULE OF PROCEDURES for details of visit schedule.

10 PARTICIPANT IDENTIFICATION

10.1 Trial Participants

Adult volunteers aged at least 50 years. Comorbidities of clinical definition mild/moderate/well-controlled will be permitted. Individuals of all ethnicities will be recruited, with recruitment of those identifying as Black, Asian and Minority Ethnic particularly encouraged.

10.2 Inclusion Criteria

- Participant is willing and able to give written informed consent for participation in the trial
- Male or Female, aged 50 years or above and in good health as determined by a trial clinician Participants may have well controlled or mild-moderate comorbidity
- Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation. See Section 13.14 for definition of child bearing potential
- In the Investigator's opinion, is able and willing to comply with all trial requirements
- Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
- Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures
- Agreement to refrain from blood donation during the course of the study

10.3 Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
- Prior or planned receipt of an investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines)
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
- Any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤14 days)

- History of allergic disease or reactions likely to be exacerbated by any component of study vaccines (e.g. hypersensitivity to the active substance or any of the SmPC-listed ingredients of the Pfizer vaccine)
- Any history of anaphylaxis
- Pregnancy, lactation or willingness/intention to become pregnant within 3 months post boost vaccine
- Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
- Suspected or known current alcohol or drug dependency
- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
- History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion
- History of laboratory confirmed COVID-19 prior to enrolment (history of SARS-CoV-2 detection by PCR or antibody to SARS-CoV-2)
- Significant renal or hepatic impairment
- Scheduled elective surgery during the trial
- Participant with life expectancy of less than 6 months
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks
- Insufficient level of English language to undertake all study requirements in opinion of the Investigators

10.3.1 Temporary exclusion criteria

If at Visit 1 Screening & Vaccination the volunteer has any of the following, they will not be enrolled that day.

- Acute respiratory illness (moderate or severe illness with or without fever)

- Fever (oral temperature greater than 37.8°C)

They may be considered for enrolment later in the trial; if they recover in sufficient time.

11 TRIAL PROCEDURES

See APPENDIX A: SCHEDULE OF PROCEDURES for details

11.1 Recruitment

11.1.1 Identification of volunteers

Volunteers will be recruited by methods that may include use of an advertisement +/- registration form formally approved by the ethics committee(s) and distributed or posted by means such as:

- In public places, including buses and trains, with the agreement of the owner / proprietor
- In newspapers or other literature for circulation
- On radio via announcements
- On a website or social media site operated by our group or with the agreement of the owner or operator (including on-line recruitment through our website)
- By e-mail distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation
- By email distribution to individuals who have already given consent to be contacted for any clinical trial at the Oxford Vaccine Centre and at trial sites
- Direct mail-out: This will involve obtaining names and addresses of adults via the most recent Electoral Roll. The contact details of individuals who have indicated that they do not wish to receive postal mail-shots would be removed prior to the investigators being given this information. The company providing this service is registered under the General Data Protection Regulation 2016/679. Investigators would not be given dates of birth or ages of individuals but the list supplied would only contain names of those aged ≥50 years (as per the inclusion criteria)
- Direct mail-out using National Health Service databases: These include the National Health Applications and Infrastructure Services (NHAIS) via a NHAIS data extract or equivalent. Initial contact to potential participants will not be made by the study team. Instead study invitation material will be sent out on our behalf by an external company, CFH Docmail Ltd, in order to preserve the confidentiality of potential participants. CFH Docmail Ltd is accredited as having exceeded standards under the NHS Digital Data Security and Protection Toolkit (ODS ID – 8HN70)
- Oxford Vaccine Centre databases and study site databases: We may contact individuals from databases of groups within the CCVTM (including the Oxford Vaccine Centre database) and other

study sites of previous trial participants who have expressed an interest in receiving information about all future studies for which they may be eligible

- Using local GP practices or Trusts as Participant Identification Centres (PICs)
- The NIHR COVID-19 vaccine volunteer database

11.2 Screening and Eligibility Assessment

11.2.1 Initial screening

Once participants express an interest in joining the trial, they will be directed to a 2 stage online screening process. The first stage will assess for obvious exclusion criteria. If they pass this stage they will be asked to indicate their electronic consent to cover:

1) Reporting their medical history (stage 2)
2) Telephone screening visits to review their medical history (if required). Requirement to be determined by review of responses to Part 2 of online questionnaire)
3) Permission to contact the participant's GP for further clarification of past medical history, should this be clinically indicated

Participants without a past medical history or drug history that requires further review may be invited directly to enrolment/vaccination visits.

11.2.2 Telephone screening visit(s)

Participants for whom further clarification of eligibility is required, may be invited for telephone screening visit(s), which would then be completed by member(s) of the clinical team, based on the assessment of the part 2 responses. This will be recorded in a screening CRF. This will reduce the amount of time participants have with the clinical team during their screening procedures, should they progress to Visit 1.

We may also contact the subject's general practitioner with the permission of the volunteer. GPs will be notified at the time of enrolment (vaccination) that the subject is taking part in the study.

The interval between the last screening process (whether on-line or by telephone screening) and V1 may be up to a maximum of 120 days. Volunteers will be asked to contact the study team in the interim if there are significant changes to their health status during this time

11.2.3 Screening during Visit 1

The final eligibility assessment and D0 vaccination visit will be combined into Visit 1 (V1). See Section 11.6.

11.3 Informed Consent

The participant will personally sign and date the latest approved version of the Informed Consent form. A written version and verbal explanation of the Study Information leaflet and Informed Consent will be presented to the participant of the participant detailing:

- The exact nature of the study
- What it will involve for the participant
- The implications and constraints of the protocol
- The known side effects and any risks involved in taking part
- The sample handling protocol – participants will be informed that anonymised samples taken during the study may be shared with study collaborators
- That individual results will not be shared with participants, with the exception of their enrolment COVID-19 antibody test. This would be done at the end of the study, if requested by the participant

The Study Information leaflet will be made available to the participant for an appropriate amount of time (where possible this will be a minimum of 24 hours) prior to consent being obtained. A video presentation of the Study Information leaflet may be screened to an audience, or made available for them to access it remotely. However, participants will have the opportunity to individually question an appropriately trained and delegated researcher before signing consent.

The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The participant may withdraw from the study at any time
- The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- That participants will not be sure whether they have received an approved COVID-19 vaccine schedule. This may have implications for any travel or other activities that may require individuals to be considered 'fully immunised'. Currently the 'Green Book' immunisation guidelines indicate that receipt of two 'spike protein' based vaccines (even if different vaccines) would mean no further vaccines doses are required. This potential downside to study participation will be minimised by expedited analysis of blood samples for the primary endpoint to conduct the non-inferiority analysis, as well as expedited secondary analyses to include participants boosted at 84 days.

Participants, like the general population, will not be exempt from following the contemporaneous government COVID-19 guidance to minimise viral transmission

- Samples taken as part of the study may be sent outside of the UK and Europe to laboratories in collaboration with the University of Oxford. These will be de-identified. Volunteers will be asked if they consent to indefinite storage of any leftover samples for use in other ethically approved research, this will be optional

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of the participant dated signature, and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator and listed on the delegation log. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the research study site, in the CRF.

Updated information that require participants to be re-consented will be sent to participants and written re-consent requested at the earliest scheduled visit. If the earliest visit to occur is in the COVID-19 Pathway (C-19P), the participant may re-consent using an electronic signature for infection control purposes. Where appropriate, and when re-consenting in person is not possible (e.g. participants in self-isolation), participants may be contacted over the phone and an appropriately trained and delegated researcher will obtain re-consent. In this instance the participant will sign the form (electronic or paper) and a copy will be signed by the researcher. The dates of signature may be different, and a copy containing both signatures will be provided to the participant at the next scheduled visit.

11.4 Randomisation

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1:1 within the immunology cohort to ChAdOx1 nCOV-19 homologous, ChAdOx1 nCOV-19 heterologous, BNT162b2 homologous and BNT162b2 heterologous groups, using block randomisation. Participants will be randomised 1:1:1:1:1:1:1:1 within the general cohort to ChAdOx1 nCOV-19 homologous, ChAdOx1 nCOV-19 heterologous, BNT162b2 homologous and BNT162b2 heterologous groups at boosting intervals of 28 and 84 days, using block randomisation. Random block sizes of 8 and 16 will be used in the general cohort and a block size of 4 will be used in the immunology cohort. The randomisation will be stratified by the study sites.

11.5 Blinding and code-breaking

The study will be single-blind. Staff involved in study delivery will be aware of which vaccine the participant is receiving (arm allocation); the participant themselves will remain blinded to their vaccine allocation.

Vaccines will be prepared out of sight of the participant and the blind will be maintained by applying a masking tape over the vaccine syringe. Laboratory staff will also be blinded to the vaccine schedule received.

If the clinical condition of a participant necessitates unblinding of the participant, this will be undertaken according to a trial specific working instruction and group allocation sent to the attending physician. This will be done if unblinding is thought to be relevant and likely to change clinical management.

11.6 Visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances (see APPENDIX A: SCHEDULE OF PROCEDURES). Each visit is assigned a time-point and a window period, within which the visit will be conducted. If a participant cannot attend a visit, where possible, this will be re-arranged to an in-person visit within the time window. A telephone visit may be conducted instead of the in-person visit to ascertain as much relevant information as possible if the participant is unable to attend a visit in person because of quarantine or self-isolation restrictions and the participant will be out of window if the visit is postponed.

11.6.1 Visit 1 (D0): Final eligibility check, Enrolment and Vaccination visit

11.6.1.1 Informed consent

The participant will have informed consent taken as described in Section 11.3, before proceeding to the final eligibility check Component of V1. A video presentation of the aims of the study and all tests to be carried out may be screened to an audience or accessed remotely before informed consent is taken. Individually, each volunteer will have the opportunity to question an appropriately trained and delegated researcher before signing the consent.

11.6.1.2 Final Eligibility Check V1

During the final eligibility check component of Visit 1 (V1):

If written consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including:

- Confirmation of medical history
- Physical examination (if required)
- Height and weight
- Blood tests including:
    - COVID-19 immunogenicity bloods
    - Baseline bloods for safety monitoring (routine haematology & biochemistry tests)
- Nasal fluid sample

- Observations (temperature, heart rate, respiratory rate, blood pressure and oxygen saturation)
- Urine pregnancy test in females of childbearing potential

The eligibility of the volunteer will be reviewed by a suitable member of the clinical team. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator. Note that the blood tests results from this visit will not ordinarily be available at the time the decision to proceed to immunisation with these approved vaccines is made. Instead, these blood tests will act as a baseline assessment for any subsequent derangements of laboratory measures. Abnormal clinical findings from blood tests at screening will be assessed by a medically qualified study member. Where available, these may be compared to blood test results taken prior to the trial as part of the participant's normal medical care, to ascertain if the derangement is an acute abnormality or is a chronic change. Abnormal blood tests following screening will be assessed according to site-specific laboratory adverse event grading tables. Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, the volunteer will be informed and appropriate medical care arranged with the permission of the volunteer.

As per Section 10.3.1 "Temporary exclusion criteria": If a volunteer has an acute respiratory illness (moderate or severe illness with/without fever) or a fever (oral temperature > 37.8°C) at Visit 1 Screening, the volunteer will not be enrolled that day, but may be considered for enrolment if they recover in sufficient time.

11.6.1.3 Vaccination at V1

Volunteers will be considered enrolled to the trial at the point of consent. All vaccines will be administered intramuscularly according to specific SOPs. The participant will stay in the trial site for observation for at least 15 minutes, in case of immediate adverse events. Photographs of vaccination sites may be taken, if required (with the participants' written, informed consent) and will not include the participants' face. Photographs will be identified by date, trial code and subject's unique identifier. Participants will be given a COVID-19 vaccination record card (the same as that used in the national vaccination program). This will not record the type or batch number of vaccine(s) received but will state "COVID-19 vaccine", "Com-COV Trial" and the date.

11.6.1.4 Diary cards

Participants will be given an oral thermometer, tape measure and diary card (electronic, but for those who are unable to use electronic diary cards, a paper version will be made available), with instructions on use. All participants will be given the emergency 24 hour telephone number to contact the on-call study physician if needed Participants will be instructed on how to self-assess the severity of these AEs. There will also be space on the diary card to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms. There will also be a separate e-diary to log any medically attended AEs up until 3 months post booster dose (any medical conditions for which a doctor/dentist is seen outside of routine, planned follow-

up), and any serious medical illnesses or hospital visits may have occurred over the entire course of the study. Participants will be asked to report on solicited AEs for 7 days (and longer if symptoms persist at day 7, until resolution or stabilisation of symptoms) and unsolicited AEs for 28 days. Diary cards will collect information on the timing and severity of the following solicited AEs:

Table 2. Solicited AEs collected on post vaccination diary cards

Local solicited AEs	Pain, Tenderness, Redness, Warmth, Itch, Swelling, Induration
Systemic solicited AEs	Fever, Feverishness, Chills, Joint pains, Muscle pains, Fatigue, Headache, Malaise, Nausea, Vomiting, Diarrhoea

Post-vaccination (7 and 28 day) diary cards will be reviewed by a clinician daily, and participants may be telephoned to discuss further, should there be any clinical concerns.

Participants will also be instructed on the use of the Medically Attended Diary Card. They will be asked to record the following healthcare encounters up until 3 months post booster dose:

- GP visits that were not planned or routine
- Attendances at A&E
- Unplanned outpatient visits to hospital e.g. attending an "Ambulatory Care" unit
- Non-routine dental visits (i.e. dental emergency)

This information will be reviewed routinely only at follow up visits. The diary card will contain an instruction to contact the trial team by telephone should any encounter be a hospitalisation, or if they have concerns about their health.

Participants entering the COVID-19 pathway will also be asked to complete a diary, see section 11.6.5below.

11.6.2 Booster Vaccination

Prior to starting the booster phase of the study, any newly available and relevant safety data will be reviewed from animal studies or clinical trials of coronavirus vaccines included in this study being tested elsewhere, and discussed with the DSMB and/or MHRA as necessary. While there will be no planned safety pause, a review of reactogenicity data will be conducted after the initial 50 - 60 participants have received a booster dose at the 28 day post prime time-point only (approximately half of which will be in the heterologous prime/boost groups). This will assess reactogenicity in the first 48 hours after immunisation. Should significant safety concerns arise at this point the DSMB will be consulted.

11.6.3 Subsequent visits

Follow-up visits will take place as per the schedule of attendances described in APPENDIX A: SCHEDULE OF PROCEDURES. Participants will be assessed for local and systemic adverse events, interim history, review of

diary cards (paper or electronic) and blood, nasal fluid and (optional) saliva tests at these time points as detailed in the schedule of attendances. Blood will also be taken for immunology purposes. Observations and physical exam will be performed as and when clinically indicated.

If participants experience adverse events (laboratory or clinical), which the investigator (physician), CI and/or DSMB chair determine necessary for further close observation, the participant may be admitted to an NHS hospital for observation and further medical management under the care of the Consultant on call.

11.6.4 Participants under quarantine

Given the evolving epidemiological situation both globally and in the UK, should a participant be unable to attend any of their scheduled or unscheduled visits, a telephone consultation will be arranged in order to obtain core study data where possible. Participants should not attend for in-person visits if they are in their period of self-isolation/quarantine – the exception to this is the COVID-19 Pathway.

11.6.5 Participants with confirmed SARS-CoV-2 infection (COVID-19 Pathway)

Participants will be counselled at enrolment that should they receive a positive SARS-CoV-2 test (e.g. an antigen detection or nucleic acid amplification test, for example, via test and trace or occupational health services) they should contact the trial team on receipt of the positive result. Participants will be reminded of this with a weekly text/email message (participant choice), which will commence after the first vaccine dose.

This COVID-19 (C-19) pathway will apply to participants tested via symptomatic and asymptomatic pathways.

Once the participant has conveyed their result to the study team, confirmatory documentation will be sought from the participant (such as a forwarded result email or a picture of a lateral flow assay result). If the participant cannot provide this, but the study team are confident that an appropriate test was used from verbal description, they may proceed without documentation. An appointment will be arranged to review the participant at the relevant study site. At this visit blood samples for safety (FBC, Biochemistry, CRP and others if deemed clinically relevant) and immunology (PBMCs and serum for cellular and humoral immune responses will be taken. Nasal fluid +/- salivary samples for mucosal immune response will be taken from participants who undergo these at their routine visits i.e. those in the immunology cohort and the subset of 100 participants from the general cohort boosted at 84 days. A nasopharyngeal swab for storage and subsequent viral isolation will be taken from all participants attending the C19P visit. Vital signs and other clinical data will be recorded. Participants will also be provided with a symptom diary, which they will fill in both solicited and unsolicited symptoms for at least 7 days and until symptom resolution (excepting persistent cough and anosmia/dysgeusia as these are recognised to be able to continue for extended periods). Additional visits on this pathway may be arranged at the clinical discretion of the investigator.

Participants will only be invited to a C-19P visit if they have access to private transport and would not require assistance to attend the visit. Participants may not attend the visit using public transport or taxis.

The window for performing this visit is within 7 days of a positive test result.

Participants should be screened for severity of disease on contacting the trial team with their positive result and referred to NHS care as appropriate.

Table 3. Remote risk stratification of COVID-19 infection

Severity of illness	Features	Advice and action
Mild	Completing full sentences	Paracetamol for fever
	No SOB (Grade 0)	Can use NSAIDs according to NHS recommendations (advise lowest dose and shortest duration possible)
	No chest tightness (Grade 0)	Regular fluids
	Able to do ADLS (Grade 0-1)	Self-isolate as per current government guidelines
	RR 12-20	Safety net re worsening symptoms: - Trial doctor for advice in hours (999 in an emergency) - 111 out of hours (non-emergent)
	No other red flags/concerning features from history	Paracetamol for fever
Moderate A	Completing full sentences	Can use NSAIDs according to NHS recommendations (advise lowest dose and shortest duration possible)
	Able to do ADLs but lethargic (Grade 1-2)	Regular fluids
	Mild chest tightness (Grade 1)	Self-isolate as per current government guidelines
	Mild SOB on exertion only (Grade 1)	Safety net re worsening symptoms: - Trial doctor for advice in hours (999 in an emergency) 111 out of hours (non-emergent)
	RR 12-20 (if can be observed)	
	Any symptoms from other systems considered to be moderate and not requiring medical review	
	No other red flag features from history	
Moderate B	Completing full sentences	For medical review - Trial doctor to arrange medical review with a non-trial medical practitioner e.g. GP or hospital doctor (in-hours) - Trial doctor to signpost to NHS services (out-of hours)
	Able to do ADLs but lethargic (Grade 1-2)	Safety net – 999 if worsening beyond current symptoms
	Mild chest tightness (Grade 1-2)	Inform senior on-call clinician
	Mild SOB on exertion only (Grade 1)	
	RR 20-24 (if can be observed)	
	Any symptoms from other systems considered to be moderate and requiring medical review	

Severe	Any one of:	Urgent medical review
	Inability to complete full sentences	Advise participant to call 999
	Unable to do any ADLs/get out of bed (Grade 3)	Inform senior on-call clinician
	RR >25 if can be observed	
	Any other clinical concerns for severe disease	
Of note, this is not an all-encompassing guide and individual clinical judgement by reviewing clinician should always be taken into account. Should the reviewing clinician have any concerns regardless of risk stratification then they can contact the appropriate senior clinician for further advice.		

11.6.6 Admission of participants to hospital with COVID-19 infection

With the participant's consent, the study team will request access to medical notes or submit a data collection form for completion by attending clinical staff on any COVID-19 episodes resulting in hospitalisation. Any data which are relevant to assessing for disease enhancement will be collected. These are likely to include, but not limited to, information on ICU admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, imaging and blood tests results, amongst others.

11.7 Sample Handling

Please refer to APPENDIX D BLOOD SAMPLING for schedule of frequency and volume of blood sampling.

11.7.1 Sample handling for trial purposes

11.7.1.1 Immunology blood tests

Immunogenicity will be assessed by a variety of immunological assays. This will include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma and flow cytometry assays, neutralising and other functional antibody assays. Other exploratory immunological assays including cytokine analysis and other antibody assays, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed at the discretion of the Investigators.

Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, plasma, PBMC and/or other study samples to these laboratories, but these would remain anonymised. The analyses and which laboratories carry these out will be specified in the laboratory analysis plan.

Subjects will be informed that there may be leftover samples of their blood (after all testing for this study is completed), and that such samples may be stored indefinitely for possible future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity. Subjects will be able to decide if they will permit such future use of any leftover samples.

With the participants' informed consent, any leftover cells and serum/plasma will be frozen indefinitely for future analysis of COVID-19 and other coronaviruses related diseases or vaccine-related responses. If a subject elects not to permit this, all of that participants' leftover samples will be discarded at the end of the trial.

Samples that are to be stored for future research will be transferred to the OVC Biobank (REC 16/SC/0141).

11.7.1.2 Nasal fluid & saliva samples

An exploratory analysis of mucosal immunity will be conducted using nasal fluid and saliva collected at each visit in the immunology cohort (n=100) and in a convenience sample of approximately 100 participants boosted at 84 days, in the general cohort, using SAM-strips (synthetic absorptive matrix). Saliva samples will be optional and only be taken from D28 onwards. All participants who have been allocated to groups who will have SAM-strip +/- saliva sampling at their routine visits, will also have SAM-strips +/- saliva taken at the C19P visit if they attend this visit. Analysis will be conducted initially with IgA and IgG ELISAs, with further exploratory immunology assays conducted based on results – more detail will be included in the laboratory analysis plan. The same statements regarding collaboration, storage and use of samples as for blood in Section 11.7.1.1 apply here.

11.7.1.3 Nasopharyngeal swabs

Participants seen in the C-19 pathway will have nasopharyngeal swabs taken (instructions on performing sampling in CSP). These swabs will be tested for presence of the SARS-Cov-2 virus centrally. This analysis is for research purposes, and will not be conducted in 'real-time', so will not be used to inform the requirements for participant self-isolation etc. Swabs, and/or samples obtained from them, will be stored for potential further analysis (e.g. whole genome sequencing of identified SARS-CoV-2).

11.7.2 Sample handling for standard of care

Urinary pregnancy testing For female participants of child bearing potential only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at screening and again immediately prior to booster vaccination. This will be a point of care test and no sample will be stored.

11.7.2.1 Safety monitoring blood tests

These will be processed at agreed NHS Trust laboratories, and destroyed in accordance with standard NHS processes. They will include:

- **Haematology** – Full Blood Count
- **Biochemistry** – Sodium, Potassium, Urea, Creatinine, Albumin, Liver Function Tests (ALT, ALP, Bilirubin) and if relevant C-reactive protein (CRP)

11.8 Early Discontinuation/Withdrawal of Participants

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participants' health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation
- Participant non-compliance with study requirements
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. The DSMB or DSMB chair may recommend withdrawal of participants.

Participants may choose to withdraw from the trial if they are offered vaccination as part of the national vaccine roll out programme. If the participant chooses to withdraw after receipt of 2 vaccine doses, they will not be unblinded as this will not change clinical action for them (The Green Book states that two doses of any licensed vaccine would not require further booster doses, even if they are heterologous). If the participant withdraws after receipt of 1 vaccine dose, but prior to booster dose, then they may be unblinded at the point of vaccine offer from the national programme.

If a participant withdraws from the study, storage of samples will continue unless the participant specifically requests otherwise. Any data collected before their withdrawal will still be used in the analysis for safety and trial integrity; if the participant requests this could be de-identified following the end of the study.

In cases of subject withdrawal, long-term safety data collection, including some procedures such as safety bloods, may continue as appropriate if subjects have received one or more vaccine doses, unless they decline any further follow-up.

11.8.1 Contraindications to receipt of second (booster) dose of vaccine

The following AEs associated with any vaccine, identified on or before the day of vaccination constitute absolute contraindications to further administration of a study vaccine to the participant in question. If any

of these events occur during the study, the subject will not be eligible to receive a booster dose and will be followed up by the clinical team or their GP until resolution or stabilisation of the event:

- Anaphylactic reaction following administration of vaccine
- Pregnancy
- Any AE that in the opinion of the Investigator may affect the safety of the participant or the interpretation of the study results

Participants who develop COVID-19 symptoms and have a positive SARS-CoV-2 nucleic acid amplification test or antigen test after the first vaccination can only receive a booster dose after a minimum 4 weeks interval from their first positive test, provided their symptoms have significantly improved. The decision to proceed with booster vaccinations in those cases will be at clinical discretion of the investigators. For participants who are asymptomatic and have a positive SARS-CoV-2 test, also a minimum of 4 weeks from first test positivity will be required before boosting provided they remain asymptomatic.

11.9 Definition of End of Trial

The end of the trial is the date of the last assay conducted on the last sample collected.

12 TRIAL INTERVENTIONS

12.1 Investigational Medicinal Product(s) (IMP) Description

The marketing authorisation status of the vaccines included here is that the ChadOx1-nCOV-19 vaccine is approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012. The BNT162b2 vaccine received a conditional marketing authorisation from the European Medicines Agency on the 21st December 2020.

There will not be IMP labelling for this trial, products will be used as supplied by manufacturer (as for national supply) and blinding performed as per section 11.5.

12.1.1.1 Vaccine A – AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19)

ChAdOx1 nCoV-19 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein with a leading tissue plasminogen activator (TPA) signal sequence. S is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the virion. The S proteins subunits are responsible for cellular receptor ACE-2 binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range.

ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for Spike protein from the SARS-CoV-2 genome sequence accession MN908947. ChAd is a non-enveloped virus, and the glycoprotein antigen is not present in the vector, but is only expressed once the genetic code within the vector enters the target cells. The vector genes are also modified to render the virus replication incompetent, and to enhance immunogenicity (Garafalo et al, 2020). Once the vector is in the nucleus, mRNA encoding the spike protein is produced that then enters the cytoplasm. This then leads to translation of the target protein which act as an intracellular antigen

12.1.1.2 Dosage, scheduling and packaging

The dose of AstraZeneca COVID-19 vaccine is 0.5ml. The vaccine should be administered intramuscularly. For homologous groups receiving this vaccine, the schedule will be two doses, a minimum of 28 days apart, in heterologous groups only a single dose is given. The AstraZeneca vaccine is supplied in packs of 10 vials. Each vial contains 8 or 10 doses of vaccine, and is a colourless to slightly yellow, clear to slightly opaque liquid. Each dose is prepared by withdrawing 0.5 mL from a vial in a sterile 1 mL or equivalent syringe.

12.1.2 VACCINE B – Pfizer BioNTech (BNT162b2)

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. BNT162b2 encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA is then degraded within days. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection.

12.1.2.1 Dosage, scheduling and packaging

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine. For homologous groups receiving this vaccine, the schedule will be two doses, a minimum of 28 days apart, in heterologous groups only a single dose is given. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 5 doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules.

12.1.3 Blinding of IMPs

See Section 11.5 for detail.

12.1.4 Storage of IMP

Vaccines will be stored in accordance with manufacturers' recommendations.

All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms. To allow for participants to receive the vaccine in a short time period, additional clinic locations may be used. In this instance vaccines will be transported in accordance with local SOP's and approvals as required.

12.1.4.1 Vaccine A – AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19)

The AstraZeneca vaccine should be stored at +2ºC to +8ºC and has a shelf life of 6 months. The vaccine does not contain any preservative. After first opening the vial, it should be used within 6 hours when stored at room temperature (up to 30º C) or within 48 hours when stored in a refrigerator (2 to 8º C [36 to 46°F]). After this time, the vial must be discarded. The total cumulative storage time once opened must not exceed 48 hours.

12.1.4.2 Vaccine B - Pfizer BioNTech (BNT162b2)

The Pfizer BioNTech vaccine should be stored at -70°C +/- 10°C and has shelf life of 6 months. Once thawed, the vaccine may be stored for 5 days at 2-8°C.

12.1.4.3

12.1.5 Compliance with Trial Treatment

All vaccinations will be administered by the research team and recorded in the CRF. The study medication will be at no time in the possession of the participant and compliance will not, therefore, be an issue.

12.1.6 Accountability of the Trial Treatment

Accountability of the IMPs will be conducted in accordance with the relevant SOPs.

12.1.7 Concomitant Medication

As set out by the exclusion criteria, volunteers may not enter the study if they have received: any vaccine other than the licensed seasonal influenza vaccine or pneumococcal vaccine in the 30 days prior to enrolment or there is planned receipt of any other vaccine within 30 days of each vaccination, any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any use of immunosuppressant medication within 6 months prior to enrolment or if receipt is planned at any time during the study period (except topical steroids and short course of low dose steroids < 14 day). Concomitant medications taken at enrolment will be recorded, as will new medications taken within the 28 days after each immunisation. Subsequently only new medications taken in response to a medically attended adverse event up until 3 months post boost will be recorded.

12.1.8 Post-trial Treatment

If any heterologous boost regimen is not found to be non-inferior participants who received this regimen will be advised of this. Decisions regarding the need for a booster dose, the nature of the booster dose and mode of delivery (e.g. NHS vs study site) will be made in consultation with the DSMB and study management group.

12.2 Other Treatments (non-IMPS)

Participants will be advised that they may take paracetamol prophylactically after vaccine administration. This will be from the participants own supplies rather than supplied by the study team

12.3 Other Interventions

There are no additional investigations other than those specified in this protocol.

13 SAFETY REPORTING

13.1 Safety reporting window

Safety reporting for the trial will commence once the first participant is consented; and will end 12 months after the last participant has received the first dose of an IMP for SAEs and Adverse Events of Special Interest (AESI)s.

For individual participants the reporting period begins when they are consented, in person, at the V1 visit , and ends 12 months after the first dose of vaccine for SAE's and AESI's.

All adverse events (AEs) that result in a participants' withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the participant consents to this).

13.2 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Adverse Events of Special Interest (AESI)	Adverse events identified as being of particular relevance to the IMP's. These will also reported as an SAE, if meeting SAE criteria (e.g. hospitalisation)
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect* Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product

	• In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

13.3 Assessment results outside of normal parameters as AEs and SAEs

13.3.1 Clinical

Abnormal clinical findings from medical history or examination will be assessed as to their clinical significance throughout the trial. If an abnormal finding is deemed to be clinically significant, the participant will be informed and appropriate medical care arranged with the permission of the participant as per Section 11.6.

13.3.2 Laboratory

Abnormal clinical findings from safety blood tests will be assessed by a medically qualified study member. Laboratory AEs will be assessed using specific toxicity grading scales adapted from the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (APPENDIX C: Toxicity grading scale for lab AEs)

Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence, if deemed appropriate to do so in the medical opinion of the investigator.

If a repeated test remains clinically significant, the participant will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer.

13.4 Assessment of severity

The severity of clinical and laboratory adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, listed in the Clinical Study Plan and in Table 4-Table 6 below.

Table 4. Severity grading for local adverse events

Adverse Event	Grade	Intensity
Pain at injection site	1	Pain that is easily tolerated

	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Induration/Swelling at injection site	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis
***erythema ≤2.5cm is an expected consequence of skin puncture and will therefore not be considered an adverse event**		

Table 5. Severity grading criteria for physical observations.

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
Fever (Oral - °C)	38.0 - 38.4	38.5 – 38.9	39.0 - 40	> 40
Tachycardia (bpm)*	101 - 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia

Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalization for malignant hypertension
Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalization for malignant hypertension
Systolic hypotension (mmHg)* **	85 - 89	80 – 84	<80	A&E visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 - 20	21-25	>25	Intubation
***Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)**				

Table 6. Severity grading for local and systemic AEs

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: Requires assessment in A&E or hospitalisation

13.5 Assessment of Causality

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the CI-delegated clinician. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy. Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (including if the study is paused by the DSMB due to safety concerns) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator, immediately, as described in SOP OVC005 Safety Reporting for CTIMPs. Causality assessment will be recorded on the eCRF.

Table 7. Guidelines for assessing the relationship of vaccine administration to an AE.

0	No relationship	No temporal relationship to study product and Alternate aetiology (clinical state, environmental or other interventions); and Does not follow known pattern of response to study product
1	Unlikely	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	Possible	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	Probable	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	Definite	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines

13.6 Procedures for Reporting Adverse Events

13.6.1 Solicited AEs

Participants will be asked to record local and systemic AE's for 7 days (and longer if symptoms persist at day seven, until resolution or stabilisation) following vaccination in the electronic diary (solicited AEs).

13.6.2 Unsolicited AEs

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the participant, whether or not attributed to study medication, will be recorded in electronic diaries or study database. All AEs that result in a participants' withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the participant consents to this) as per Section 11.8.

SAEs and AESIs will be actively solicited at each study visit throughout the entire trial period.

13.6.3 Medically attended AEs

A medically attended AE, is defined as any adverse event for which the participant seeks medical attention either at hospital or from primary care. This explicitly excludes seeking medical attention solely for a SARS-

CoV2 test. Participants will be asked to record any medically attended AEs on their diary cards. Medically attended AEs occurring up to 3 months post boost, will be directly solicited and reviewed at each study visit.

13.7 Reporting Procedures for Serious Adverse Events

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported to members of the study team immediately the Investigators become aware of their occurrence, as described in the clinical study plan. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The DSMB will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMB will be notified immediately (within 24 hours) of the sponsor being aware of their occurrence. SAE/AESIs will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial participants, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAE/AESIs in the annual Development Safety Update Report (DSUR) report.

Grade 4 laboratory AEs should be reported as SAEs and under the category of outcome of an important medical event.

Cases falling under the Hy's Law should be reported as SAEs. A Hy's Law Case is defined by FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (2009). Any study participant with an increase in Aspartate Aminotransferase (AST) or **Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin ≥2xULN**, **where no other reason can be found to explain the combination of these abnormal results**, e.g., elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis A, B or C, another drug capable of causing the observed injury, amongst others.

In participants who have received at least one dose of the ChAdOx1-nCoV-19 vaccine, SAE's will be reported to AstraZeneca according to the conditions and timelines outlined in the contemporaneous version of the 'Pharmacovigilance Agreement by and between AstraZeneca UK Limited and Oxford University Innovation Limited for ChAdOx1 nCoV-19/AZD1222'.

13.7.1 Events exempt from immediate reporting as SAEs

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

13.8 Expectedness

13.8.1 SAEs

With the exception of SAEs described below for BNT162b2 there are no expected serious adverse events in either homologous or heterologous study arms. All other SARs will therefore be reported as SUSARs.

13.8.1.1 AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19)

No SAEs are expected.

13.8.1.2 Pfizer BioNTech (BNT162b2)

Anaphylaxis following immunisation is reported in the BNT162b2 Summary of Product Characteristics as an expected adverse event of unknown frequency. Accordingly, anaphylaxis within 24 hours of receipt of BNT162b2 as a prime dose, or as a boost in a homologous prime/boost schedule, will be considered an expected SAR to this vaccine. Acute peripheral facial nerve palsy and lymphadenopathy are described as rare and uncommon (respectively) adverse events following BNT162b2; should these be observed in participants receiving BNT162b2 and no other vaccine, and if they met the criteria for an SAE, these would be considered an expected SAE. If experienced in participants receiving BNT162b2 and another COVID-19 vaccine then they should be classified as 'unexpected'.

13.8.2 Foreseeable adverse reactions

The foreseeable ARs following vaccination are as follows:

13.8.2.1 AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19)

Local reactions

The following local reactions at the injection site are common and expected:

- tenderness, pain, warmth, redness, itching, swelling or bruising where the injection is given a lump at the injection site

Systemic reactions

Common and expected mild to moderate systemic reactions are:

- Fatigue
- Headache
- Myalgia
- Arthralgia
- Nausea or vomiting
- Malaise
- Chills

- Feverishness
- Fever >38^{o}
- Coryza (sore throat, runny nose)

Uncommon and expected mild to moderate systemic reactions

- Abdominal pain
- Feeling dizzy
- Decreased appetite
- Enlarged lymph nodes
- Excessive sweating, itchy skin or rash

These are expected to be less common after the second dose.

Laboratory events

Transient neutropaenia from baseline is common and expected.

13.8.2.2 Pfizer BioNTech (BNT162b2)

(Taken from SPC)

Very common

- Headache
- Arthralgia
- Myalgia
- Injection site pain/swelling
- Fatigue
- Chills
- Pyrexia

Common

- Nausea
- Injection site redness

Uncommon

- Lymphadenopathy
- Insomnia
- Pain in extremity
- Malaise
- Injection site pruritis

Rare

- Acute peripheral facial paralysis

Not known

- Anaphylaxis, hypersensitivity

13.9 Adverse events of special interest (AESI)

The following adverse events are considered adverse events of special interest.

Table 8. AESIs

Immunologic	Anaphylaxis	
Neurological	Isolated anosmia/ageusia* Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Aseptic meningitis	Meningoencephalitis Peripheral facial nerve palsy Generalised convulsion Myelitis
Haematological	Thrombosis** Stroke Thrombocytopaenia*** Eosinophilia****	Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
Cardiac	Acute cardiovascular injury (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	
Dermatological	Chilblain-like lesions Single organ cutaneous vasculitis	Erythema multiforme Alopecia
Gastrointestinal	Acute liver injury †††	Appendicitis
Respiratory	ARDS††	
Renal	Acute kidney injury	
Other	COVID-19 disease†	SARS-CoV2 positivity on a validated test

*In the absence of COVID-19

** Excluding superficial thrombophlebitis (including line-associated)

*** G3 or above

**** This will be used as a marker of skewed Th2 responses and will be routinely monitored in participants attending the COVID-19 Pathway and follow-up visits. Only G2 and above.

† In particular, any occurrence of suspected vaccine associated enhanced disease (VAED) as defined by most recent Brighton Collaboration Case Definition (REF)

†† In the absence of an infective aetiology (including COVID-19)

††† As defined in Hy's Law (see Cases falling under the Hy's Law should be reported as SAEs. A Hy's Law Case is defined by FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing

Clinical Evaluation" (2009). Any study participant with an increase in Aspartate Aminotransferase (AST) or **Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin ≥2xULN, where no other reason can be found to explain the combination of these abnormal results**, e.g., elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis A, B or C, another drug capable of causing the observed injury, amongst others.)

AESIs should be collected and recorded in the AE reporting form in RedCap throughout the duration of this study. These should also be reported as SAEs if they fulfil the definition criteria for SAEs. All AESI's not already reported as SAEs should be included in the reports to the DSMB.

Disease enhancement following vaccination

Severe COVID-19 disease will be defined as hospitalisation, with further grading of severity according to the WHO ordinal scale (June 2020)(W. H. O. Working Group on the Clinical Characterisation Management of Covid Infection 2020). Cases of COVID-19 disease will be examined for the possibility of vaccine associated enhanced disease (VAED). This will be evaluated on the basis of the most recent recommendations of the Brighton Collaboration.(Brighton Collaboration) Detailed clinical parameters will be collected from medical records and aligned with agreed definitions, as they emerge. Samples will be collected for evaluation of immunological evidence of VAED. Investigations will be defined by the laboratory analysis plan.

13.10 SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

13.11 Development Safety Update Reports

A Development Safety Update Report (DSUR) will be prepared annually for each vaccine, within 60 days of the anniversary of:

- The date of conditional marketing approval from the European Medicines Agency for BNT162b2
- The date of the MHRA's first authorisation for the University of Oxford to conduct a clinical trial for ChAdOx1-nCOV19

The DSUR will be submitted by the CI to the Competent Authority, Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

13.12 Interim reviews

The safety profile will be assessed on an on-going basis by the Investigators. The CI and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise. A review of reactogenicity data will occur after the first 50-60 participants have been boosted, as per section 11.6.2.

The DSMB will evaluate safety data every 4-8 weeks and/or as required and will review safety data accumulated when the study is fully recruited. The DSMB may also be consulted should safety concerns arise at any point.

13.13 Safety Holding Rules

There will be no formal pausing rules given the vaccines used in this study will be approved for use in the general public, and the Immunisation 'Green Book' is permissive of the administration of heterologous prime/boost schedules in the general community. Reactogenicity data will be reviewed after the first 50-60 participants have received a booster dose.

The study can be put on hold upon advice of the DSMB, Chief Investigator, Study Sponsor, regulatory authority, Ethical Committee(s), for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

13.14 Contraception and pregnancy

13.14.1 Contraception

Female participants of childbearing potential are required to use an effective form of contraception from one month before prime until three months after boost immunisation. A woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant. Menopause can be diagnosed in a woman aged over 50 after one year of amenorrhoea (this applies only if the woman is not using hormonal contraception).

Acceptable forms of contraception for volunteers of female sex include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Total hysterectomy
- Bilateral Tubal Occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicide)
- Male sterilisation, if the vasectomised partner is the sole partner for the subject
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)

13.14.2 Pregnancy

Should a participant become pregnant during the trial, no further study IMP will be administered. They will be followed up for clinical safety assessment with their ongoing consent and in addition will be followed until pregnancy outcome is determined. We would not routinely perform venepuncture in a pregnant participant unless there is clinical need.

14 STATISTICS

14.1 Sample size

The primary analysis of this study will be a non-inferiority comparison between schedules using a homologous versus heterologous boost within each group of approved COVID-19 vaccines, e.g., Group ChAdOx1 nCOV-19/ BNT162b2 will be compared with group ChAdOx1 nCOV-19 / ChAdOx1 nCOV-19 and group BNT162b2 / ChAdOx1 nCOV-19 will be compared with group BNT162b2/ BNT162b2, separately. We will combine the immunology cohort (N=100) and the general cohort boosted at D28 (N=360) in the primary analysis. The analysis will be repeated in the general cohort boosted at D84 (N=360), and all the study population in the secondary analysis (N=820).

The below sample size calculation is based on the primary analysis conducted in the participants boosted at D28. The current available data from the ongoing ChAdOx1 nCoV-19 trial suggests the GMC of anti-spike IgG measured by standardised ELISA is around 500 EU/ml at D56 (4 weeks after booster at Day 28) among participants aged 56-69 years old (n=29) with a standard deviation of 0.4.

The sample calculation is based on the following assumptions:

1. The non-inferiority margin is 0.63 fold-difference between the GMC in the heterologous boost arm and that in the homologous boost arm or -0.2 absolute difference of GMC on log scale (base 10).
2. The standard deviation of GMC on log scale (base 10) is 0.4 based on the current available data.
3. The true difference of GMC on log scale (base 10) is 0.

Based on the above assumptions, the study will need to recruit 86 participants who are seronegative for SARS-CoV-2 IgG at baseline in each arm to achieve 90% of power at one-sided 2.5% significance level. We assume ~25% of study participants will be excluded from the primary analysis due to seropositive for SARS-CoV-2 IgG at baseline or loss of follow-up. Therefore, the sample size in each arm boosted at D28 will be expanded to 115. This means that if the study has two vaccines the total sample size for participants boosted at D28will be 460 for four arms. If we decide to add groups as new vaccines are made available for use by the Department of Health and Social Sciences, the sample sizes will be adapted accordingly. The immunogenicity cohort will used for exploratory analyses to generate hypothesis, and thus no formal sample size calculation

was carried out for this cohort. The sample size of 25 per arm was therefore chosen based on practical constraints. This means we will have around 20 seronegative participants in each arm for analysis.

Of note, should a correlate of protection against SARS-CoV-2 infection become apparent during the study then the sample size calculations will be re-visited to determine the power to demonstrate non-inferiority based on a margin of 10% between the above study arms, and potentially revised on this basis. Based on the sample size anticipated for two vaccines in the study, we summarised the study power for different proportion of protection at one-sided significant level 0.05 (with no adjustment for multiple testing).

Proportion of protection	Study power
0.85	58%
0.9	71%
0.95	91%

We chose the sample size of 360 (effective sample size N=270) in the general cohort who will be boosted at D84 for two reasons: 1) simplifying the study management and randomisation; 2) >80% power to test non-inferiority of the heterologous schedule compared with the homologous schedule at one-sided 2.5% significance level, assuming there is no interaction between vaccine schedules and prime-boost intervals. In addition, with a combined analysis (all study population, N=820) to assess the immunogenicity at D28 post boost, the study will have >95% power and the conclusion will have a broader generalisability to the UK population.

14.2 Description of Statistical Methods

The primary endpoint is anti-spike IgG measured by standardised ELISA at Day 56. The geometric mean concentrations (GMC) of anti-spike IgG will be compared between heterologous boost arms and homologous boost arms under the hypothesis:

H_0: GMC $_{heterologous}$ / GMC $_{homologous} \leq 0.63$ or $log10$ GMC $_{heterologous}$ - $log10$ GMC $_{homologous} \leq -0.2$;

H_1: GMC $_{heterologous}$ / GMC $_{homologous} > 0.63$ or $log10$ GMC $_{heterologous}$ - $log10$ GMC $_{homologous} > -0.2$.

The GMC will be transferred using logarithmic transformations (base 10) to render a normal distribution. We will test the above hypothesis using the multiple regression on log_{10}GMC adjusting for design variables, if any, and the pre-specified prognostic factors. The adjusted mean difference of log_{10}GMC will be presented with the two-sided 95% confidence interval (CI). We will claim heterologous boost arm is non-inferior to homologous boost arm if the lower CI lies above -0.2.

The primary analysis will be conducted on the modified intent-to-treat basis among the participants boosted D28, i.e. we will only include people who were seronegative at baseline and whose primary endpoint at D56 is available. The per-protocol analysis will be considered as a sensitivity analysis if the protocol deviation rate,

e.g. the timing of blood sample for primary endpoint, is high in this trial. The primary analysis will be carried out when the primary endpoint of D56 anti-spike IgG data become available.

The secondary analysis on D28 post boost anti-spike IgG in the participants boosted at D84 (D112) will follow the primary analysis, and will be carried out when the D112 data become available. We will also combine the participants boosted at D28 and D84 as a secondary analysis to compare the D28 post boost anti-spike IgG between heterologous and homologous schedules.

A fully detailed statistical analysis plan will be prepared and will be signed off by the Chief Investigator prior to conducting any data analyses.

14.3 Interim analysis

We will carry out an interim analysis to review the seropositive rate at baseline after the D0 immunogenicity data for the first 100 participants becomes available. If there is a significant deviation from our assumption, we will adjust the sample size accordingly.

14.4 Missing data

The level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any missing data will be investigated and documented as far as possible. Any missing data will be dealt with using methods appropriate to the conjectured missing mechanism and level of missing.

15 DATA MANAGEMENT

The Chief Investigator will be responsible for all data that accrues from the study.

15.1 Access to Data & Data Protection

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

15.2 Data Recording

All study data including participant diary will be recorded directly into an EDC system (REDCap) or onto a paper source document for later entry into EDC if direct entry is not available. This includes safety, laboratory and outcome data. Any additional information that needs recording, but is not relevant for the eCRF (e.g

signed consent forms) will be recorded on separate paper source documents. All documents will be stored safely and securely in confidential conditions. The EDC online data is stored on University of Oxford servers.

All participant reported adverse event data (both solicited & unsolicited) will be entered onto electronic diary cards (e-diaries) for a maximum of 28 days following administration of the IMP. The eDiary provides a full audit trial of edits and will be reviewed at time-points as indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF as required for safety review.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, with the exception of the electronic diaries, for which consent will be obtained to store the participant email address for quality control purposes. Only site research staff and sponsor data managers have access to view the email address.

The EDC system (CRF data) uses a relational database (MySQL/ PostgreSQL) via a secure web interface with data checks applied during data entry to ensure data quality. The database includes a complete suite of features which are compliant with GCP, EU and UK regulations and Sponsor security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL and PostgreSQL database and the webserver will both be housed on secure servers maintained by the University of Oxford IT personnel. The servers are in a physically secure location in Europe. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. The IT servers provide a stable, secure, well-maintained, and high capacity data storage environment. REDCap is a widely-used, powerful, reliable, well-supported system. Access to the study's database will be restricted to members of the study team by username and password.

15.3 Record keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Identifiable information such as contact details will be stored for a minimum of 5 years from the end of the study. This includes storage of consent forms. Storage of these data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required. Considerations at the time of this review will include the value of retaining this information for participant safety (e.g. to inform participants of unexpected safety signals emerging from post-licensing surveillance), as a resource for the participants (e.g. if they wish to check which vaccines they have received in the study) and any regulatory requirements. Financial

information will be stored for 7 years. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained and stored securely and separately from the research data. If volunteers consent to have their samples stored and used in future research, information about their consent form will be retained and stored securely as per Biobanking procedures and SOP.

15.4 Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the participant file. Source documents are original documents, data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, medical records and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, safety blood results, adverse event data and details of vaccinations. All source data and participant files will be stored securely.

To prevent withdrawal of a participant due to relocation, if there is a nearby participating site and with the consent of the participant, copies of relevant participant research records (such as ICF, paper source documents) will be transferred to the local site using secure email addresses such as nhs.net or by password protected sheets. The electronic research data stored on REDCap will also be transferred to the new site. The original records will be retained by the recruiting site.

15.5 Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented

15.6 Data Sharing

For participants who are also registered on NHS Digital's '*Sign up to be contacted for coronavirus vaccine studies'* service, we will share the minimum amount of information necessary with NHS Digital in order to

allow them to update their database so that participants are not contacted about further trials, as participants are permitted only to be in one vaccine study at a time.

Personally identifiable information will be shared with Public Health England regarding SARS-CoV2 PCR test results depending on the most up to date legal requirement to report on Notifiable Diseases at the time.

16 QUALITY ASSURANCE PROCEDURES

16.1 Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

16.2 Monitoring

Monitoring will be performed according to Good Clinical Practice (GCP) guidelines by an external monitor. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor or the Host institution and inspection by local and regulatory authorities

16.3 Trial committees

16.3.1 Trial Steering Committee

A Trial Steering Committee will be formed to oversee the study, and advise the Study Management Committee on key issues of study conduct, including, but not limited to, study pauses due to safety concerns on the advice of the DSMB.

16.3.2 Safety Monitoring Committee

A Data Safety Monitoring Board (DSMB) will be convened. The DSMB will evaluate frequency of events, safety and efficacy data as specified in the DSMB charter. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons to the Trial Steering Committee.

The DSMB will review SAEs or AESIs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMB can recommend placing the study on hold if deemed necessary following a study intervention-related SAE.

16.3.3 Study Management Committee

Consists of the site Investigators and the Laboratory lead for Public Health England.

17 PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be documented in a protocol deviation form according to SOP OVC027 and filed in the trial master file.

These will be managed as per SOP OVC027.

18 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

19 ETHICAL AND REGULATORY CONSIDERATIONS

19.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

19.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

19.3 Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

19.4 Other Ethical Considerations

Study team members are not eligible for participation in the study. Family members of the study team are not barred from inclusion in the trial.

Participants eligible for routine SARS-CoV-2 immunisation as per national guidelines will not be excluded from participation in the trial; but will be counselled specifically on the risks of receiving an unapproved schedule. In particular, the risks of reduced efficacy and unforeseen safety concerns will be discussed.

19.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

19.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

19.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of informed consent forms, participant ID log and electronic diaries. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the current data protection legislation. Photographs of vaccination sites if required (with the participants' written, informed consent), will not include the participants' face and will be identified by the date, trial code and subject's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

19.8 Expenses and Benefits

Volunteers will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. The total amount compensated will depend on the exact number of visits, and whether any repeat or additional visits are necessary. For all trial visits compensation will be calculated according to the following:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per blood donation
- Time required for visit: £20 per visit

20 FINANCE AND INSURANCE

20.1 Funding

The study is funded by the UK Government through the National Institute for Health Research (NIHR).

20.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

20.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

21 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Data from the study may also be used as part of a thesis for a PhD or MD.

22 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

23 ARCHIVING

Study data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 5 years after the study has finished with 5 yearly reviews. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the site at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. Where relevant participants' bank details will be stored for 7 years in line with the site financial policy. De-identified research data maybe be stored indefinitely, but with 5 yearly review.

General archiving procedures will be conducted in compliance to SOP OVC020 Archiving.

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25 APPENDIX A: SCHEDULE OF PROCEDURES

General cohort boosted at 28 days

	Screening	V1	V2	V3	V6	V7	(VPP) Only if enter C19P
Study timeline		D0	D28	D56	D182	D364	(D0-D364)
Study window		Within 120 days of screening	Day 28–35 post V1	Day 25–32 post V2	Day 142-166 post V2	Day 349-379 post V1	Within 7 days of positive test
Informed consent	X*	X					
Safety bloods		X	X	X			X
Medical history	X						
Interim medical history		X	X	X	X	X	X
Physical examination (as required)		(X)	(X)	(X)	(X)	(X)	X
Urine test (Pregnancy) (if required)		X	X				
COVID-19 vaccination		X	X				
COVID-19 immunogenicity bloods		X	X	X	X	X	X
SARS-Cov-2 viral swab							X
Diary card review			X	X			X
SAE/AESI/Medically attended AE check			X	X	X	X	X

*Online Consent. Restricted to taking a limited medical history online, contacting the GP for further medical record if required and telephone screening visit(s)

General cohort boosted at 84 days

	Screening	V1	V3	V4	V5	V6	V7	(VPP) Only if enter C19P
Study timeline		D0	D56	D84	D112	D182	D364	(D0-D364)
Study window		Within 120 days of screening	Day 53–60 post V1	Day 84-91 post V1	Day 25–32 post V4	Day 91-105post V4	Day 349-379 post V1	Within 7 days of positive test
Informed consent	X*	X						
Safety bloods		X		X	X			X
Medical history	X							
Interim medical history		X	X	X	X	X	X	X
Physical examination (as required)		(X)	(X)	(X)	(X)	(X)	(X)	X
Urine test (Pregnancy) (if required)		X		X				
COVID-19 vaccination		X		X				
COVID-19 immunogenicity bloods		X	X	X	X	X	X	X
SAM-strip**		X	X	X	X	X	X	X
Saliva**			X	X	X	X	X	X
SARS-Cov-2 viral swab								X
Diary card review			X	X				X
SAE/AESI/Medically attended AE check			X	X	X	X	X	X

*Online Consent. Restricted to taking a limited medical history online, contacting the GP for further medical record if required and telephone screening visit(s)

**Only from participants recruited at nominated sites

Immunology cohort boosted at 28 days

	Screening	V1	V1A	V1B	V2	V2A	V2B	V3	V5	V6	V7	(VPP) Only if enter C19P
Study timeline		**D0**	**D7**	**D14**	**D28**	**D35**	**D42**	**D56**	**D112 (optional)**	**D182**	**D364**	**(D0-D364)**
Study window		Within 120 days of screen	Day 5-9 post V1	Days 12–16 post V1	Day 28–35 post V1	Day 5–9 post V2	Days 12–16 post V2	Day 25–32 post V2	Day 78–91 post V2	Day 142-166 post V2	Day 349-379 post V1	Within 7 days of positive test
Informed consent	X*	X										
Safety bloods		X			X	X		X				X
Medical history	X											
Interim medical history		X	X	X	X	X	X	X	X	X	X	X
Physical examination (as required)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Urine test (pregnancy) (if required)		(X)			(X)							
COVID-19 vaccination		X			X							
COVID-19 immunogenicity bloods		X	X	X	X	X	X	X	X	X	X	X
SAM-strip		X	X	X	X	X	X	X	X	X	X	X
Saliva					X	X	X	X	X	X	X	X
SARS-CoV-2 viral swab												X
Diary card review			X	X	X	X	X	X				X
SAE/AESI/Medically attended AE check			X	X	X	X	X	X	X	X	X	X

*Online Consent. Restricted to taking a limited medical history online, contacting the GP for further medical record if required and telephone screening visit(s)

26 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	28 Jan 2021	R Shaw/M. Snape/ A.Stuart	Section 5 (synopsis) and 8 Addition of day 14 for humoral immunity endpoints Removal of day 14 for anti-nucleocapsid IgG Section 10.3 Exclusion criteria modified to remove reference to angioedema, and carrying of adrenaline pen, and to add: • 'hypersensitivity to the active substance or any of the SmPC-listed ingredients of the Pfizer vaccine)' Section 13.1 Safety reporting period modified to commence from time of consent, rather than enrolment Section 11.7.1.3 Amended to state that swabs taken for SARS-CoV-2 testing at the C19P visit will be processed centrally, and not at local sites. Appendix D

				Changes to allocation of blood for serology (3 aliquots rather than 2 aliquots) and cellular immunology (2 aliquots rather than 3 aliquots) in the general cohorts Removal of ICS for C19 pathway in general cohorts Addition of humoral immunity endpoints for Day 14 bloods in immunology cohort Removal of D14 anti-nucleocapsid IgG
2	2.1	10-Feb-2021	R.Shaw	Modification of section 7.2.1 and tables in section 28 Appendix D: Blood sampling, to change blood volumes to 'up to'. Safety blood volumes changed to allow variation between sites' local laboratory SOPs. Tables in section 25 Appendix A: Schedule of Procedures amended as SAE checks occur at each visit but had been omitted from two.
3	3.0	09-Mar-2021	R.Shaw	Addition of saliva samples Addition of optional D112 visit to immunology cohort Update of background information of COVID and COVID vaccines Update of WHO advice surrounding vaccine scheduling Addition of CRP gradings

				Typographical errors and clarity including blood sample tables
4	3.1	29-Mar-2021	R.Shaw	Removal of laboratory names from appendix D to allow flexibility due to lab capacity limits.

27 APPENDIX C: Toxicity grading scale for lab AEs

		Units	Lab range	Grade 1	Grade 2	Grade 3	Grade 4
Haematology							
Haemoglobin Absolute	Male	g/l	130-170	115-125	100-114	85-99	<85
Haemoglobin Absolute	Female	g/l	120-150	105-113	90-104	80-89	<80
Haemoglobin change from baseline			n/a	10-15	16-20	21-50	>50
White Blood Cells	Elevated	x 10^9/L	11.00	11.50-15.00	15.01-20.00	20.01-25.00	>25.00
White Blood Cells	Low	x 10^9/L	4.00	2.50-3.50	1.50-2.49	1.00-1.49	<1.00
Platelets	Low	x 10^9/L	150-400	125-140	100-124	25-99	<25
Neutrophils	Low	x 10^9/L	2.00-7.00	1.50-1.99	1.00-1.49	0.50-0.99	<0.50
Lymphocytes	Low	x 10^9/L	1.00-4.00	0.75-0.99	0.50-0.74	0.25-0.49	<0.25
Eosinophils	Elevated	x 10^9/L	0.02-0.50	0.65-1.50	1.51-5.00	>5.00	Hypereosinophilia
Biochemistry							
Sodium	Elevated	mmol/L	145	146-147	148-149	150-155	>155
Sodium	Low	mmol/L	135	132-134	130-131	125-129	<125
Potassium	Elevated	mmol/L	5.0	5.1-5.2	5.3-5.4	5.5-6.5	>6.5
Potassium	Low	mmol/L	3.5	3.2-3.3	3.1	2.5-3.0	<2.5
Urea	Elevated	mmol/L	2.5-7.4	8.2-9.3	9.4-11.0	>11.0	Requires dialysis
Creatinine	Elevated	µmol/L	49-104	1.1-1.5xULN 114-156	>1.5-3.0xULN 157-312	>3.0xULN >312	Requires dialysis
Bilirubin	Elevated Normal LFTs	µmol/L	0-21	1.1-1.5xULN 23-32	>1.5-2xULN 33-42	>2-3xULN 43-63	>3xULN >63
Bilirubin	Elevated Abnormal LFTs	µmol/L	0-21	1.1-1.25xULN 23-26	>1.25-1.5xULN 27-32	>1,5-1.75xULN 33-37	>1.75xULN >37
ALT	Elevated	IU/L	10-45	1.1-2.5xULN 49-112	>2.5-5xULN 113-225	>5-10xULN 226-450	>10xULN >450
ALP (Alkaline phosphatase)	Elevated	IU/L	30-130	1.1-2xULN 143-260	>2-3xULN 261-390	>3-10xULN 391-1300	>10xULN >1300
Albumin	Low	g/L	32-50	28-31	25-27	<25	-
CRP	Elevated	mg/L	0-10	11-30	31-100	101-200	>200

Normal ranges may vary between sites and gradings may be adapted between sites

28 APPENDIX D BLOOD SAMPLING

General Cohort – 28 day boost

	V1	V2	V3	V6	V7	(VPP) Only if enter C19P
Study timeline	**D0**	**D28**	**D56**	**D182**	**D364**	**(D0-D364)**
Safety bloods	1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)	1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)	1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)			1 x FBC (up to 2ml) 1 x biochem (up to 5ml)
COVID-19 vaccination	**X**	**X**				
Primary endpoint			Anti-spike IgG			
Secondary endpoints	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot
No of tubes & colours	Up to 30ml Red Up to 20ml Green (LiHep)* 1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)	Up to 30ml Red Up to 20ml Green (LiHep)* 1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)	Up to 30ml Red Up to 20ml Green (LiHep)* 1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)	Up to 30ml Red Up to 20ml Green (LiHep)*	Up to 30ml Red Up to 20ml Green (LiHep)*	Up to 30ml Red Up to 20ml Green (LiHep)* 1 x FBC (up to 2ml) 1 x Biochem (up to 5ml)
Total volume per visit	Up to 57ml	Up to 57ml	Up to 57ml	Up to 50ml	Up to 50ml	Up to 57ml
Total volume by end of study	At any point in the study, a repeat of safety bloods may be recommended at the clinical discretion of the investigator. This will result in up to an extra 7ml per repeat blood sample.				Up to 271ml	+ Up to 57ml per C-19 pathway attended

***LiHep tube or equivalent**

General Cohort – 84 day boost

	V1	V3	V4	V5	V6	V7	(VPP) Only if enter C19P
Study timeline	**D0**	**D56**	**D84**	**D112**	**D182**	**D364**	**(D0-D364)**
Safety bloods	1xFBC (up to 2ml) 1xBiochem (up to 5ml)		1xFBC (up to 2ml) 1xBiochem (up to 5ml)	1xFBC (up to 2ml) 1xBiochem (up to 5ml)			1xFBC (up to 2ml) 1xBiochem (up to 5ml)
COVID-19 vaccination	**X**		**X**				
Secondary endpoints	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot	Anti-spike IgG Neutralising Abs Anti-nuclesocapsid IgG Pseudo-neut Abs ELIspot
No of tubes & colours	Up to 30ml Red Up to 20ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	30ml Red 20ml Green (LiHep)*	Up to 30ml Red Up to 20ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 30ml Red Up to 20ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 30ml Red Up to 20ml Green (LiHep)*	Up to 30ml Red Up to 20ml Green (LiHep)*	Up to 30ml Red Up to 20ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)
Total volume per visit	Up to 57ml	Up to 50ml	Up to 57ml	Up to 57ml	Up to 50ml	Up to 50ml	Up to 57ml
Total volume by end of study	At any point in the study, a repeat of safety bloods may be recommended at the clinical discretion of the investigator. This will result in up to an extra 7ml per repeat blood sample.					Up to 321ml	+ Up to 57ml per C-19 pathway attended

***LiHep tube or equivalent**

Immunology Cohort (28 day boost)

	V1	V1A	V1B	V2	V2A	V2B	V3	V5	V6	V7	(VPP) Only if C19P
Study timeline	**D0**	**D7**	**D14**	**D28**	**D35**	**D42**	**D56**	**D112 (optional)**	**D182**	**D364**	**(D0-D364)**

	V1	V1A	V1B	V2	V2A	V2B	V3	V5	V6	V7	(VPP) Only if C19P
Safety bloods	X			X	X		X				X
COVID-19 vaccination	**X**			**X**							
Primary endpoint							Anti-spike IgG				
Secondary endpoints	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot ICS	Anti-spike IgG	Anti-spike IgG Neutralising Ab Pseudo-neut Ab ELISpot ICS	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot	Anti-spike IgG	Serum ELISpot ICS	Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot	Anti-spike IgG Neutralising Ab Anti-N IgG Pseudo-neut Ab ELISpot ICS
No of tubes & colours	Up to 20ml Red Up to 50ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 20ml Red	Up to 20ml Red Up to 50ml Green (LiHep)*	Up to 20ml Red Up to 30ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 20ml Red 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 20ml Red Up to 50ml Green (LiHep)*	Up to 20ml Red Up to 30ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)	Up to 20ml Red Up to 30ml Green (LiHep)*	Up to 20ml Red Up to 30ml Green (LiHep)*	Up to 20ml Red Up to 30ml Green (LiHep)*	Up to 20ml Red Up to 50ml Green (LiHep)* 1xFBC (up to 2ml) 1xBiochem (up to 5ml)
Total volume per visit	Up to 77ml	Up to 20ml	Up to 70ml	Up to 57ml	Up to 27ml	Up to 70ml	Up to 57ml	Up to 50ml	Up to 50ml	Up to 50ml	Up to 77ml
Total volume (study end)	At any point in the study, a repeat of safety bloods may be recommended at the clinical discretion of the investigator. This will result in up to an extra 7ml per repeat blood sample.								Up to 528ml		+ Up to 77ml per C-19P attended

***LiHep tube or equivalent**