Trial Title: Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine

Short Title: Safety & immunogenicity extension study for ChAdOx1 nCoV-19

Study Reference: COV009
(OVG2021/03)

EudraCT number: 2021-003382-36

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and other regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Prof Andrew Pollard.

Statement of Compliance

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, Medicines for Human Use (Clinical Trial) Regulations 2004 (as amended) and all other applicable regulatory requirements.

Investigator Agreement and Notification of Conflict of Interest

I approve this protocol for use in the above-named clinical trial and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no-conflict of interest

Chief Investigator Signature  Date 5/8/24

Statistician Signature  Date 5/8/24

Details for Site Investigators can be found in Appendix E

Contents

1 Lay Summary

SARS-CoV-2 has swiftly spread around the world and is known to have infected more than 196 million people, implicated in more than four million deaths, across 192 countries.(1)

The COV001 trial administered the first dose of the Oxford/AstraZeneca ChAdOx1 nCoV-19 vaccine on the 23rd April 2020 as a phase I/II to evaluate the safety and immunogencity of this new vaccine. The COV002 trial began just over one month later, as a phase II/III to determine efficacy to prevent the symptoms of COVID-19. Together both trials administered vaccine to more than 13,000 participants at multiple collaborating sites around the UK.

Since the emergency approval for use in the UK and elsewhere, the ChAdOx1 nCoV-19 vaccine has been shown to reduce patients' emergency admissions to hospital, and their risks of death from COVID-19. Public Health England estimates that more than 7 million infections and 27,000 deaths have been prevented by the rapid rollout of vaccines in England alone. (2) (3) (4)

There is a need for ongoing monitoring of adverse events and further investigations of immunity, which will be achieved in this safety and immunogenicity extension study.

A subset of participants will also be offered a further dose of the ChAdOx1 nCoV-19 vaccine within the trial to help us understand the impact of the vaccine on the immune system, and to help inform health policy should further COVID-19 vaccine doses be required in the national vaccination programme.

2 Synopsis

Study Title	Post-approval follow-up for the COV001 and -002 trials, to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 coronavirus vaccine
Internal ref no	COV009
Short Title	Global safety & immunogenicity extension study for ChAdOx1 nCoV-19
Study Participants	Cohort 1: volunteers from the phase I/II trial of ChAdOx1 nCoV-19 (COV001) Cohort 2: volunteers from the phase II/III trial of ChAdOx1 nCoV-19 (COV002)
Planned Sample Size	Cohort 1: up to 1,077 participants (COV001) Cohort 2: up to 10,812 participants (COV002)
Study Duration	**Group 1 (comprising of participants from cohorts 1 and 2): 12months** Group 2 (comprising of subset of up to 150 participants from cohort 2): 6 months from 4th dose vaccination
Planned Study Period	August 2021 - December 2024 (assuming 12 months follow-up under this study)

	Objectives	Outcome Measures	Evaluation Time Points
Primary	· Assessment of **long-term safety of ChAdOx1 nCoV-19**	· **Registry** of: - serious adverse events (SAEs) - adverse events of special interest (AESIs)	- Visit 1 (6 months, +/- 28 days) - Visit 2 (12 months, +/- 28 days) - As may be reported by Participant at other times
Secondary	To investigate the relationship between vaccination, immunological profile, and subsequent SARS-CoV-2 infection, COVID-related hospitalisation, morbidity or mortality Evaluation of the safety and immunogenicity of **ChAdOx1 nCoV-19 as a 4th dose booster in individuals who have received 2 doses of ChAdOx1 nCoV-19 as a primary schedule in COV002, followed by an external 3rd dose of BNT162b2**	**· Measurement of immune responses** - anti-SARS-CoV-2 spike protein immunoglobulins - neutralising antibodies against SARS-CoV-2 (for a subset of participants, where local lab facilities permit): - cellular immune response to SARS-CoV-2 spike protein by IFNg ELIspot, ICS or whole blood assay - anti-vector immunity, to ChAdOx1 virus Recording of solicited and unsolicited AEs for 7 days post 4th dose booster vaccine via electronic diaries Recording of unsolicited AEs for 28 days post 4th dose booster vaccine. Recording of COVID-19 diagnoses throughout.	Group 1 **- Visit 1 (6 months +/- 28 days)** **- Visit 2 (12 months +/-28 days)** **Group 2** **-Baseline, 1 month and 6 month post vaccine**
Exploratory	· · To assess any differences in immunological profile or immunological persistence by age, sex, ethnicity, and reactogenicity.	**· Measurement of immune responses** (as above)	- Visit 1 (6 months, +/- 28 days) - Visit 2 (12 months, +/- 28 days)

3 Abbreviations

AdHu	Human Adenovirus
AE	Adverse event
AZD1222	AZ's R&D designation for the Oxford/AstraZeneca vaccine
BNT162b2	the mRNA vaccine developed by Pfizer/BioNTech
CBF	Clinical Bio-Manufacturing Facility
ChAdOx	Oxford University Chimpanzee Adenovirus
ChAdOx1 nCoV-19	Generic designation for the Oxford/AstraZeneca vaccine
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine Dipeptidyl
CTL	Cytotoxic T-lymphocyte
Covishield	Serum Institute of India's brand name for Oxford/AstraZeneca vaccine
DPP4	Peptidase 4
ELIspot	Enzyme-Linked Immunospot
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
HEK	Human Embryonic Kidney Cells
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
ICS	Intracellular Cytokine Staining
IFN γ	Interferon gamma
IU	Infectious units
MenACWY	Quadrivalent capsular group A,C,W&Y meningococcal protein-polysaccharide conjugate vaccine
MERS	Middle East Respiratory Syndrome
MERS-CoV	Coronavirus responsible for Middle East Respiratory Syndrome
MHRA	UK Medicines and Healthcare Products Regulatory Agency
mRNA-1273	the mRNA vaccine developed by Moderna
MVA	Modified Vaccinia virus Ankara
NAAT	Nucleic acid amplification (swab PCR) test
PBMC	Peripheral blood mononuclear cells
PB	Post Boost
PCR	Polymerase chain reaction process employed in NAAT testing
RGEA	Research Governance, Ethics & Assurance
Vaxzevria	AstraZeneca's commercial name for the Oxford/AstraZeneca vaccine
vp	Viral Particles
WHO	World Health Organization
S	Spike glycoprotein
SAE	Serious adverse event
SARS-CoV	Coronavirus responsible for severe acute respiratory syndrome
SARS-CoV-2	Coronavirus responsible for COVID-19

SII	Serum Institute of India
SmPC	Summary of Product Characteristics
SV	Site Visit
WHO	World Health Organization

4 Background and Rationale

4.1 Summary of the Clinical Trials

This COV009 trial will continue follow-up of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials.

4.1.1 Single blind phase I/II (COV001) trial

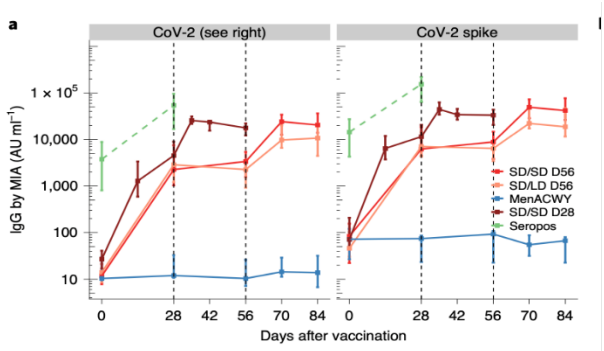
COV001 was conducted at five sites across the UK. The trial enrolled 1,077 healthy adults, 18-55 years of age, randomly allocating them 1:1 to either an active ChAdOx1 nCoV-19 arm (N=543), or a placebo MenACWY arm (N=534). MenACWY is a licensed, quadrivalent conjugate vaccine to prevent meningitis, chosen to elicit post-injection symptoms, in order to maintaining blinding.

The first participants received an initial priming dose and were intensively monitored. Once safety had been ascertained, the next cohorts received a prime dose followed by a booster at 8 weeks or later.

ChAdOx1 nCoV-19 was associated more commonly than MenACWY with local and systemic reactions, including pain, fever, chills, myalgia, headache, and malaise, with highest severity within the first 24 hours. The majority were of mild to moderate severity, and all self-resolved. Prophylactic paracetamol significantly ameliorated reported symptoms. There were no serious adverse events related to ChAdOx1 nCoV-19.

Immunologically, CD8 T-cell responses specific for the SARS-CoV-2 spike protein peaked 14 days after vaccination (median 856 spot forming cells per million PBMCs). Anti-spike IgG antibody levels peaked at four weeks (median 157 ELISA units), remained elevated until eight weeks, and were boosted further by second vaccination (median 639 ELISA units). In a sub analysis, 91% of participants generated neutralising antibody responses against SARS-CoV-2 after a single dose; 100% after being boosted. (5)(6)

Figure 1. Immunogenicity of different dosing and prime-boost intervals compared



It was concluded that ChAdOx1 nCoV-19 was safe, well tolerated, and immunogenic. Observed reactogenicity could be managed with prophylactic paracetamol.

4.1.2 Single blind phase II/III (COV002) trial

Progressing into COV002, 10,812 participants were enrolled at 20 UK centres.

There were 12 groups, employing age escalating recruitment, initially into the younger (18-55 years) adult groups, before the 56-69 years of age, and finally the 70+ years groups. As in the phase I/II (COV001) participants were randomised to receive ChAdOx1 nCoV-19 active or MenACWY placebo vaccines.

For the ChAdOx1 nCoV-19 active vaccine, local pain and tenderness were common at injection sites, within the first 48 hours, at all age groups. Fatigue, headache, feverishness, and myalgia were commonly reported systemic reactions. Intriguingly, younger age groups were more likely to experience generalised symptoms; 86% of 18–55-year-olds, vs 77% of 56–69-year-olds, vs 65% of those aged 70 years and older.

Prime vaccination with ChAdOx1 nCoV-19 stimulated similar anti-spike antibodies for both lower and standard dose participants, by day 28. Advanced age was correlated with reduced formation of immunity, with anti-spike IgG observed to decrease with age (median 10k arbitrary units per ml, for 18–55-year-old groups, vs 5k AU/ml for 56–69-year-olds, vs 4k AU/ml for 70+ year olds, all receiving single standard dose). However, participants receiving a booster generated similar antibody titres at 28 days after their second dose, in all age groups regardless of dose regime. (7)

4.2 Rationale for this study

With the encouragement of national expert advisory bodies and the World Health Organization (WHO), many countries have commenced expedited vaccination campaigns to protect their populations, and consequently their economies, against COVID-19.

The technologies from which current COVID-19 vaccines are derived have largely been developed over the past decade. Since achieving regulatory approvals, national vaccination campaigns, in the US, UK, Chile, Israel and the UAE in particular, have achieved unprecedented population reach. The clinical experience remains positive, supporting an evidence base that favours the population benefits of reduced symptomatic disease, hospitalisation, and mortality, outweighing individual risks, typically of transient symptoms.

However, with immunisation at scale, it is possible that extremely rare adverse events, may emerge, but these cannot be measured in clinical trials. Clinical trials can identify more common adverse events and safety follow up of trial participants will provide earlier information on these since they were exposed to the vaccines before the global roll out. Currently, long-term experience of COVID-19 vaccine safety and efficacy, within clinical trials, is limited to 12 months post-vaccination. In addition, the quality and durability of the immune response that is stimulated has yet to be characterised beyond that period. Many of the participants will have been offered a 3rd dose COVID-19 booster vaccine via a national vaccination programme. A subset of participants from the COV002 parent trial (Group 2) will also be offered a 4th dose booster to assess the impact of additional doses of vaccine on immunogenicity.

Understanding these factors will be important to health policymakers, in order to design optimal booster strategies.

4.3 Aim of the study

This study aims to:

1. document the long-term safety profile of ChAdOx1 nCoV-19 vaccine,
2. Investigate the relationship between ChAdOx1 nCoV-19 vaccination, immunological profile, and subsequent SARS-CoV-2 infection, COVID-related hospitalisation, morbidity or mortality
3. Evaluation of the safety and immunogenicity of ChAdOx1 nCoV-19 as a 4th dose booster in individuals who have received 2 doses of ChAdOx1 nCoV-19 as a primary schedule in COV002, followed by an external 3rd dose of BNT162b2

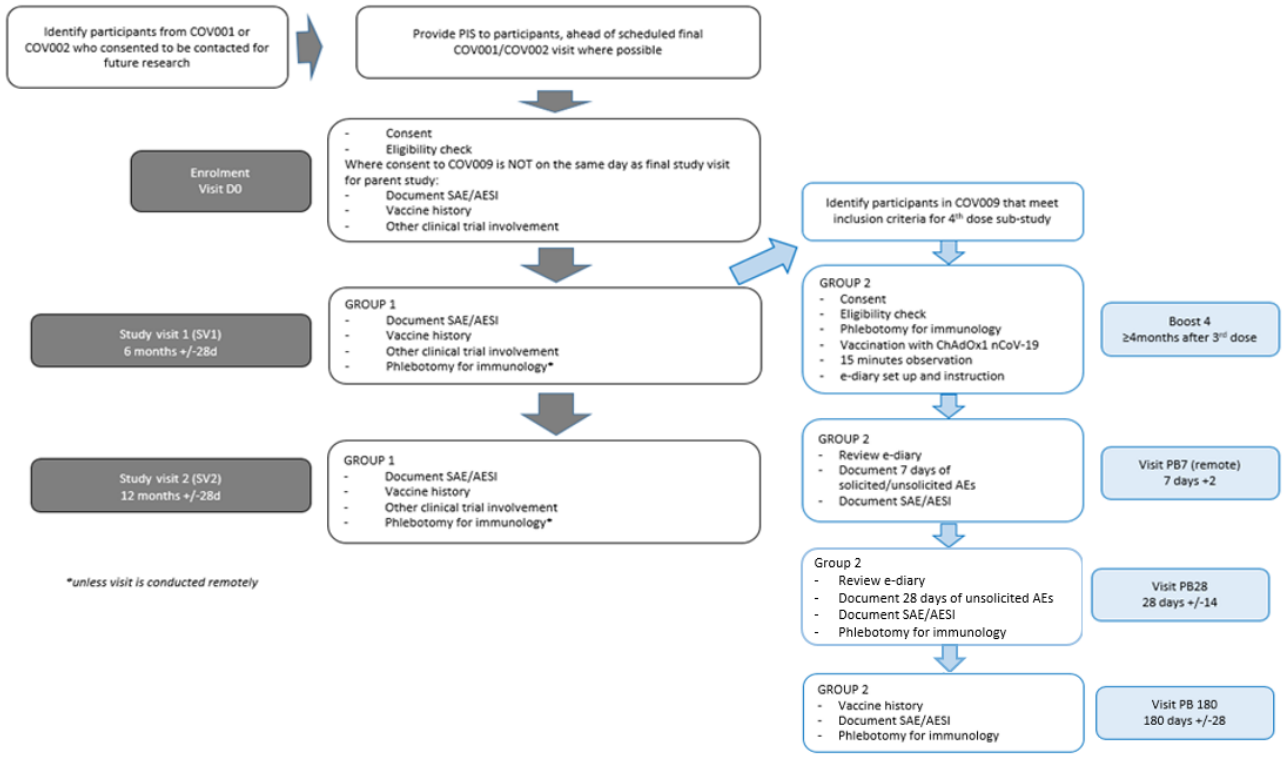
5 Objectives and Outcome Measures

5.1 Study Design

COV009 is a prospective safety study designed to extend the follow-up period for participants of the COV001 and COV002 trials for an additional 12 months. We aim to capture serious adverse events (SAEs), adverse events of special interest (AESIs), COVID-19 diagnoses and exposure to other vaccines. A subset of participants who received 2 doses of ChAdOx1 nCoV-19 within the COV002 parent trial and received an external 3rd dose of BNT162b2 vaccine will be offered ChAdOx1 nCoV-19 as a 4th dose booster. Solicited and unsolicited Adverse Events (AEs) will be collected for this subset of participants for 7 and 28 days respectively.

In addition, phlebotomy will be performed to enable the evaluation of immunological persistence. Where participants are known to experience new COVID-19 disease, attempts will be made to obtain the viral sequencing from the NHS.

Figure 4. Activities flow chart for the COV009 study



Group 1
Study visits will be conducted as follows:

	Consent & enrolment	**Study Visit 1 (SV1)**	**Study Visit 2 (SV2)**
Timepoint (window) →	At final study visit of parent trial (or at extra visit)[a]	6 months post enrolment (+/-28d)	12 months post enrolment (+/-28d)
Informed Consent[b]	X	(X)[c]	(X)[c]
Immunology bloods[g]		X	X
SAE/AESI	(X)	X	X
Externally administered vaccines[d]	(X)	X	X
End of study Form[e]			X
Telephone contingency[f]		(X)	(X)

X = activity to occur at visit
(X) = activity optional at visit (subject to other specified conditions)

a. Where last study visit has already taken place in parent trial participants will be asked to attend an extra visit dedicated to consent and enrolment for COV009
b. Informed written consent is sought to access all clinical and non-clinical data held about the participant by parent study.
c. Re-consent at subsequent visits may be necessary subject to protocol amendments
d. Check if any vaccines have been administered after parent study ended / since enrolment onto COV009, with details of vaccine and administration date.
e. To be completed at SV2 making note of any outstanding SAEs that requires further follow up. If this is the case, the end of study form to be finalised once no further outstanding SAEs under follow up.
f. In the event a participant has relocated or in extenuating circumstances where they cannot attend a face-to-face clinic visit, telephone assessments can be carried out instead and blood testing omitted.
g. Except those originally in COV002 Group 12.

Group 2

Study Visits will be conducted as follows:

	Boost 4	**PB7PB7 (Phone or email)[d]**	**PB28**	**PB180**
Timepoint (window) →	≥ 4 months since 3rd dose BNT162b2	7 days +2 post vaccine	28 days +/- 14 days post vaccine	180 days +/- 28 days post vaccine
Informed Consent[a]	X	(X)	(X)	(X)
Review eligibility	X			
Immunology bloods	X		X	X
Pregnancy test	X			
Diary	X	X		
AE (solicited and unsolicited)	X	X	X	
SAE/AESI	X	X	X	X
Externally administered vaccines	X	X	X	X
End of study Form[b]				X
Telephone contingency[c]			(X)	(X)

X = activity to occur at visit
(X) = activity optional at visit (subject to other specified conditions)

a. Re-consent at subsequent visits may be necessary subject to protocol amendments
b. To be completed at PB180 making note of any outstanding SAEs that requires further follow up. If this is the case, the end of study form to be finalised once no further outstanding SAEs under follow up.
c. In the event a participant has relocated or in extenuating circumstances where they cannot attend a face-to-face clinic visit, telephone assessments can be carried out instead and blood testing omitted.
d. Post boost day 7 (PB7), the visit could be conducted by telephone or the safety questions sent by email

6 Participant Identification

6.1 Study Participants

All participants enrolled in the COV001 and COV002 trials are eligible for this study. Participants enrolled into COV009 will have the same participant ID numbers as their parent trial to allow data to be linked.

6.2 Inclusion criteria

- Enrolled in COV001 or COV002 trials
- Able and willing to provide written informed consent to participate in the study.
- Able and willing (in the investigator's opinion) to comply with all study requirements.
- Consent to their general practitioner or responsible physician being notified of their participation in the study.

- Consent to allow investigators to discuss their medical information with their general practitioner or responsible physician and access any medical records where relevant to the study.
- Consent to access NHS SARS-CoV-2 NAAT results including viral sequencing results from NHS Digital and local labs, as well as COVID-19 vaccination records if available.

6.3.1. Additional inclusion criteria for Group 2

- Previous participant in COV002 study
- Randomised and received 2 doses of ChAdOx1 nCoV-19 in the parent COV002 study
- Provided blood sample for serology at 28day post second vaccine in COV002
- Received external non-study vaccination with BNT162b2 ≥ 4 months before vaccination with 4th dose
- Willing and able to receive an additional 4th dose vaccination with ChAdOx1 nCoV-19

6.3 Exclusion criteria

- Participants who have enrolled on a COVID-19 vaccine clinical trial of investigational medicinal product (CTIMP), other than COV001 and COV002, will be excluded. Examples include but are not limited to COV-Variant or COV-Boost, where ongoing safety follow up would be duplicated by enrolling in this study.
- Participants must be enrolled within 26 weeks of when the last study visit of their parent study was due.

6.3.1 Additional exclusion criteria for Group 2

- Female participant who is pregnant at time of vaccination
- Allergy or other contraindication to vaccination with ChAdOx1 nCoV-19
- History of Guillain-Barré syndrome
- Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia; recurrent severe infections and use of immunosuppressant medication within the last 6 months, except topical steroids or short-term oral steroids (course lasting <14 days)
- History of clinically significant thrombocytopenia and/or thrombosis or clinically significant bleeding (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venepuncture
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/ moderate well-controlled comorbidities are allowed
- Plans to move outside the study area
- Receipt of additional COVID-19 vaccines other than those listed in the inclusion criteria
- Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after the study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)

6.3.2 Temporary exclusion criteria for Group 2

If at vaccination visit 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)

Positive test for COVID-19 within the past 28 days. They may be considered for enrolment later in the trial; if they recover in sufficient time

7 Study Procedures

7.1 Recruitment

We aim to enrol participants in parallel with the final visit of their parent trial. Provided they have consented to be contacted for future research, participants who remain actively enrolled in COV001 or COV002 trials will be contacted prior to the final visit of their parent study to inform them about COV009.
Where participants have already completed the parent study last visit and consented to be approached for future research, these participants will be invited to participate in COV009 and will need to attend a dedicated consent and enrolment visit.

Participants will be able to contact their local research site for more information.

7.2 Informed consent and enrolment

The participant will have sufficient opportunity to read and understand the contents of the PIS prior to being invited to give informed written consent, with further opportunities to ask questions and seek clarification at the consent and enrolment visit.

As part of the informed consent process, permission will be sought for the local research site to have continued access to each participant's data from their parent study, including but not limited to demographic descriptors, contact details, clinical, non-clinical and immunological data previously collected.

Participants will be consented to allow the central study team to access their NHS SARS-CoV-2 NAAT results including viral sequencing where it is available, from NHS digital and local sequencing labs, using the participants NHS number or other personal identifiers in the event of a diagnosis of COVID-19 during the study period. Consent will also be sought to access all participant's COVID-19 vaccination records through NHS digital or by accessing medical records.

Each participant must give informed written consent for the current study and will be asked to sign and date the latest approved version of the informed consent form before any study-specific procedures are performed. Written and verbal versions of the participant information sheet and informed consent form will be presented to the participant, detailing no less than:

- the exact nature of and the rationale for performing the study
- implications and constraints of the protocol
- the risks and benefits involved in taking part

It will be clearly stated that there will be no provisions to supply participants with their individual blood results at any time, the participant is free to withdraw from the study at any time for any reason, and that they are under no obligation to give the reason for withdrawal. Written informed consent will be obtained by means of a dated signature of the participant and a signature of the study staff member who presented informed consent. A copy of the signed informed consent will be given to the participant and the original signed form will be retained at the study site.

7.3 Enrolment visit

Informed Consent will be collected and eligibility criteria checked.
The following data will be collected for any participant that has completed the final study visit for the parent trial on a different day to enrolment in COV009. Any new:

- COVID-19 diagnoses,
- Serious adverse events (SAEs)
- Adverse events of special interest (AESI),
- Administration of any vaccines,
- Participation in other clinical trials

7.4 Subsequent Visits

Participants in Group 1 will be assessed at two study visits after consent and enrolment:

- at 6 months (Study visit 1 – SV1)

- and 12 months (Study visit 2 – SV2)

  (See schedule of procedures table for acceptable time windows) following enrolment.

Participants identified as having had previous COVID-19 infection will be allocated to the exploratory immunology subgroup based on site ability to process blood samples for PBMCs. Pregnant participants will not be allocated into the 'exploratory immunology' subgroup due to the higher blood draw volumes.

Participants eligible for Group 2 will invited to receive an additional 4th dose booster of ChAdOx1 nCoV-19 delivered at the trial site (Boost 4). They will have the following visits after vaccination:

- 7 days post vaccine -PB7 (can be conducted via phone or email)
- 28 days post vaccine -PB28
- 180 days post vaccine PB180

(See schedule of procedures table for acceptable time windows).

Each study visit, except for PB7, will consist of a blood draw for immunology (see blood tables in section 7.6.1). At each visit, participants will be asked questions to capture details of any of the following new events since enrolment:

- COVID-19 diagnoses,

- Serious adverse events (SAEs) – the participant may also be asked about any new medical diagnoses or medically attended adverse event to ensure any SAEs are not missed.
- Adverse events of special interest (AESI),
- Administration of any vaccines (any vaccine including but not limited to COVID vaccines are permissible but must be recorded in the eCRF),
- Participation in other clinical trials

In addition, participants in Group 2 will be required to keep an electronic diary of adverse events for 7 days post vaccination. The study team will monitor recordings in the electronic diaries daily and remind participants to complete their entries if needed. In the event that a participant is unable to attend an in-person clinic visit, telephone safety assessments may be conducted instead.

Direct data entry into the Electronic Data Capture (EDC) system REDCap, will be the preferred method for data collection at each study visit, Paper CRFs can be used as a backup in the event of a systems issue and retrospectively entered into the eCRF.

7.5 Data collection outside of study visits

If a participant contacts the study team outside of study visits and reports a new medical event such as those listed in section 8.1, a member of the study team will discuss the details with the participant and record this information in the relevant CRF.

7.6 Sample Collection, Handling and Storage

For most participants (except those in COV002 Group 12) up to10mls blood will be taken at each of the two visits, totalling 20mls for the study. For those participants allocated to the 'exploratory immunology' subgroup, a larger volume of blood, up to 50mls at each visit will be taken. Participants in group 2 will have up to 50ml of blood taken at each in person visit.
Sample collection will be recorded in the CRF and the laboratory requisition form.
Sample collection, handling, storage and laboratory analysis will be described in the laboratory analysis plan and relevant SOP's.
All study-related samples will be stored under the ethical approval for this study until study completion.

Participants who consent to samples being stored in a biorepository, will have their samples transferred to the OVC biobank, for future research. If a study participant does not consent to storage in a biorepository, all remaining samples will be destroyed after completion of the study, according to the procedures outlined in the local SOPs.

Samples may be processed at collaborating laboratories in the UK and overseas.

7.6.1 Blood Tables

Table 2. Sample collection (all Group 1 participants except Exploratory Immunology subgroup and COV002 Group 12)

	Study Visit 1 6 months post enrolment (+/-28d)	Study Visit 2 12 months post enrolment (+/-28d)
SARS CoV-2 serology	Up to 10mls	Up to 10mls
Blood volume per visit	Up to 10mls	Up to 10mls
Cumulative blood volume	10mls	20mls

Table 3. Sample collection Group 1 Exploratory Immunology subgroup

	SV1 6 months post enrolment (+/-28d)		SV2 12 months post enrolment (+/-28d)	
	18-55 years	>56years	18-55 years	>56years
Exploratory Immunology	Up to 50 ml			
Blood volume per visit	Up to 50 ml			
Cumulative blood volume	100 ml			

Blood volumes for Group 2

	Boost 4	PB28	PB180
Serology/exploratory immunology	Up to 50ml	Up to 50ml	Up to 50ml
Cumulative blood volume	150 ml*		

*If moving to Group 2 from Group 1 after SV1 cumulative blood volume may be up to 200ml
NB a subset of participants in Group 2 will have exploratory immunology performed in addition to serological testing

7.7 Risks of participation

The main potential risks are those associated with phlebotomy and vaccination

Venepuncture
Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. The total volume of blood drawn over a 6 month period is unlikely to cause any health concerns.

Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of the IMP. Anaphylaxis is extremely rare but can occur in response to any vaccine or medication.

Vaccination
Vaccine side effects as listed in the Summary of Product Characteristics (SmPC). Such side effects will be explained to the participant prior to vaccination.

7.8 Discontinuation/Withdrawal of Participants

Each participant may exercise his or her right to withdraw from the study at any time. In addition, the investigator may terminate a participant's involvement in the study, at any time, if the investigator considers it necessary for any reason including, though not exclusive to, the following:

- ineligibility (either arising during the study or in the form of new information not declared or detected during the eligibility assessment)
- significant protocol deviation
- significant non-compliance with study requirements
- any adverse event which requires discontinuation of the study procedures or results in an inability to continue to comply with study procedures
- consent withdrawn
- lost to follow up
- subsequent enrolment in another trial which may duplicate COV009 study procedures including safety monitoring e.g., trials that involve further doses of COVID-19 vaccines

The reason for withdrawal will be recorded in a CRF. The withdrawn participant will not be replaced. Withdrawal from the study will not result in exclusion of the data generated by that participant from analysis, unless the participant requests this.

7.9 Definition of End of Study

The end of the study will be defined as the time the last blood sample is analysed (for secondary endpoint).

8 Investigational Medicinal Product

8.1 4th dose booster study

Recombinant Covid-19 vaccine (AstraZeneca) containing chimpanzee adenovirus codifying Spike SARS-CoV-2 glycoprotein will be used for the 4th dose booster sub-study at the standard dose of $5x10^{10}$vp in 0.5ml. The vaccine should be administered intramuscularly. The AstraZeneca vaccine is supplied in packs of 10 vials, using national supply. Each vial contains 8 to 10 doses of vaccine, and is a colourless to slightly yellow, clear to slightly opaque liquid. The IMP will not be labelled for clinical trial use.

The AstraZeneca vaccine should be stored at +2°C to +8°C 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 30°C) or within 48 hours when stored

in a refrigerator (2 to 8°C). After this time, the vial must be discarded. The total cumulative storage time once opened must not exceed 48 hours.

8.2 Compliance with the investigational treatment

All vaccines will be administered by the research team (doctors or nurses) and recorded in the CRF. The study medication will not be in the participant's possession at any time and, therefore, compliance will not be a problem.

8.3 Investigational treatment accounting

IMP accounting will be performed in accordance with the relevant local SOPs.

8.4 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.

9 Safety Reporting

For Group 1 Safety reporting for participants in this study begins at the point of consent and ends at 12 months post enrolment. All safety reporting relates to the prior administration of ChAdOx1 nCoV-19 during the parent trial. Safety data will be recorded at study visit 1 and study visit 2 during which participants will be asked for details of any SAEs and AESIs. Safety data will also be collected at the consent and enrolment visit to capture any SAEs and AESIs that occurred between completion of parent trial and commencing this study and assessed as set out in section 9.1.1 and 9.1.2.

For Group 2, Safety reporting begins at the point of consent and ends at 6 months after administration of the 4th dose booster vaccination.

Solicited adverse events

Solicited AEs are those listed as foreseeable adverse reactions to ChAdOx1 nCoV-19 as listed in the Summary of Product Characteristics (SmPC).

Solicited adverse events will be recorded by the participant in an electronic diary and graded for severity (as per Table 7 below) by the participant alone from the time of each vaccine administration for 7 days post-vaccination (day of vaccination and seven subsequent days). Unsolicited AEs will be recorded at day 28 post vaccination. AE severity will be determined as per Section 9.1.3 below .
Causality will be assigned by PI-delegated clinicians. Any solicited AE which meets the definition of a SAE will be managed and reported as per Section 9.2.1.2

SAEs and AESIs will be recorded for the duration of participation in the study.
All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of a subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline if a baseline value/status is available
- The event can be attributed to agents other than to ChAdOx1 nCoV-19 or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

9.1 Adverse Event Definitions

Table 4. Adverse Events

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.
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. NOTE: Pregnancy is not, in itself an SAE, but an adverse outcome of pregnancy, for example spontaneous miscarriage, may be judged to be an SAE if clinically appropriate.
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.

Adverse Events of Special Interest (AESI)
For the purposes of this study AESIs are based on the Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. The list of AESIs are as below:

Table 5 Adverse Events of Special Interest

AESI	Medical Concept
Neuroinflammatory disorders	Cranial nerve neuropathy including palsy and paresis (eg, Bell's palsy) Optic neuritis Multiple sclerosis Transverse myelitis Guillain-Barré syndrome, including Miller Fisher syndrome and other variants Acute disseminated encephalomyelitis, including site-specific variants, eg: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis Myasthenia gravis, including Lambert-Eaton myasthenic syndrome Peripheral demyelinating neuropathies, including: • Chronic inflammatory demyelinating polyneuropathy • Multifocal motor neuropathy Polyneuropathies associated with monoclonal gammopathy

	Narcolepsy Generalised convulsions
Musculoskeletal disorders	Systemic lupus erythematosus and associated conditions Systemic scleroderma (systemic sclerosis) including: • Diffuse scleroderma • Calcinosis, Raynaud's phenomenon, Oesophageal dysmotility, Sclerodactyly and telangiectasia syndrome (CREST) Idiopathic inflammatory myopathies including: • Dermatomyositis • Polymyositis • Anti-synthetase syndrome Rheumatoid arthritis and associated conditions including: • Still's disease Polymyalgia rheumatica Spondyloarthropathies including: • Ankylosing spondylitis • Reactive arthritis (Reiter's syndrome) • Undifferentiated spondyloarthritis
Skin disorders	Psoriasis Vitiligo Erythema Nodosum Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis) Lichen planus Sweet's syndrome Localized scleroderma (morphea)
Vasculitis	Large vessel vasculitis including: • Giant cell arteritis (temporal arteritis) • Takayasu's arteritis Vasculitis of medium and/or small vessels including: • Polyarteritis nodosa • Kawasaki disease • Microscopic polyangiitis • Wegener's granulomatosis (granulomatosis with polyangiitis)

	• Churg-Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis) • Buerger's disease (thromboangiitis obliterans) • Necrotizing vasculitis (cutaneous or systemic) • Vasculitis positive for anti-neutrophil cytoplasmic antibody (type unspecified) • Henoch-Schonlein purpura (immunoglobulin A vasculitis) • Behcet's syndrome • Leukocytoclastic vasculitis
Blood disorders	Autoimmune haemolytic anaemia Autoimmune thrombocytopenia Antiphospholipid syndrome Pernicious anaemia Autoimmune aplastic anaemia Autoimmune neutropenia Autoimmune pancytopenia Anti-platelet antibodies Vascular thrombosis Stroke
Liver disorders	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis
Gastrointestinal disorders	Inflammatory bowel disease including: • Crohn's disease • Ulcerative colitis • Microscopic colitis • Ulcerative proctitis • Celiac disease • Autoimmune pancreatitis
Endocrine disorders	Autoimmune thyroiditis (Hashimoto's thyroiditis) Grave's or Basedow's Disease Type 1 diabetes mellitus Addison's Disease Polyglandular autoimmune syndrome Autoimmune hypophysis.
Others	Autoimmune glomerulonephritis including: • Immunoglobulin A nephropathy • Rapidly progressive glomerulonephritis • Membranous glomerulonephritis • Membranoproliferative glomerulonephritis • Mesangioproliferative glomerulonephritis

	• Tubulointerstitial nephritis and uveitis syndrome Autoimmune eye diseases including: • Autoimmune uveitis • Autoimmune retinitis

9.1.1 Assessment of causality

Adverse Event with a Causal Relationship to ChAdOx1 nCoV-19
Causality in Group 1will be assessed relative to ChAdOx1 nCoV-19 administered during the parent trial, and in Group 2 relative to ChAdOx1 nCoV-19 administered as a 4th dose booster study vaccine. Causality will be assessed by a CI delegated clinician. An adverse event is considered to have a causal relationship to ChAdOx1 nCoV-19 if the attribution is possible, probable, or definite by the definitions listed below. An adverse event is considered to have no causal relationship to ChAdOx1 nCoV-19 if the attribution is 'No relationship' or unlikely by the definitions listed below.

Table 6. Guidelines for assessing the relationship of vaccine administration to an AE

Causality term	Assessment criteria
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

9.1.2 Reporting procedures for non-serious adverse events

For Group 2, all local and systemic AE's after vaccination can be reported either

- In the study CRF if observed by the study team immediately post vaccination or as reported by the participant directly to the study team
- In the ediary by the participant (solicited only)

Any safety event that results in the withdrawal of a participant from the study will be followed up until a satisfactory resolution occurs (if the participant agrees to do so), or until a causality unrelated to the study is assigned.

9.1.3 Severity Criteria

The severity of 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 tables below.

Table 7 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
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**		

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 8. Severity grading criteria for physical observations

Table 9. 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

9.2 Safety Reporting Procedures

For Group 1, SAEs and AESIs will be reported. Non-serious AEs will not be reported unless they meet the criteria for AESI (i.e., on the list of conditions defined in the AESI table 5). Assignments of causality will only be made in relation to the administration of ChAdOx1 nCoV-19 during the parent study.

For Group 2 participants who receive a further dose of ChAdOx1 nCoV-19 as a 4th dose booster, solicited and unsolicited AEs will be collected up to 28 days post vaccination. Additionally, AESIs and SAEs will be reported. Assignments of causality will be made in relation to the 4th dose booster vaccination.

Any SAEs which occur following externally administered vaccines e.g., those given as part of national rollout programmes, will be judged to be unrelated to the study vaccine and should additionally be reported through national pharmacovigilance mechanisms as applicable.

The following information will be reported on the AE CRF: diagnosis, date of onset and end date, severity, assessment of relatedness to ChAdOx1 nCoV-19 or to a COVID 19 diagnosis and any medications taken to treat event. Follow-up information should be provided, as necessary and the above information updated as required.

9.2.1 Serious Adverse Events (SAE) reporting procedures

All SAEs, including those occurring between completion of parent trial and commencing this study, must be reported on the SAE Reporting Form to the Sponsor or delegate immediately or within 24 hours of the Site Study Team becoming aware of the event being defined as serious.

9.2.1.1 Events exempt from reporting as SAEs

Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing (existing prior to administration of ChAdOx1 nCoV-19 in the parent trial) condition that has not worsened unexpectedly does not constitute an SAE. Emergency department attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

9.2.1.2 Procedure for reporting of Serious Adverse Events

The procedure for reporting of Serious Adverse Events is as follows:

- Site study team will complete an SAE report form for all reportable SAEs.
- SAE report form will be submitted to the sponsor delegate (CI team) via the appropriate REDCap form immediately i.e., within 24 hours of site study team becoming aware of the event. A backup paper form can be used in the event of a systems issue and information will be retrospectively entered into REDCAp by site or Sponsor team.
- Site study team will provide additional, missing or follow up information in a timely fashion.

An acknowledgement of receipt will be sent via email to the reporting site, and review of reported SAEs at the sponsor delegate's office will be carried out by a nominated clinician. Review of SAEs will be timely, taking into account the reporting timeline for a potential SUSAR.

9.2.2 Expectedness

SAE that are considered related to the study vaccine will be classified as SARs. Expectedness of SARs will be determined according to the Sponsor and MHRA approved Reference Safety Information section of the Summary of Product Characteristics at the time of the event

occurrence. Assessment of expectedness will be completed by the reporting investigator and reviewed centrally by the sponsor delegate.

9.2.3 SUSAR reporting procedure

SUSARs will be communicated by the sponsor's delegate to the Competent Authority, (MHRA) REC and other parties, as applicable. For fatal and life-threatening SUSARs, this will be done within 7 calendar days after the Sponsor or delegate becomes aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be informed within 15 calendar days. The principal investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, even if the event occurred or not in the present study.

9.2.4 Adverse Events of Special Interest

Adverse events of special interest as defined in table 5 will be recorded.

9.2.5 Development Safety Update Reports

Global DSUR will be compiled by AstraZeneca, the CI or delegate will submit (in addition to the expedited reporting above)a DSURonce a year throughout the clinical trial, or on request, to the Competent Authority (MHRA), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

9.2.6 Reporting to AstraZeneca

SAEs will be reported to the global AstraZeneca team as per the Pharmacovigilance Agreement (PVA). All SUSARs and all non-related deaths or life-threatening SAEs will be reported within 3 calendar days from receipt, other non-related SAEs will be reported within 21 calendar days from receipt, unless agreed otherwise.

9.3 Data Safety Monitoring Board

The safety profile will be continuously assessed by the Investigators. The CI and relevant investigators (according to the study delegation record) will also review safety and SAE issues as they arise. The DSMB will assess the frequency of events and safety data when requested to do so by the CI (or delegate). The DSMB will make recommendations regarding the conduct, continuation, or modification of the study.

DSMB that is in force for the parent studies will also oversee this study and review the safety data for this study. The DSMB chair can be contacted for independent advice and review by the CI or Study Sponsor in the following situations:

- Follow-up on any SAE considered possibly, probably or definitely related to a study treatment to which they will be notified within 24 hours after the Sponsor become aware of the occurrence.
- Any other situation in which the CI or Study Sponsor feels that independent advice or review is important.

10 Statistics

The main analyses will be descriptive in nature and presented by original randomised group as well as time since most recent study vaccination as determined in the parent trial. Counts and percentages for safety outcomes will be presented, with medians and inter-quartile ranges for immunological outcomes.

10.1 Sample Size Determination

The participants for this study will be recruited from the UK phase I/II (COV001) and phase II/III (COV002) trials. This amounts to approximately up to 12,000 potentially eligible participants but sample size will depend on the number of eligible individuals who consent to participation. As such, there will be no provision for replacement of participants.

Baseline characteristics and initial study outcomes of enrolled participants will be compared to those who did not enrol in the follow up study to determine the extent of bias present in the self-selected cohort enrolled.

10.1.1 Fourth dose boost substudy

Up to 150 participants will be enrolled in the 4th dose boost study. A subset of sites with larger numbers of participants enrolled who meet eligibility criteria will be selected and participants invited until the total of 150 has been met or no further participants are available.

Data are available from Flaxman et al to inform sample size calculations as follows (https://www.sciencedirect.com/science/article/pii/S0140673621016998)

Table 8 Data available for sample size calculation from flaxman et al

Assay	**Visit**	**N**	**Mean (log10)**	**SD (log10)**	**Pearson correlation coefficient**
Anti-spike IgG (ELISA)	Dose 2 + 28 days	71	3.28169	0.51413	0.33506
	Dose 3 + 28 days	71	3.55010	0.38949	
	Difference	**71**	**0.26841**	**0.53089**	

Assuming the standard deviation for the difference between dose 2 and dose 4 is similar to the standard deviation for the difference between dose 2 and dose 3 as seen in Flaxman et al, then 150 participants will provide 98% power to show non-inferiority of the 4th dose compared with the 2nd dose, assuming a non-inferiority margin for the lower bound of the GMFR of 2/3 (-0.176 on $\log_{10}$ scale), and alpha of 0.025.

Table 9 Power available for different levels of recruitment to the 4th dose sub-study

Power	**N**	**SD**	**Alpha**
81%	75	0.531	0.025
91%	100		
98%	150		

The immune response 28 days after the 4th dose boost, will be compared to the immune response 28 days after the 2nd dose using non-inferiority comparisons. The within-person difference between $\log_{10}$-transformed responses (dose $4^{+28\ days}$ minus dose $2^{+28\ days}$) will be computed and non-inferiority will be concluded if the lower bound of the confidence interval for mean of the differences is not less than -0.176 (equivalent to a GMR of 2/3).

10.2 Procedure for Accounting for Missing, Unused, and Spurious Data

Reasons for missing data (including withdrawal of consent or inability to obtain any laboratory results) will be indicated, but missing data will not be imputed. Laboratory values below the lower limit of an assay will be replaced with values half the lower limit.

10.3 Inclusion in analysis

Laboratory data from all participants who enrol in the study will be included in the analysis.

11 Data Management

The plan for the data management of the study is summarised below, with the details fully described in the data management plan.

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

11.1 Source data

All protocol-required information will be collected and directly entered into REDCap, CRFs designed by the sponsor delegate. CRF entries will be considered source data where the CRF is the site of the original recording (i.e., there is no other written or electronic record of data). Any additional 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, GP response letters, laboratory records, medical records, and correspondence. As part of the informed consent process, permission will be sought to access the participant's data from pertaining to basic demographic information, contact details, and all clinical and non-clinical data previously collected by their parent trial.

All source data and participant files will be stored securely.

11.2 Access to Data

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

11.3 Data Recording and Data Keeping

Each study participant will retain the unique participant number, as assigned in their previous parent trial. Samples sent to laboratories for processing will be identified by participant number. All clinical study data will be recorded as set out in Section 10.1. All documents will

be stored safely and securely in confidential conditions. Direct access will be granted to authorised representatives from the Sponsor and host institution(s) and the regulatory authorities to permit study-related monitoring, audits and inspections. Participant name and any other identifying detail will NOT be included in any trial data electronic file.

The EDC system, REDCap, is a widely used, powerful, reliable, well-supported system. It us 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. Access to the study's database will be restricted to the members of the study team by username and password.

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. Participants shall be approached should there be any unexpected safety signals emerging post-licensing surveillance. 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, 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. Anonymised 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.

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.

12 Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Approved and relevant Standard Operating

Procedures (SOPs) and Laboratory and Clinical Study Plans will be used at all clinical and laboratory sites.

12.1 Risk Assessment

The study 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 study to reflect significant changes to the protocol or outcomes of monitoring activities. The risk assessment and monitoring plan will be updated following the addition of group 2,

12.2 Study Monitoring

This study involves a maximum of 12,000 participants. The study will be monitored by an OVG Monitor. Monitoring will be performed according to Good Clinical Practice (GCP). The monitor will verify that the clinical study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Monitoring of sites will be performed by a combination of site visits and remote monitoring via self-monitoring questionnaires. A triggered site visit will be performed if serious noncompliance with the protocol is observed.

The Quality Assurance manager operates an internal audit program to ensure that the systems used to conduct clinical research are present, functional, and enable research to be conducted in accordance with study protocols and regulatory requirements. Audits include laboratory activities covering sample receipt, processing and storage and assay validation. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor. The Sponsor may carry out audits to ensure compliance with the protocol, GCP and appropriate regulations. GCP inspections may also be undertaken by the MHRA to ensure compliance with the protocol and the Medicines for Human Use Regulations 2004 and amendments.

12.3 Study Committees

The DSMB that is in force for the parent studies will also oversee this study and review the safety data.

13 Protocol Deviations

Any deviations will be documented in a protocol deviation form and filed in the TMF. Each deviation will be assessed as to its impact on participant safety and study conduct. Significant protocol deviations will be listed in the end of study report.

14 Serious Breaches

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.

15 Ethical and Regulatory Considerations

15.1 Declaration of Helsinki

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

15.2 Guidelines for Good Clinical Practice

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

15.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) MHRA and host institution(s), for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4 Other Ethical Considerations

There is no other ethical consideration in relation to this study protocol.

15.5 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.

15.6 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.

15.7 Participant Confidentiality

The study will comply with the United Kingdom General Data Protection Regulation (UK-GDPR) and Data Protection Act 2018 in the UK which require data to be anonymised as soon as it is practical to do so. The processing of the 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). 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.

15.8 Expenses & Benefits

Participants will receive £10 per in-person visit to cover travel expenses in this study and £20 per vaccination visit.

16 Finance and Insurance

16.1 Funding

The funding of the study is provided by AstraZeneca.

16.2 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).

16.3 Contract arrangements

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

17 Publication Policy

The Chief Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator and by the Sponsor prior to submission.

18 Development of a new product/process or the generation of intellectual property

Not applicable

19 References

1. Center for Systems Science and Engineering at Johns Hopkins. Coronavirus COVID-19 (2019-nCoV) [Internet]. COVID-19 Dashboard. 2021 [cited 2021 Apr 29]. Available from: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
2. Public Health England. PHE monitoring of the effectiveness of COVID-19 vaccination - GOV.UK [Internet]. 2021 [cited 2021 Apr 28]. Available from: https://www.gov.uk/government/publications/phe-monitoring-of-the-effectiveness-of-covid-19-vaccination
3. Public Health England. Public Health England vaccine effectiveness report March 2021 [Internet]. 2021. Available from: https://www.gov.uk/government/publications/phe-monitoring-of-the-effectiveness-of-covid-19-vaccination
4. Public Health England. Impact of COVID-19 vaccines on mortality in England December 2020 to March 2021. 2021;(April):1–8. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/977249/PHE_COVID-19_vaccine_impact_on_mortality_March.pdf
5. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467–78.
6. Barrett JR, Belij-Rammerstorfer S, Dold C, Ewer KJ, Folegatti PM, Gilbride C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. 2021;27(2):279–88.
7. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020;396(10267):1979–93.
8. Brighton Collaboration. Safety Platform for Emergency vACcines: Priority List of COVID-19 Adverse events of special interest. 2021.

20 Appendices

20.1 Appendix A: Parent trials of the ChAdOx1 nCoV-19 vaccines

ChAdOx1 nCoV-19 (AZD1222) has been shown to be safe, well tolerated, immunogenic and effective against COVID-19 disease. Preliminary data supporting emergency use has been published in peer reviewed scientific journals and the UK regulatory authority website. The publications with full details on safety, immunogenicity and efficacy data generated thus far can be found in the appendix.

20.1.1 COV001

COV001	
Synopsis Item	Description
Title	A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers.
Design	Phase I/II, multi-centre, single blinded, randomised controlled trial
Location	Multi-centre, UK
Start date	First visit of first volunteer 23/04/2020
Study status	Ongoing
Number of subjects	1,077 (of those 544 received ChAdOx1 nCoV-19)
Sex	Male, female
Age	Adults aged 18-55
Health status	Healthy
Dose group(s)	Groups 1, 2 and 4: 5×10^{10} vp (single dose) Group 3: 5×10^{10} vp (two doses, 4 weeks apart) Up to 62 volunteers in group 2 were invited to receive a booster dose (ChAdOx1 nCoV-19 high or low OR MenACWY) at 8 weeks interval.
Control injection	MenACWY
Administration route	All IM
Primary Endpoint	Virologically confirmed (PCR positive) symptomatic cases of COVID-19 Occurrence of serious adverse events
Publication	Folegatti et al. Lancet 2020 (32) Ewer et al. Nat Med 2020 (28) Barrett et al. Nat Med 2020 (29)

20.1.2 COV002

COV002	
Synopsis Item	Description
Title	A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19
Design	Phase II/III, multi-centre, single blinded, randomised controlled trial
Location	Multi-centre, UK
Start date	First visit of first volunteer 29/05/2020
Study status	Ongoing
Number of subjects	Up to 12330
Sex	Male, female
Age	Adults aged ≥18
Health status	Healthy or with controlled comorbidities Subset of 60 participants HIV positive
Dose group(s)	Group 1a (56-69 years old): 2.2×10^{10}vp (single dose) Group 1b: (56-69 years old):2.2×10^{10}vp (two-dose dose) Group 2a (≥70 years old): 2.2×10^{10}vp (single dose) Group 2b (≥70 years old): 2.2×10^{10}vp (two dose) Group 3 (5-12 years old): 2.5×10^{10}vp (single dose) Group 4a (18-55 years old): 2.2×10^{10}vp (single dose) Group 4b (18-55 years old): 2.2×10^{10}vp (two dose) Group 4c (18-55 years old): 2.2×10^{10}vp prime, 5×10^{10}vp boost Group 5a (18-55 years old): 2.2×10^{10}vp (single dose) Group 5b/c (18-55 years old): 5×10^{10}vp (single dose) Group 5d (18-55 years old): 5×10^{10}vp (two dose) Group 6a (18-55 years old): 5×10^{10}vp (single dose) Group 6b (18-55 years old): 5×10^{10}vp (two dose) Group 7a (56-69 years old): 5×10^{10}vp (single dose) Group 7b (56-69 years old): 5×10^{10}vp (two-dose dose) Group 8a (≥70 years old): 5×10^{10}vp (single dose) Group 8b (≥70 years old): 5×10^{10}vp (two dose) Group 9 (56-69 years old): 5×10^{10}vp (single dose) Group 10 (≥70 years old): 5×10^{10}vp (two dose) Group 11 (18-55 years old): 5×10^{10}vp (two dose) – previous ChAdOx1 vectored vaccines. Group 12 (18-55 years old): 5×10^{10}vp (two dose) – well controlled HIV positive individuals
Control injection	MenACWY
Administration route	All IM
Primary Endpoint	Virologically confirmed (PCR* positive) symptomatic cases of COVID-19 Occurrence of serious adverse events (SAEs)
Publication	Ramasamy et al. Lancet 2020 (30) Voysey et al. Lancet 2020 (31)

20.2 Appendix B: Participant groups in COV001 and COV002

20.2.1 COV001 groups

ChAdOx dosing			ChAdOx active arm			MenACWY control arm		
Prime	Boost	Boost 2						
			GROUP 1 (phase I safety with intensive early follow-up)					
5 x 10^{10} vp			gp 1a	prime	N = 44	gp 1b	prime	N = 44
5 x 10^{10} vp	3.5-6.5 x 10^{10} vp		gp 1c	prime (gp 1a) + boost LV	N = 44			
3.5-6.5 x 10^{10} vp	3.5-6.5 x 10^{10} vp		gp 1d	MenACWY (gp 1b) + prime LV + boost LV2	N = 44			
					N = 88			
			GROUP 3 (non-randomised prime-boost)					
5 x 10^{10} vp	5 x 10^{10} vp		gp 3	prime + boost wk 4	N = 10			
					N = 10			
			GROUP 2 (immunogenicity - humoral & cellular)					
5 x 10^{10} vp			gp 2a	prime	N = 206	gp 2b	prime	N = 206
5 x 10^{10} vp	5 x 10^{10} vp		gp 2c	prime (gp 2a) + boost wk 8	N = 20	gp 2e	prime (gp 2b) + boost wk 8	N = 10
5 x 10^{10} vp	2.5 x 10^{10} vp		gp 2d	prime (gp 2a) + boost wk 8	N = 32	gp 2g	prime (gp 2b) + LD boost	N = 196
5 x 10^{10} vp	3.5-6.5 x 10^{10} vp		gp 2f	prime (gp 2a) + boost	N = 154			
					N = 206			
			GROUP 4 (immunogenicity - humoral only)					
5 x 10^{10} vp			gp4a	prime	N = 290	gp 4b	prime wk 0	N = 290
5 x 10^{10} vp	3.5-6.5 x 10^{10} vp		gp 4c	prime (gp 4a) + boost	N = 290	gp 4d	booster	N = 290
					N = 580			
			GROUP 5 (3rd vaccine ChAdOx + ChAdOx vaccinated MenACWY controls)					
3.5-6.5 x 10^{10} vp			gp 5a	from groups 2c, 2f, 4c with <16wk interval	N = 80			
3.5-6.5 x 10^{10} vp	3.5-6.5 x 10^{10} vp		gp 5b	from groups 2e, 2g, 4d with <16wk interva	N = 40			
					N = 120			

20.2.2 COV002 groups

ChAdOx dosing		18-55yo				56-69yo			70+ yo			
Prime	Boost	active (ChAdOx)		control (MenACWY)		active (ChAdOx)		control (MenACWY)	active (ChAdOx)		control (MenACWY)	
						GROUP 1 (phase II safety & efficacy)						
5×10^{10} vp	N/A					gp 1A1	prime only	N = 30	gp 1A2	prime only	N = 10	
5×10^{10} vp	5×10^{10} vp					gp 1A3	prime-boost	N = 30	gp 1A4	prime-boost	N = 10	
		GROUP 4 (phase III efficacy)							GROUP 2 (phase II safety & efficacy)			
5×10^{10} vp	N/A	gp 4A1	prime only	N = 1,775	gp 4A2	prime only	N = 1,775		gp 2A1	prime only	N = 50	gp 2A2	prime only	N = 10
5×10^{10} vp	$3.5–6.5 \times 10^{10}$ vp	gp 4C1	prime-boost	N = 1,725	gp 4C2	prime-boost	N = 1,725		gp 2A3	prime-boost	N = 50	gp 2A4	prime-boost	N = 10
5×10^{10} vp	2.2×10^{10} vp	gp 4B1	prime-boost	N = 50	gp 4B2	prime-boost	N = 50		gp 2B1	prime-boost	N = 50	gp 2B2	prime-boost	N = 10
		GROUP 5 (phase II safety & efficacy)												
5×10^{10} vp	N/A	gp 5A1	prime only	N = 50	gp 5A2	prime only	N = 50							
5×10^{10} vp	$3.5–6.5 \times 10^{10}$ vp	gp 5A3	prime-boost	N = 50	gp 5A4	prime-boost	N = 50							
5×10^{10} vp	N/A	gp 5B1	prime only	N = 25	gp 5B2	prime only	N = 25							
5×10^{10} vp	N/A	gp 5C1	prime only	N = 25	gp 5C2	prime only	N = 25							
$3.5–6.5 \times 10^{10}$ vp	$3.5–6.5 \times 10^{10}$ vp	gp 5D1	prime-boost	N = 50	gp 5D2	prime-boost	N = 10							
0.9×10^{11} vp	0.9×10^{11} vp	gp 5E	prime-boost	N = 15										
0.9×10^{11} vp	0.9×10^{11} vp	gp 5F	prime-boost	N = 15										
		GROUP 6 (phase III efficacy)							GROUP 8					
5×10^{10} vp	N/A	gp 6A1	prime only	N = 3,000	gp 6A2	prime only	N = 3,000		gp 8A1	prime only	N = 50	gp 8A2	prime only	N = 10
5×10^{10} vp	$3.5–6.5 \times 10^{10}$ vp	gp 6B1	prime-boost	N = 3,000	gp 6B2	prime-boost	N = 3,000		gp 8B1	prime-boost	N = 50	gp 8B2	prime-boost	N = 10
						GROUP 7								
5×10^{10} vp						gp 7A1	prime only	N = 30	gp 7A2	prime only	N = 10			
5×10^{10} vp	5×10^{10} vp					gp 7B1	prime-boost	N = 30	gp 7B2	prime-boost	N = 10			
		GROUP 11				GROUP 9 (phase III efficacy)						GROUP 10 (phase III efficacy)		
$3.5–6.5 \times 10^{10}$ vp	$3.5–6.5 \times 10^{10}$ vp	gp 11A1	boost-boost	N = 60		gp 9A1	prime-boost	N = 500	gp 9A2	prime-boost	N = 500	gp 10A1	prime-boost	N = 500	gp 10A2	prime-boost	N = 500
		(adults 18-55yo previous ChAdOx)												
		GROUP 12												
$3.5–6.5 \times 10^{10}$ vp	$3.5–6.5 \times 10^{10}$ vp	gp 12A1	prime-boost	N = 60										
		(adults 18-55yo HIV +ve)												
		N = 5,075			N = 4,935			N = 560			N = 520			N = 650			N = 530

20.3 Appendix C: Links to regulatory publications

20.3.1 MHRA Public Assessment Report for ChAdOx1 nCoV-19

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963928/UKPAR_COVID_19_Vaccine_AstraZeneca_23.02.2021.pdf

20.3.2 MHRA Conditions of Authorisation for ChAdOx1 nCoV-19

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963841/AZ_Conditions_for_Authorisation_final_23.02.21.pdf

20.3.3 MHRA Information for Healthcare Professionals

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

20.4 Appendix D: Amendment History

Amendment No.	**Protocol Version No.**	**Date issued**	**Author(s) of changes**	**Details of Changes made**
Response to REC / SA1	2.0	18 Aug 2021	Jonathan Kwok, Hannah Robinson, Parvinder Aley Andrew Pollard	Correction of trial site details and contact details for monitor Addition of statistician signature Simplification of lay summary, protocol synopsis and background and rationale to focus on key points; Removal of duplicated text Clarification that pregnant participants will not be allocated to exploratory immunology subgroup due to higher blood draw Clarification on safety collection and reporting requirements with regards participants who have a unmonitored period between completion of parent trial and commencing COV009 Addition of reimbursement for travel expenses related to in person visits.
SA1	2.1	24 Aug 2021	Parvinder Aley	Correction of typographical errors

				Correction that primary evaluation timepoint may include ad hoc unsolicited contact by participants Moving details with regards not allocating pregnant women to exploratory immunology from section 7.6 to section 7.4
SA2	3.0	28 Oct 2021	Nasir Kanji/ Timothy Lubinda	Updated section 7.4 to include group 12 participants to the exploratory immunology subgroup Included group 12 (HIV +) in Table 3, section 7.6.1 Changed end of planned study period from August 2023 to August 2024
SA3	4.0	18 Jul 2022	Maheshi Ramasamy, Merryn Voysey, Hannah Robinson, Nasir Kanji	Addition of 4th dose subgroup, key changes made in sections; 5.0 – Study design and study procedures table6.0 – Addition of vaccine related inclusion/exclusion criteria 7.4 – Clarification of how participants are identified for exploratory immunology subgroup 7.7 - Addition of risk section 8.0 – Addition of IMP section 9.0 – Safety section updated to include solicited and unsolicited AE reporting, including ediary use 10.1.1 – statistics section updated to include 4th dose subgroup Participant reimbursement increased for vaccination visit (Group 2) 7.6.1 Exploratory Immunology table updated, Serum collection from Group 12 removed 15.7 GDPR wording changed from ‘de-identified’ to ‘anonymised’
NSA1	4.1	18 Jul 2024	Eleanor Wilson	Changed end of planned study period from August 2024 to December 2024

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.

20.5 Appendix E: Investigator Agreement and Notification of Conflict of Interest

Site:

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no / the following (delete as appropriate) conflict of interest

Principal Investigator

Signature

Date