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; Prof. Sir Andrew Pollard; Signature  Date 17 Nov 2021

Statistician Dr Merryn Voysey Signature  Date 17 Nov 2021

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.

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)
Treatment Duration	No treatment arm - therefore not applicable
Study Duration	**12months**
Planned Study Period	August 2021 - August 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	· Evaluation of **character and durability of the immune response** to vaccination	· **Measurement of immune responses** (for a subset of participants, in exploratory immunology group): - anti-SARS-CoV-2 spike protein immunoglobulins - neutralising antibodies against SARS-CoV-2	**- Visit 1 (6 months +/- 28 days)** **- Visit 2 (12 months +/-28 days)**
Exploratory	· To investigate the relationship between vaccination, immunological profile, and subsequent SARS-CoV-2 infection, COVID-related hospitalisation, morbidity or mortality · To assess any differences in immunological profile or immunological persistence by age, sex, ethnicity, and reactogenicity.	· **COVID19 diagnoses** · **Immunological profiling** (as above, plus in addition) - pseudo-neutralising antibodies - cellular immune response to SARS-CoV-2 spike protein by IFNg ELIspot, ICS or whole blood assay, ICS or whole blood assay - anti-vector immunity, to ChAdOx1 virus	- 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
PCR	Polymerase chain reaction process employed in NAAT testing
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
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

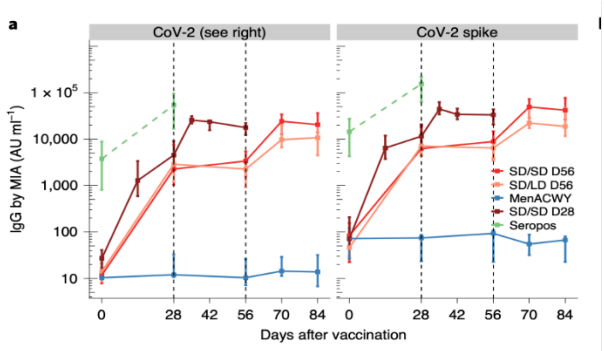
COV001 was conducted at five sites across the UK. The trial enrolled 1,077 healthy adults, 18-55 years of age, randomly allocating them 1:1 to either an active ChAdOx1 nCoV-19 arm (N=543), or a placebo MenACWY arm (N=534). MenACWY is a licensed, quadrivalent conjugate vaccine to prevent meningitis, chosen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

It has been hypothesised that some patients may also form responses against the ChAdOx1 virus of the Oxford/AstraZeneca vaccine which might then suppress immunity to similar vaccines given in the future.

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. evaluate the character and durability of immune responses that are stimulated by ChAdOx1 nCoV-19 vaccine

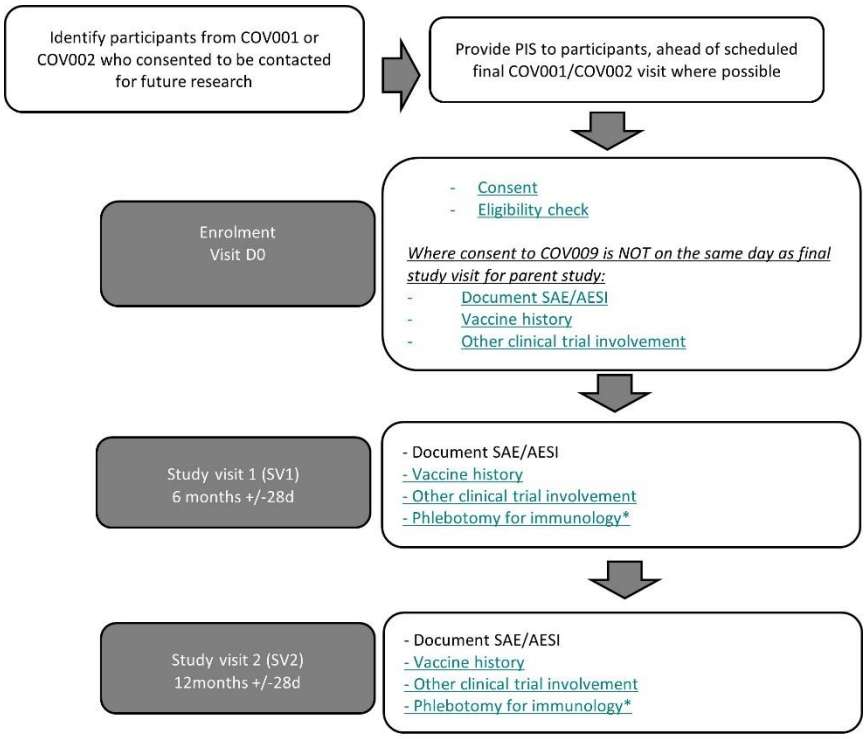
5 Objectives and Outcome Measures

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 severe adverse events (SAEs), adverse events of special interest (AESIs), COVID-19 diagnoses and exposure to other vaccines.

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



**unless visit is conducted remotely*

Study Visit 1 (SV1) at 6 months (+/-28 days) post enrolment and Study Visit 2 at 12 months (+/-28 days) post enrolment, 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		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.

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 trialto 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 Exclusion criteria

- Participants who have enrolled on a COVID-19 vaccine clinical trial of investigational medicinal product (CTIMP) 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.

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 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 from groups 5 and 6 (18-55 years), group 7 (56–69 years), group 8 (+70years), and group 12 (HIV positive participants) in the COV002 trial will be allocated sequentially at enrolment to the exploratory immunology subgroup (Oxford and Southampton sites only). Pregnant participants will not be allocated into the 'exploratory immunology' subgroup due to the higher blood draw volumes.
Each study visit will consist of a blood draw for immunology (see blood tables in section 7.6.1) and 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 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 back up 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 1 and 2 and reports a new medical event such as those listed in section 9.4, 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 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.

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 participants except Exploratory Immunology subgroup)

	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 Exploratory Immunology subgroup

	SV1 6 months post enrolment (+/-28d)					SV2 12 months post enrolment (+/-28d)				
	18-55 years		56-69 years	+70 years	HIV +	18-55 years		56-69 years	+70 years	HIV +
	4wk prime-boost interval (Oxford) (n=30)	12wk prime-boost interval (Oxford) (n=30)	(Oxford) (n=30)	(Southampton) (n=30)	n = 54	4wk prime-boost interval (Oxford) (n=30)	12wk prime-boost interval (Oxford) (n=30)	(Oxford) (n=30)	(Southampton) (n=30)	n = 54
Exploratory Immunology	Up to 50 ml					Up to 50 ml				
Blood volume per visit	Up to 50 ml					Up to 50 ml				
Cumulative blood volume	50 ml					100 ml				

7.7 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.

7.8 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 Safety Reporting

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 8.1.1 and 8.1.2.

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).

8.1 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 include but are not limited to the following, (8):

Table 5 Adverse Events of Special Interest

AESI	Medical Concept
Neurologic	Generalized convulsion Other neurologic events of ≥Grade 3 severity
Vascular	Thrombotic, thromboembolic, and neurovascular events
Hematologic	Thrombocytopenia
Immunologic	Vasculitides Anaphylaxis Potential vaccine-associated enhanced respiratory disease Potential immune-mediated conditions including but not limited to: • Gastrointestinal disorders o Celiac disease o Crohn's disease o Ulcerative colitis o Ulcerative proctitis • Liver disorders o Autoimmune cholangitis o Autoimmune hepatitis o Primary biliary cirrhosis o Primary sclerosing cholangitis • Metabolic diseases o Addison's disease o Autoimmune thyroiditis (including Hashimoto thyroiditis) o Diabetes mellitus type I o Grave's or Basedow's disease

	• Musculoskeletal disorders o Antisynthetase syndrome o Dermatomyositis o Juvenile chronic arthritis (including Still's disease) o Mixed connective tissue disorder o Polymyalgia rheumatic o Polymyositis o Psoriatic arthropathy o Relapsing polychondritis o Rheumatoid arthritis o Scleroderma, including diffuse systemic form and CREST syndrome o Spondyloarthritis, including ankylosing spondylitis, reactive arthritis o (Reiter's Syndrome) and undifferentiated spondyloarthritis o Systemic lupus erythematosus o Systemic sclerosis
	The following conditions will be recorded as AESIs: o Cerebral Venous Sinus Thrombosis o Heparin-Induced Thrombocytopenia o Major thrombosis with concurrent thrombocytopenia

8.1.1 Assessment of causality

Adverse Event With a Causal Relationship to ChAdOx1 nCoV-19
Causality will be assessed relative to ChAdOx1 nCoV-19 administered during the parent trial by a CI delegated clinician. An adverse event is considered to have a causal relationship to ChAdOx1 nCoV-19 administered during the parent trial if the attribution is possible, probable, or very likely by the definitions listed below. An adverse event is considered to have no causal relationship to ChAdOx1 nCoV-19 administered during the parent trial if the attribution is not related 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

8.1.2 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 table below.

Table 7. Severity Criteria for Adverse Events

Severity grade	**Assessment criteria**
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

8.2 Safety Reporting Procedures

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. 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.

8.2.1 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.

8.2.1.1 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.

8.2.1.2 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.

8.2.2 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.

8.2.3 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.

8.2.4 Adverse Events of Special Interest

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

8.2.5 Development Safety Update Reports

The CI or delegate will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

8.2.6 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.

8.3 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.

9 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.

9.1 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.

9.2 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.

9.3 Inclusion in analysis

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

10 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.

10.1 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.

10.2 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

10.3 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. 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.

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.

11 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.

11.1 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.

11.2 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.

11.3 Study Committees

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

12 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.

13 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.

14 Ethical and Regulatory Considerations

14.1 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.

14.2 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.

14.3 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.

14.4 Other Ethical Considerations

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

14.5 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.

14.6 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.

14.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 in the UK which require data to be de-identified 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.

14.8 Expenses & Benefits

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

15 Finance and Insurance

15.1 Funding

The funding of the study is provided by AstraZeneca.

15.2 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).

15.3 Contract arrangements

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

16 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.

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

Not applicable

18 References

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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.

19 Appendices

19.1 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.

19.1.1 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)

19.1.2 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)

19.2 Appendix B: Participant groups in COV001 and COV002

19.2.1 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			

19.2.2 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 x 10^{10} vp	N/A					gp 1A1	prime only	N = 30	gp 1A2	prime only	N = 10		
5 x 10^{10} vp	5 x 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 x 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 x 10^{10} vp	3.5-6.5 x 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 x 10^{10} vp	2.2 x 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 x 10^{10} vp	N/A	gp 5A1	prime only	N = 50	gp 5A2	prime only	N = 50								
5 x 10^{10} vp	3.5-6.5 x 10^{10} vp	gp 5A3	prime-boost	N = 50	gp 5A4	prime-boost	N = 50								
5 x 10^{10} vp	N/A	gp 5B1	prime only	N = 25	gp 5B2	prime only	N = 25								
5 x 10^{10} vp	N/A	gp 5C1	prime only	N = 25	gp 5C2	prime only	N = 25								
3.5-6.5 x 10^{10} vp	3.5-6.5 x 10^{10} vp	gp 5D1	prime-boost	N = 50	gp 5D2	prime-boost	N = 10								
0.9 x 10^{11} vp	0.9 x 10^{11} vp	gp 5E	prime-boost	N = 15											
0.9 x 10^{11} vp	0.9 x 10^{11} vp	gp 5F	prime-boost	N = 15											
		GROUP 6 (phase III efficacy)								GROUP 8					
5 x 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 x 10^{10} vp	3.5-6.5 x 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 x 10^{10} vp								gp 7A1	prime only	N = 30	gp 7A2	prime only	N = 10		
5 x 10^{10} vp	5 x 10^{10} vp							gp 7B1	prime-boost	N = 30	gp 7B2	prime-boost	N = 10		
		GROUP 11								GROUP 9 (phase III efficacy)					
3.5-6.5 x 10^{10} vp	3.5-6.5 x 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
		(adults 18-55yo previous ChAdOx)													
		GROUP 12													
3.5-6.5 x 10^{10} vp	3.5-6.5 x 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

19.3 Appendix C: Links to regulatory publications

19.3.1 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

19.3.2 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

19.3.3 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

19.4 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

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.

19.5 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