Study Title: A Randomized, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine.

Study Reference: COV003

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Chief Investigator:	Prof. Andrew J Pollard
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Funder	OXFORD University and external donors (Fundação Lemann, Instituto D'or de Ensino e Pesquisa and AstraZeneca Brasil)

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Compliance Statement

The study will be conducted in compliance with the Protocol, the principles of Good Clinical Practices, Standards for Medicines for Human Use (Clinical Trial) 2004 (as amended), and all other applicable regulatory requirements.

Investigator's Agreement and Conflict of Interest Notification

I approve this Protocol for use in the abovementioned clinical trial and agree to comply with all provisions established therein.

In accordance with Declaration of Helsinki, 2008, I have read this protocol, and declare that I have no conflict of interest.

Lead Investigator Signature Date

Research Site

I have read this protocol and agree to comply with all the provisions established therein.

In accordance with Declaration of Helsinki, 2008, I have read this protocol, and declare that I have no conflict of interest.

Principal Investigator	Signature	Date

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Regarding the differentiation of ADE and the lack of effectiveness of the vaccine: there is no internationally accepted definition of ADE. Differences in disease severity between groups will be

1 SYNOPSIS

Title	A Randomized, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine.
Study Identifier	COV003
Trial Record	https://www.isrctn.com/ (registration number: ISRCTN89951424)
Study Sites	Centro de Referência para Imunobiológicos Especiais (CRIE) - UNIFESP, Universidade Federal de São Paulo, Rua Borges Lagoa, 770, Vila Clementino, Zip Code 04038-001, São Paulo/SP, Brazil Instituto D'Or de Pesquisa e Ensino Rua Diniz Cordeiro, 30, Botafogo, Zip Code 22281-100, Rio de Janeiro - RJ, Brazil Instituto D'Or de Pesquisa e Ensino Avenida São Rafael, 2152, São Marcos, Zip Code 41253-190, Salvador - BA, Brazil Centro de Pesquisas Clinicas de Natal (CPCLIN) Rua Dr Ponciano Barbosa, 282 – Cidade Alta Natal – RN, 59025-050, Brazil Universidade Federal de Santa Maria (UFSM) Av. Roraima, 1000 Cidade Universitária Bairro Camobi

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Clinical Phase	3
Design	A Single-Blind, Randomized Study of Safety, Efficacy, and Immunogenicity.
Population	Health professionals and adults with high potential for exposure to SARS-CoV-2, aged ≥18 years.
Planned Sample Size	The total sample size will be up to 10,300 participants (with a margin of 1%).
Planned Duration	12 months post final vaccine, per participant

	Objective	Endpoint Measure
Primary Objective	To evaluate the efficacy of ChAdOx1 nCoV-19 vaccine against COVID-19 disease confirmed with PCR.	a) COVID-19 virologically confirmed symptomatic cases (PCR positive).

Secondary Objectives	To evaluate the safety, tolerability, and reactogenicity profile of ChAdOx1 nCoV-19 candidate vaccine.	a) Occurrence of signs and symptoms of local and systemic reactogenicity requested during 7 days after vaccination (in a subset of 200 participants*); b) Occurrence of serious adverse events; c) Occurrence of disease enhancement episodes .
	To evaluate the efficacy of ChAdOx1 nCoV-19 candidate vaccine against severe and non-severe COVID-19 disease.	a) Hospitalization for COVID-19 disease confirmed by PCR; b) COVID-19 severe disease confirmed by PCR; c) Death associated with COVID-19 disease; d) Antibodies against SARS-CoV-2 non-Spike protein (efficacy against non-spike seroconversion rates).
	To assess the humoral immunogenicity of ChAdOx1 nCoV-19 candidate vaccine.	a) Antibodies against SARS-CoV-2 spike protein (sero-conversion rates). b) Virus neutralizing antibodies (NAb) against live and/or pseudotyped SARS-CoV-2 virus.

	To assess the cellular immunogenicity of ChAdOx1 nCoV-19 candidate vaccine.	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein;
Investigational Products	a) ChAdOx1 nCoV-19, an adenoviral vector of replication-defective monkey expressing the SARS-CoV-2 spike (S) protein; b) MenACWY vaccine; c) Saline Placebo (for the control arm boosting dose)	

*Detailed assessments of local and systemic reactogenicity for 7 days after vaccination with ChAdOx1 nCoV-19 compared to MenACWY as a control have been documented in a sufficient number of participants in previous studies. In study COV003, detailed local and systemic reactogenicity will be evaluated in 200 randomized participants, a quantity determined to ensure proportionality and comparative representativeness compared to studies COV001 and COV002.

Formulation	ChAdOx1 nCoV-19: Liquid
	MenACWY: powder and solvent for solution for injection
Route of Administration	Intramuscular (IM)
Doses per Administration	ChAdOx1 nCoV-19: 5 x 10^{10} vp
	ChAdOx1 nCoV-19: 0.5mL (3.5 x 10^{10} to 6.5 x 10^{10})
	MenACWY: 0.5 mL
	0.9% saline solution: 0.5mL
	Both groups will receive prophylactic paracetamol: 500mg - 1 g q6h/24 hours.

2 ABBREVIATIONS

AdHu	Human adenovirus
AdHu5	Human adenovirus serotype 5
ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
AID	Autoimmune Disease
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine, Oxford
CBF	Clinical Bio manufacturing Facility
ChAdOx	Chimpanzee adenovirus 1
CI	Confidence interval
COP	Code of Practice
CRF	Clinical Record or Clinical Research Facility
CTRG	Clinical Trials & Research Governance Office, University of Oxford
CTL	Cytotoxic T Lymphocyte
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report
ELISPOT	Enzyme-linked immunospot
GCP	Good Clinical Practices
GMO	Genetically modified organism
GMT	Geometric mean titer
GP	General Practitioner
HCG	Human Chorionic Gonadotrophin
HEK	Human embryonic kidney
HLA	Human leukocyte antigen
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonization

ICMJE	International Committee of Medical Journal Editors
ICS	Intracellular Cytokine Staining
ID	Intradermal
IFNγ	Gamma interferon
IM	Intramuscular
IMP	Investigational medicinal product
IMP-D	Investigational Medicinal Product Dossier
IV	Intravenous
MenACWY	Quadrivalent meningococcal conjugate vaccine (protein-polysaccharide) against group A, C, W, and Y capsular serotype
MHRA	Medicines and Healthcare Products Regulatory Agency
MVA	Modified Vaccinia Ankara virus
NHS	National Health Service
NIH	National Institutes of Health
NIHR	National Institute for Health Research
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PI	Principal Investigator
QP	Qualified Person
qPCR	Quantitative polymerase chain reaction
REC	Research Ethics Committee
SAE	Serious adverse event
SC	Subcutaneous
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
µg	Microgram
VP	viral particle
VV	viral vector

WHO	World Health Organization

3 BACKGROUND AND RATIONALE

3.1 Background

In December 2019, a group of pneumonia patients of unknown cause was linked to a wholesale seafood market in Wuhan, China, and it was later confirmed that they were infected with a new coronavirus, known as 2019-nCoV [1]. The virus was later renamed SARS-CoV-2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a betacoronavirus lineage B. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of betacoronavirus lineage C[2]. Covid-19 is the infectious disease caused by SARS-CoV-2. In January 2020, there was an increase in evidence of human-to-human transmission as the number of cases began to increase rapidly in China. Despite the unprecedented containment measures adopted by the Chinese government, SARS-CoV-2 has spread rapidly across the world. WHO declared the COVID-19 outbreak as an international public health emergency on January 30, 2020.

Coronaviruses (CoVs) are large, spherical, and enveloped single-stranded RNA genomes. A quarter of its genome is responsible for encoding structural proteins, such as glycoprotein spike (S), envelope (E), membrane (M) and nucleocapsid proteins (N). E, M, and N are mainly responsible for virion assembly, while protein S is involved in binding to the receptor, mediating the entry of the virus into host cells during CoVs infection through different receptors. [3] SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus* and recognizes the angiotensin-converting enzyme 2 (ACE2) as an input receptor[4]. This is the seventh CoV that has been proven to cause infections in humans and the third that has been proven to cause serious illness after SARS-CoV and MERS-CoV.

The spike protein is a type I transmembrane, trimeric, type I glycoprotein located on the surface of the viral envelope of CoVs, which can be divided into two functional subunits: the N-terminal S1 and the C-terminal S2. S1 and S2 are responsible for the binding to the cellular receptor through the receptor binding domain (RBD, for its acronym in-English) and fusion of virus and cell membranes, respectively, thereby mediating the entry of SARS-CoV-2 into

target cells. [3] The functions of S in receptor binding and membrane fusion make it an ideal target for vaccine and antiviral development, as it is the main target for neutralizing antibodies.

ChAdOx1 nCoV-19 vaccine consists of a replication-deficient monkey adenoviral vector ChAdOx1, containing the SARS CoV-2 structural surface glycoprotein antigen (spike protein) (nCoV-19), with a signal sequence from the leading tissue plasminogen activator (tPA). ChAdOx1 nCoV-19 expresses a codon-optimized coding sequence for the Spike protein from GenBank genomic sequence access: MN908947. The leader tPA sequence was shown to be beneficial in increasing the immunogenicity of another CoV vaccine vectorized by ChAdOx1 (ChAdOx1 MERS)[5].

3.2 Pre-clinical Studies

Refer the Investigator's Brochure for the most recent update of preclinical data.

3.2.1 Immunogenicity (Jenner Institute)

The mice (balb/c and CD-1) were immunized with ChAdOx1 which expresses the SARS-CoV-2 Spike protein or green fluorescent protein (GFP). From 9 to 10 days after vaccination, spleen samples were used to assess IFN-γ ELISpot responses and serum samples for assessments of S1 and S2 antibody responses with ELISA. The results of these studies show that a single dose of ChAdOx1 nCoV was immunogenic in mice.

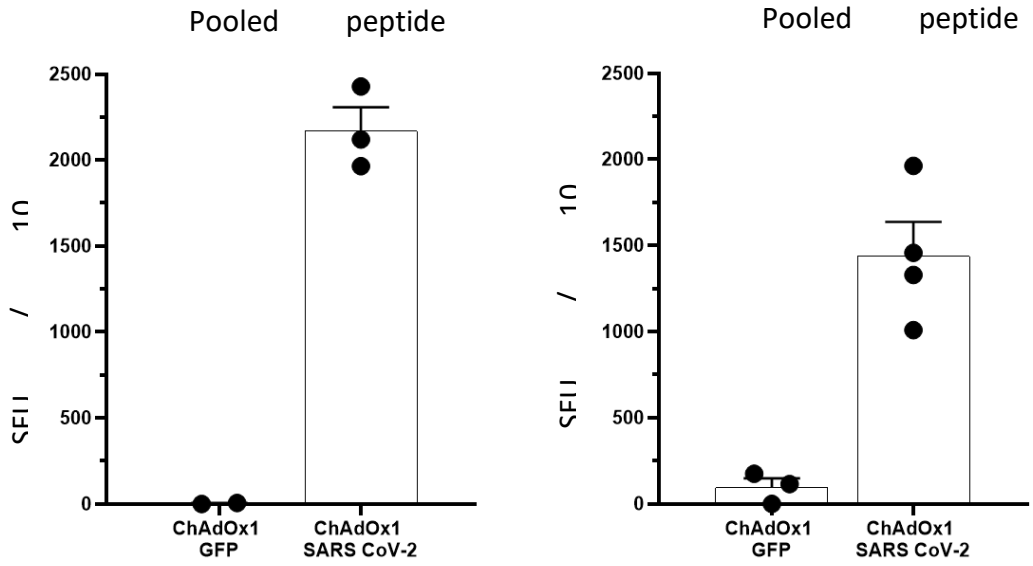


Figure 1. Splenic responses combined with IFN-γ ELISpot from BALB/c (left panel) and CD-1 (right panel) mice, in response to peptides that comprise the SARS-CoV-2 spike protein, nine or ten days after vaccination, with 1.7×10^{10} pv ChAdOx1 nCoV-19 or 8×10^{9} pv ChAdOx1 GFP. The means with SEM are described.

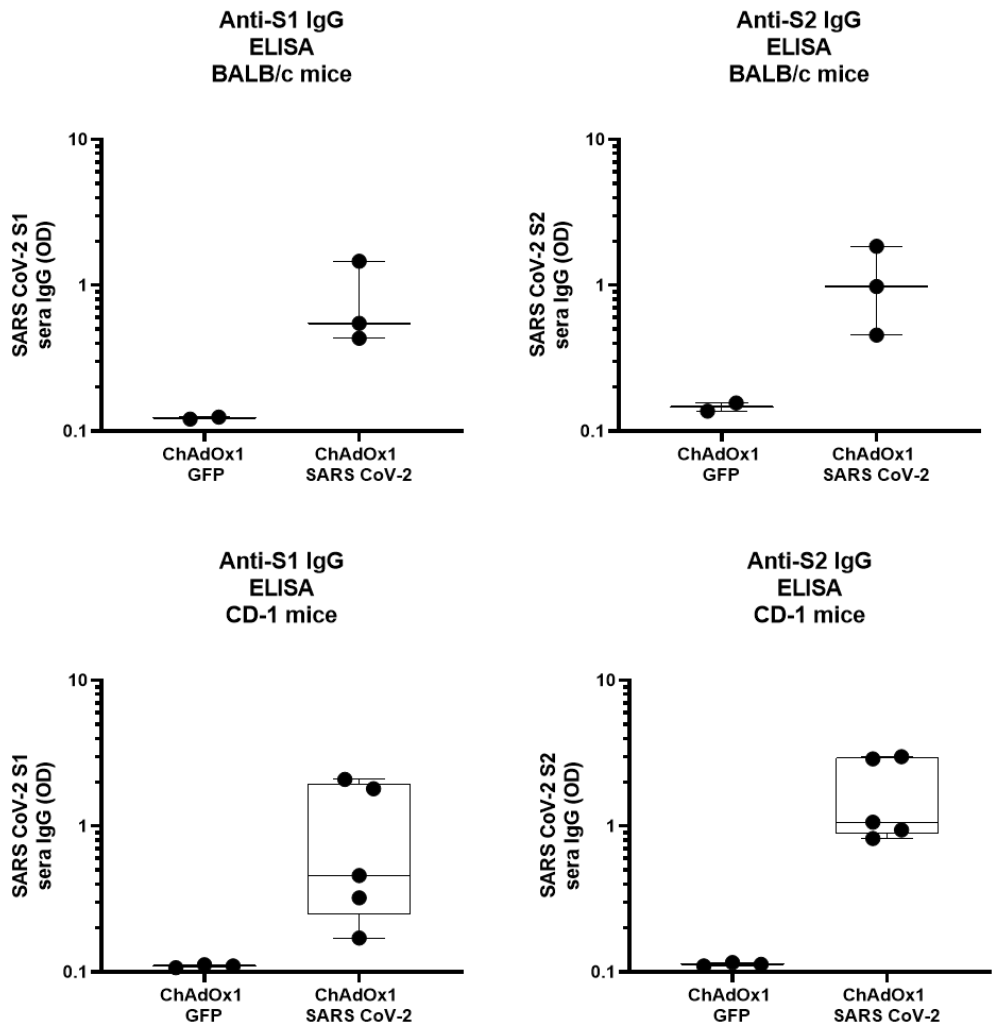
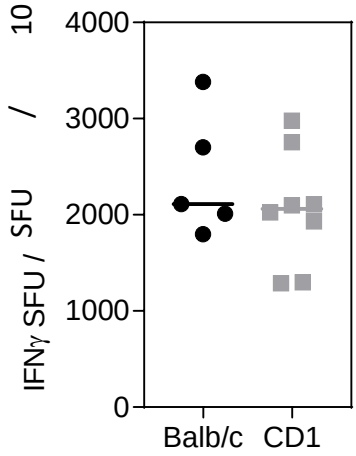


Figure 2. Box and mustache plot of optical densities after ELISA analysis of BALB/C mouse serum (top panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV spike -2 nine or ten days after vaccination, with 1.7×10^{10} pv ChAdOx1 nCoV-19 or 8×10^{9} pv ChAdOx1 GFP. Box and mustache plots of optical densities after ELISA analysis of CD-1 mouse serum (bottom panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV spike -2.

A second experiment was performed with a different dose. The results are summarized in the figure below. Intracellular cytokine staining shows a pattern consistent with predominantly Th1 responses.

A. ELISpot Responses



B. Intracellular cytokine staining

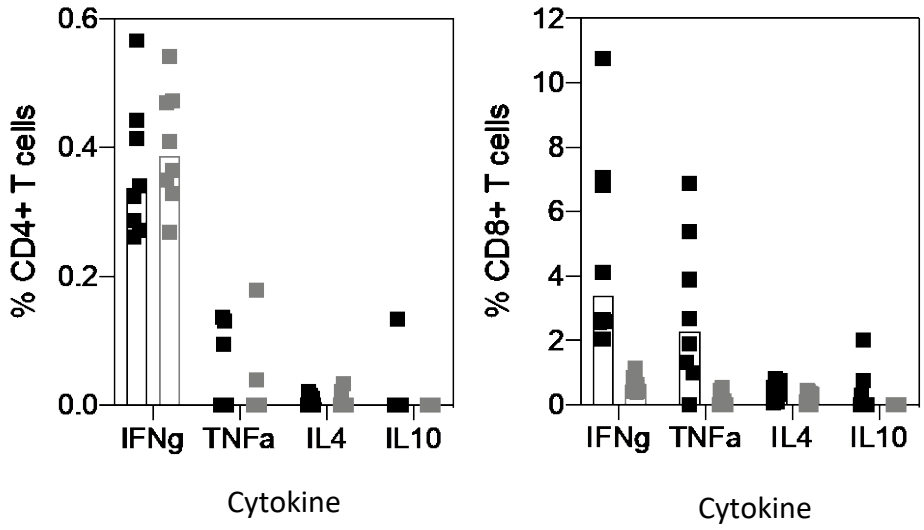


Figure 3. Specific antigen responses after vaccination with ChAdOx nCov19. 10^8 UI ChAdOx nCoV-19 was administered intramuscularly to heterogeneous BALB/c mice (CD1). Fourteen days later, the harvested spleens and cells stimulated peptides that span the extension of S1 and S2.

A. The graph shows the IFN-γ ELIspot responses summed up in BALB/c (black circles) and heterogeneous cd1 (gray squares) mice.

B. The graphs show the frequency of cytokine positive CD4 (left) or CD8 (right) cells, measured by intracellular cytokine staining after splenocyte stimulation with clustered S1 (black) or clustered S2 (gray) peptides in CD1 mice.

3.2.2 Efficacy

Pre-clinical efficacy studies of ChAdOx1 nCoV-19 in ferrets and non-human primates are ongoing. Once available, the results will be included in the Investigator's Brochure.

3.2.3 Immunopathology and antibody-dependent potentiation

Safety concerns have arisen around the use of coronavirus Spike glycoproteins to their full extent and other viral antigens (nucleoprotein) as vaccine antigens after historical and limited reports of immunopathology and antibody dependent potentiation (ADE) reported *in vitro* and post challenge with SARS-CoV in mice, ferrets and non-human primates immunized with vaccines based on inactivated complete SARS-CoV or protein S in its full extension, including a study that used modified Vaccinia Ankara as a vector. [6-8] So far, there has been a report of pulmonary immunopathology after the challenge with MERS-CoV in mice immunized with a candidate vaccine against inactivated MERS-CoV. [9] However, in preclinical trials of immunization with ChAdOx1 and challenge with MERS-CoV, ADE was not observed in hDPP4 transgenic mice, dromedary camels or non-human primates (van Doremalen et al, submitted manuscript).[10.11]

The risks of inducing pulmonary immunopathology in the case of COVID-19 after vaccination with ChAdOx1 nCoV-19 are unknown. The NHP study conducted by NIH described in the investigator's brochure showed no evidence of immune-enhanced inflammation in ChAdOx1 nCoV-19 vaccinated animals who underwent SARS-CoV-2 challenge 4 weeks post immunization, at 7 days post challenge. Results from a separate challenge study conducted on a purified inactivated SARS-CoV-2 vaccine also corroborate with NIH findings where no ADE has been detected in vaccinated animals [1]. However, the negative findings on ADE and lung immunopathology from both reports should be interpreted with caution, as challenged animals were sacrificed and examined shortly after challenge (7 days post inoculation).

Challenge studies in ferrets and non-human primates (PNH) are ongoing and these pre-clinical trials will report on the presence or absence of pulmonary pathology. The results will be reviewed as soon as they are available and will be part of the risk/benefit discussions for participants who receive the investigational product (IMP). All pathological data from challenge studies of other SARS-CoV-2 candidate vaccines will also be taken into account.

3.3 Previous clinical experience

Prior to current studies, vaccines vectorized by ChAdOx1 that express different inserts have been used previously in more than 320 healthy volunteers participating in clinical trials conducted by University of Oxford in the United Kingdom and abroad (tables 1 and 2). Most importantly, a ChAdOx1 vector vaccine expressing the total Spike protein from another Betacoronavirus, MERS-CoVCoV, has been administered to 31 participants, so far, as part of the MERS001 and MERS002 studies. ChAdOx1 MERS was administered in doses ranging from $5x10^9$ pv $5x10^{10}$ pv (table 2) with no serious adverse reactions reported. Further references and results on safety and immunogenicity about ChAdOx1 MERS can be found in the ChAdOx1 Investigator's Brochure nCoV-19.

Clinical trials of ChAdOx1 vectorized vaccines encoding antigens for Influenza (NP + M1 fusion protein), Tuberculosis (85A), Prostate Cancer (5T4), Malaria (LS2), Chikungunya (structural polyprotein), Zika (prM and E) , MERS-CoV (total spike protein) and Meningitis B are listed below.

None of the clinical trials mentioned below reported serious adverse events associated with the administration of ChAdOx1, which had a good safety profile.

Phase I/II testing of ChAdOx1 nCov19 vaccine is currently ongoing in the United Kingdom. Since 4/May/2020, 600 volunteers have been vaccinated.

Table 1. Clinical experience with ChAdOx1 viral vector vaccines.

Country	Study	Vaccine	Age	Route	Dose	Number of volunteers (received ChAdOx1)	Publication/Registration Number
UK	FLU004	ChAdOx1 NP + M1	18-50	IM	$5x10^8$ pv	3	Antrobus et al, 2014. Molecular Therapy. DOI: 10.1038/mt. 2013.284 [2]
					$5x10^9$ pv	3	
					$2.5x10^{10}$ pv	3	
					$5x10^{10}$ pv	6	
UK	FLU005	ChAdOx1 NP + M1 MVA NP + M1 (week 8)	18-50	IM	$2.5x10^{10}$ pv	12	Coughlan et al, 2018. EBioMedicine DOI: 10.1016/j.ebiom.2018.02.011 DOI: 10.1016/j.ebiom.2018.05.001 [3]
		ChAdOx1 NP + M1 MVA NP + M1 (week 52)	18-50	IM	$2.5x10^{10}$ pv	12	
		MVA NP+M1 ChAdOx1 NP + M1 (week 8)	18-50	IM	$2.5x10^{10}$ pv	12	

Country	Study	Vaccine	Age	Route	Dose	Number of volunteers (received ChAdOx1)	Publication/Registration Number
		MVA NP+M1 ChAdOx1 NP + M1 (week 52)	18-50	IM	$2.5x10^{10}$ pv	9	
		ChAdOx1 NP + M1	>50	IM	$2.5x10^{10}$ pv	12	
		ChAdOx1 NP + M1 MVA NP + M1 (week 8)	>50	IM	$2.5x10^{10}$ pv	12	
		ChAdOx1 85A	18-50	IM	$5x10^{9}$ pv	6	Wilkie et al, 2020 Vaccine
					$2.5x10^{10}$ pv	12	
UK	TB034	ChAdOx1 85A MVA85A (week 8)	18-50	IM	$2.5x10^{10}$ pv	12	
		ChAdOx1 85A (x2, 4 weeks apart)	18-50	IM	$2.5x10^{10}$ pv	12	

Country	Study	Vaccine	Age	Route	Dose	Number of volunteers (received ChAdOx1)	Publication/Registration Number
		MVA85A (in 4 months)					
Switzerland	TB039 (ongoing)	ChAdOx1 85A	18-55	Aerosol	$1x10^9$ pv	3	Clinicaltrials.gov: NCT04121494
				Aerosol	$5x10^9$ pv	3	
				Aerosol	$1x10^{10}$ pv	11	
				Aerosol/IM	$1x10^{10}$ pv	15	
Uganda	TB042 (ongoing)	ChAdOx1 85A	18-49	IM	$5x10^9$ pv	6	Clinicaltrials.gov: NCT03681860
					$2.5 x10^{10}$	6	
UK	VANCE01	ChAdOx1.5T4 MVA.5T4	18 - 75	IM	$2.5x10^{10}$ pv	34	Clinicaltrials.gov: NCT02390063
UK	ADVANCE (ongoing)	ChAdOx1.5T4 MVA.5T4	≥18	IM	$2.5x10^{10}$ pv	23 (on Feb 20)	Clinicaltrials.gov: NCT03815942

Country	Study	Vaccine	Age	Route	Dose	Number of volunteers (received ChAdOx1)	Publication/Registration Number
UK	VAC067	ChAdOx1 LS2	18-45	IM	$5x10^9$ pv	3	Clinicaltrials.gov: NCT03203421
					$2.5x10^{10}$ pv	10	
UK	VAMBOX	ChAdOx1 MenB.1	18-50	IM	$2.5x10^{10}$ pv	3	ISRCTN46336916
					$5x10^{10}$ pv	26	
UK	CHIK001	ChAdOx1 Chik	18-50	IM	$5x10^9$ pv	6	Clinicaltrials.gov: NCT03590392 DOI: https://doi.org/10.4269/ajtmh.abstract2019 Abstract # 59, page 19.
					$2.5x10^{10}$ pv	9	
					$5x10^{10}$ pv	9	
UK	ZIKA001 (ongoing)	ChAdOx1 Zika	18-50	IM	$5x10^9$ pv	6	Clinicaltrials.gov: NCT04015648
					$2.5x10^{10}$ pv	3 (on Feb 20)	
					$5x10^{10}$ pv	-	

Table 2. Clinical experience with ChAdOx1 MERS

Country	Study	Vaccine	Age	Route	Dose	Number of volunteers (received ChAdOx1)	Publication/Registration Number
UK	MERS001 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ pv	6	Clinicaltrials.gov: NCT03399578 Folegatti et.al. 2020, Lancet Infect.Dis DOI: https://doi.org/10.1016/S1473-3099(20)30160-2
					$2.5x10^{10}$ pv	9	
					$5x10^{10}$ pv	9	
					$2.5x10^{10}$ pv		
					Initiation homologous reinforcement -	3	
Saudi Arabia	MERS002 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ pv	4	Clinicaltrials.gov: NCT04170829
					$2.5x10^{10}$ pv	3	
					$5x10^{10}$ pv	-	

The first clinical trial of the ChAdOx1 nCoV-19 candidate vaccine started on April 23, after approval by the IRB and CTA by the MHRA. The study included healthy adults between the ages of 18 and 55 at various research sites in the UK. The objectives of the study are to assess vaccine

safety, reactogenicity and immunogenicity, as well as the collection and analysis of any confirmation of COVID-19 by PCR. These cases will be analyzed in a meta-analysis, together with case collections from other studies (methodology still under review). The study involved approximately 1070 individuals who are in the follow-up period. The Independent Safety Data Monitoring Committee (DSMB), which continuously monitors the study, has so far not reported any concerns to the MHRA or the study sponsor (secure follow-up of one to four weeks per participant). Safety follow-up for the full four weeks will be available to a subset of participants prior to the application of the first vaccine in Brazil.

In addition, before the start of the COV003 study in Brazil, another phase II study, COV002, will be initiated at various locations in the United Kingdom. In a first stage, COV002 will include 80 healthy adults from 56 to 69 years old, 120 elderly people over 70 with no upper age limit and 60 children from 5 to 12 years old. The assessed endpoints will be safety and immunogenicity, including T cell immunity. This study will be expanded in stage 2 to a phase III study of safety, immunogenicity and efficacy, including 10,000 adults over 18 years of age, with an increased risk of infection by COVID-19 at various research sites in the United Kingdom. The safety and efficacy assessments of the phase III part of the British study COV002 are the same as those of the COV003 protocol in Brazil. This will allow for the eventual grouping of effectiveness data between studies.

3.4 Rationale

The epidemic of COVID-19 has caused a major disruption in health systems with significant socioeconomic impacts. Containment measures have failed to stop the spread of the virus, which has reached pandemic levels. Currently, there are no specific treatments available against COVID-19 and accelerated vaccine development is sorely needed.

Live attenuated viruses have historically been one of the most immunogenic platforms available, as they have the ability to present multiple antigens throughout the viral life cycle in their native conformations. However, the manufacture of live attenuated viruses requires complex measures of containment and biosafety. In addition, live attenuated viruses carry the risk of inadequate attenuation, causing widespread disease, particularly in immunocompromised hosts. Given that COVID-19 is a serious and potentially fatal disease, which disproportionately affects elderly people with comorbidities, producing a vaccine with live attenuated viruses is the least viable option. The replication of competent viral vectors may pose a similar threat in relation to the disease spread in immunosuppressed individuals. Vectors with poor replication, however, avoid this risk by maintaining the advantages of the presentation of native antigens, increased immunity of T cells and the ability to express multiple antigens[15]. Subunit vaccines generally require the use of adjuvants and, although DNA and RNA vaccines can offer manufacturing advantages, they are often precariously immunogenic and require multiple doses, which is highly undesirable in the context of a pandemic.

Chimpanzee adenovirus vaccine vectors have been safely administered to thousands of people targeting a wide range of infectious diseases. ChAdOx1 vectorized vaccines were administered to more than 320 volunteers without safety concerns and were shown to be highly immunogenic with the administration of single doses. Relevant information refers to recent clinical trials where a single dose of a vectorized ChAdOx1 vaccine expressing the total spike protein of another beta-choronavirus (MERS-CoV) has been shown to induce neutralizing antibodies.

The use of an active vaccine as a comparator for the control group will minimize the chances of accidentally unblinding the participant, reducing the bias in the analysis of reactogenicity,

in the safety report and/or changes in the search for health services once that were symptomatic for COVID-19.

Groups 1c and 1d have been added following interim immunogenicity results on homologous prime-boost groups (as part of the COV001 UK study – see investigator's brochure for further details) showing improved neutralising antibody titres after 2 doses when compared to 1 dose regimen. A saline placebo will be used in place of an active comparator in group 1d. As we have seen less reactogenicity when giving the booster dose in the UK studies, there is less risk of unblinding the participant by using placebo as a comparator for the booster dose.

4 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint Measure
Primary Objective	To evaluate the efficacy of ChAdOx1 nCoV-19 vaccine against COVID-19 disease confirmed with PCR.	a) COVID-19 virologically confirmed symptomatic cases (PCR positive).
Secondary Objectives	To evaluate the safety, tolerability and reactogenicity profile of ChAdOx1 nCoV-19 candidate vaccine.	a) Occurrence of signs and symptoms of local and systemic reactogenicity requested during 7 days after vaccination (in a subset of 200 participants*); b) Occurrence of serious adverse events; c) Occurrence of disease enhancement episodes
	To evaluate the efficacy of ChAdOx1 nCoV-19 candidate vaccine against severe and non-severe COVID-19 disease	a) Hospitalization for COVID-19 disease confirmed by PCR; b) COVID-19 severe disease confirmed by PCR;

		c) Death associated with COVID-19 disease; d) Antibodies against SARS-CoV-2 non-Spike protein (efficacy against non-spike seroconversion rates).
	To evaluate the humoral immunogenicity of ChAdOx1 nCoV-19.	a) Antibodies against the SARS-CoV-2 spike protein (sero-conversion rates); b) Virus neutralizing antibodies (NAb) against live and/or pseudotyped SARS-CoV-2 virus.
	To assess the cellular immunogenicity of ChAdOx1 nCoV-19 candidate vaccine**.	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein;

*Detailed assessments of local and systemic reactogenicity for 7 days after vaccination with ChAdOx1 nCoV-19 compared to MenACWY as a control have been documented in a sufficient number of participants in previous studies. In study COV003, detailed local and systemic reactogenicity will be evaluated in 200 randomized participants, a quantity determined to ensure proportionality and comparative representativeness compared to studies COV001 and COV002.

** Cellular immune responses will be measured in a subset of individuals only (up to 60 volunteers who will be recruited from the CRIE-UNIFESP site, sequentially)

5 STUDY DESIGN

This is a phase III, controlled, randomized, single-blind study to be conducted in adults with high exposure to COVID-19, who are administered two-doses of ChAdOx1 nCoV-19 or MenACWY and saline placebo by means of an IM injection with co-administered paracetamol.

After reviewing all available data from animal studies and UK studies (COV001 and COV002), participants will be randomized to ChAdOx1 nCoV-19 or MenACWY vaccine in a 1:1 ratio in blocks of 4, and all participants will be blinded to the allocation of the vaccine groups. The DSMB will periodically evaluate safety and efficacy data, every 4-8 weeks and/or as needed. The DSMB will consist of the members of the DSMB currently convened who oversee trials in the UK.

Following the immunogenicity results of the UK phase I/II study which showed higher levels of neutralizing antibodies with a prime-boost schedule (https://doi.org/10.1016/S0140-6736(20)31604-4), a booster dose of vaccine will be offered to all participants in the study. Participants enrolled on version 4.0 of the protocol onwards will only be allowed to take part in the study if they agree to receive 2 doses of either ChAdOx1 nCoV-19 or MenACWY/saline placebo. Participants who already received a dose of either ChAdOx1 nCoV-19 or MenACWY (before approvals for the second dose were in place) will be offered a booster dose 4-12 weeks after the prime dose of either ChAdOx1 nCoV-19 or saline placebo, depending on which arm they were originally allocated to. Any volunteers enrolled prior to the booster dose protocol amendment will be able to refuse a second dose and will continue their follow-up as per their previously agreed schedule of attendances.

Participants will be followed for the duration of the study to record adverse events and episodes of symptomatic COVID-19 confirmed by PCR. Participants will be assessed for COVID-19 if they have a new fever (≥ 37.8 ºC) OR cough OR shortness of breath OR anosmia/ageusia.

Moderate and severe COVID-19 disease will be defined by clinical criteria. Detailed clinical parameters will be collected from medical records and aligned with the definitions of moderate and severe disease agreed by the international scientific community, such as a score greater than 6 on the NEWS-2 scale, or a score of 4 and above on ISARIC/WHO (International Severe Acute Respiratory and Emerging Infection Consortium; WHO Working Group on Clinical Characterisation and Management of COVID-19). Such parameters include, but are not limited to oxygen saturation, need for oxygen therapy, respiratory rate, and other vital signs, need for ventilatory support, radiographic and computed tomography, and blood test results, among other clinically relevant parameters. Considering that the NEWS-2 scale is

not used in the clinical routine of the research site, all staff involved in conducting the project will receive specific training.

NEWS-2 scoring system for serious COVID-19 assessment:

				Score			
Physiological parameter	3	2	1	0	1	2	3
Breathing rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO2 Scale 2 (%) - use in hypercapnic respiratory failure	≤83	84–85	86–87	88–92 ≥93 in the air	93–94 in oxygen	95–96 in oxygen	≥97 in oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale

ECMO=extracorporeal membrane oxygenation. FiO2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO2=partial pressure of oxygen. SpO2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

5.1 Study groups

Vaccine	Number of Participants	Participants
1a) Single dose of ChAdOx1nCOV19 vaccine, $5x10^{10}$ vp + paracetamol	N = up to 1600 participants	Health professionals and adults with high known likely exposure to COVID-19.

1b) Single dose of MenACWY + paracetamol	N = up to 1600 participants	Health professionals and adults with high known likely exposure to COVID-19.
1c) Two doses of ChAdOx1 nCoV-19 vaccine, $5x10^{10}$vp (prime) and 0.5mL boost ($3.5 – 6.5 \times 10^{10}$ vp), 4-12 weeks apart + paracetamol	N= up to 5150 (up to 1600 invited from 1a to receive a booster dose and new volunteers recruited)	Participants recruited in group 1a will be invited to receive a booster dose, 4-12 weeks apart) and new participants recruited on version 4.0 of the protocol onwards will consent to receive a 2-dose schedule.
1d) MenACWY prime, and Saline Placebo boost (0.5mL)), 4-12 weeks apart + paracetamol.	N= up to 5150 (up to 1600 invited from 1b to receive a booster dose and new volunteers recruited)	Participants recruited in group 1b will be invited to receive a booster dose, 4-12 weeks apart) and new participants recruited on version 4.0 of the protocol onwards will consent to receive a 2-dose schedule.

The overall sample size will be up to 10,300 (with a margin of 1%) participants. All volunteers previously enrolled in groups 1a and 1b will be offered a booster dose. Any new participants recruited into the study on version 4.0 of the protocol onwards will necessarily have to consent to a 2-dose schedule.

5.2 Study participants

Adult participants over the age of 18 will be enrolled in the study. Participants will be considered enrolled immediately after the vaccine is administered. Recruitment will focus on healthcare professionals and those with likely high known exposure to COVID-19. For example, they are health professionals: students, residents and professionals who perform health care activities such as nurses and nursing technicians, pharmacists, doctors, physiotherapists, speech therapists and radiology technicians. High exposure adults will be

considered: cleaning and hygiene personnel; safety; reception and concierge; volunteers; drivers, among others. Participants in older age groups (56-69 years and 70 years and above) will be recruited at the investigators' discretion. Their likelihood of COVID-19 exposure will be judged on a case-by-case basis, regardless of their previous occupation.

5.3 Definition of the End of Study

The end of study is the date of the last test performed on the last sample collected.

5.4 Potential risks for participants

Potential risks are those associated with phlebotomy, vaccination, and disease potentiation.

Venipuncture

Hematomas and discomfort located at the venipuncture site may occur. More rarely. Fainting may occur. These will not be documented as AE if they occur. The total volume of blood drawn during the study period will be approximately 330 mL, excluding any necessary repeated extraction (blood volumes may vary slightly between participants due to the use of different volume vacutainers, the operational procedures of the research sites and the number of symptomatic visits). Participants will be asked to refrain from donating blood during the period of their involvement in the study.

Allergic reactions

Mild to severe allergic reactions can occur in response to any component of a drug preparation. Anaphylaxis is extremely rare (about 1 in 1,000,000 doses of vaccine), but it can occur in response to any vaccine or medication.

Vaccination

Local reaction due to IM vaccination

The typical local reaction as a result of the IM injection is temporary pain, tenderness, redness and swelling at the injection site.

Systemic reactions

Constitutional symptoms similar to the flu, such as fatigue, headache, malaise, feverish sensation and muscle pain can occur with any vaccination and last from 2 to 3 days. Pre-syncopal and syncopal episodes may occur at the time of vaccination. Participants will be asked to administer prophylactic paracetamol for 24 hours to minimize possible fever and flu-like symptoms. As with many vaccines, temporary ascending paralysis (Guillain-Barré syndrome, GBS) or immune-mediated reactions can occur that can lead to organ damage, but this should be extremely rare (1 in 100,000-1,000,000 doses vaccine).

Transient neutropenia and thrombocytopenia have been described after immunization with other adenoviral vectorized vaccines, but it is not perceived as clinically significant.

Control group participants will receive a single dose of an authorized MenACWY vaccine, the risks of which are described in the vaccine package insert.

Disease Enhancement

The risks of inducing disease enhancement and pulmonary immunopathology in case of COVID-19 disease after vaccination with ChAdOx1 nCoV-19 are unknown. Challenge studies on ferrets and PNH are ongoing and the results will be reviewed as they arise. Two studies on PNH so far have shown no evidence of disease potentiation until day 7 after the challenge. All preclinical data from challenge studies using ChAdOx1 nCoV-19 and other candidate vaccines (where available) will guide risk/benefit decisions for participants who receive the IMP. Any

safety signs associated with the enhancement of the disease potentially observed in COV001/COV002 will also guide these decisions.

5.5 Known potential benefits

Participants enrolled in the control groups will receive MenACWY, a licensed vaccine that has been administered to adolescents on routine vaccination schedules in several countries, including the United Kingdom, and is used as a travel vaccine for high-risk areas. Most of the participants in this study will not have received this vaccine before and therefore will gain the benefit of protection against meningococci in groups A, C, W and Y. Participants who had previously been vaccinated with MenACWY will have their immunity enhanced against these organisms and are not exposed to additional risks when receiving the additional dose of the comparator vaccine. Participants receiving ChAdOx1 nCoV-19 will have no guaranteed benefit, however, it is expected that the information obtained in this study will contribute to the development of a safe and effective vaccine against COVID-19. All participants will obtain information about their general health.

If the effectiveness of the vaccine against COVID-19 is proven, after the analysis of the effectiveness results and approval by the Data and Safety Monitoring Committee, the sponsor will make this vaccine available to the research participants who received the control vaccine, MenACWY.

6 RECRUITMENT AND WITHDRAWAL OF STUDY PARTICIPANTS

6.1 Identification of Participants

Participants can be recruited through advertisements approved by the local Ethics Committee. The leaflets will be distributed, including the name of the study, information from the centers, age group, disease, and vaccine.

6.2 Informed Consent Form

The participant will sign and date personally or electronically the last approved version of the Informed Consent Form. When the process is carried out in person, it will be presented to the participants, individually, a written version and verbal explanation of the Informed Consent

Form. When the process is carried out electronically, participants will individually receive a link to access the electronic version of the Informed Consent Form. In both cases, it will be detailed:

- the exact nature of the study;
- what it will imply for the participant;
- the implications and restrictions of the protocol;
- the known side effects and any risks involved in participating;
- sample manipulation - participants will be informed about the samples that will be collected anonymously during the course of the study and that can be shared with the study collaborators;
- that individual results will not be shared with participants.

The Informed Consent Form will be made available to the participant before obtaining consent. However, participants will have the opportunity to individually question a properly trained and delegated researcher before signing the consent.

The following general principles will be emphasized:

- Participation in the study is completely voluntary;
- Refusal to participate does not involve a penalty or loss of medical benefits;
- The participant can withdraw from the study at any time;
- The participant is free to ask questions at any time to understand the purpose of the study and the procedures involved;
- The study involves researching an investigational vaccine;
- There is no direct benefit expected for the participant;
- The general practitioner/personal physician of the participant can be contacted to corroborate his/her medical history. Written or verbal information about the participant's medical history can be requested from the general practitioner/personal physician or other sources;
- Blood samples taken as part of the study can be sent abroad, to the United Kingdom, to laboratories at the University of Oxford. These will not be identified. Participants

will be asked whether they agree to biorepository storage for future use, but this will be optional.

The participant will have as much time as he/she wishes to consider the information and the opportunity to question the Investigator, his/her clinical physician or other independent parties to decide whether to participate in the study. The electronic Informed Consent Form must be signed and dated electronically by the adult participant, and the printed Informed Consent Form must be signed and dated by the adult participant and by the person responsible for obtaining the informed consent. This person must be suitably qualified and experienced, have been authorized to do so by the Lead/Principal Investigator and be listed on the delegation´s record. In the case of the printed Informed Consent Form, a copy of the signed document will be given to the participant. The signed original document will be retained at the research study sites.

6.3 Inclusion and exclusion criteria

This study will be performed in healthy adults, who meet the following inclusion and exclusion criteria:

6.3.1 Inclusion Criteria

The participant must meet all the following criteria to be eligible for the study:

- Adults from 18 to 55 years of age.
- Adults aged 56-69 years old (after review of safety data by DSMB in this age group in the UK trial)
- Adults aged 70 and above years old (after review of safety data by DSMB in this age group in the UK trial)
- Able and willing (in the Investigator's opinion) to fulfill all study requirements;
- Health professionals and/or adults at high risk of exposure to SARS-CoV-2, as defined in section 5.2 of this protocol;
- Serology with SARS-CoV-2 negative IgG antibodies; This inclusion criteria does not apply to participants enrolled from version 4.0 of the protocol onwards.

- Willing to allow investigators to discuss the participant's clinical history with their GP/personal physician and access medical records relevant to the study procedures;
- Only for women of childbearing age willing to practice continuous effective birth control (see below) during the study, and a negative pregnancy test on the screening and vaccination day(s);
- Consent to abstain from blood donation during the course of the study;
- Provide informed consent in writing.

The DSMB will review safety data from volunteers aged 56 and above recruited as part of the COV002 UK study. Recruitment of older adults will only be allowed following advice from the DSMB.

6.3.2 Exclusion Criteria

The participant will not be eligible for the study if any of the following criteria apply:

- Participation in trials of prophylactic drugs for COVID-19 during the course of the study;

  Note: Participation in COVID-19 treatment trials is permitted in case of hospitalization due to COVID-19, after confirmation of positive PCR. The study team should be informed as soon as possible. Participants with COVID-19 not hospitalized with positive PCR results for COVID-19 may be medicated according to standard clinical practice, however, participation in treatment trials will not be allowed.

- Planned receipt of any vaccine (authorized or investigational), within 30 days before and after vaccination;
- Prior receipt of an investigational or licensed vaccine with the possibility of impacting the interpretation of the study data (for example, Adenovirus vector vaccines , any vaccines against coronavirus);
- Administration of immunoglobulins and/or any blood products in the three months prior to the planned administration of the candidate vaccine;
- Any confirmed or suspected immunosuppressive or immunodeficiency state, including HIV (regardless of treatment, CD4 count or viral load status); asplenia; severe recurrent infections and chronic use (more than 14 days) of immunosuppressive medication in the last 6 months, except for topical steroids or short-term oral steroids (cycle lasting ≤14 days);
- History of allergic disease or reactions possibly exacerbated by any component of ChAdOx1 nCoV-19 or MenACWY or paracetamol;
- Any history of angioedema;
- Any history of anaphylaxis;
- Pregnancy, lactation or willingness/intention to become pregnant during the study;
- Current diagnosis or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ);
- History of severe psychiatric illness that possibly affects your participation in the study;

- Hemorrhagic disorder (for example, factor deficiency, coagulopathy or platelet disorder), or a previous history of significant bleeding or bruising after IM injections or venipuncture;
- Current suspected or known dependence on alcohol or drugs;
- Severe and/or uncontrolled cardiovascular diseases, respiratory diseases, gastrointestinal diseases, liver disease, kidney disease, endocrine disorder, and neurological disease (mild/moderate well-controlled comorbidities are allowed);
- History of COVID-19 confirmed by laboratory (serology, rapid tests based on antigen or antibody or PCR);
- Seropositive for antibodies to SARS-CoV-2 before recruitment; This exclusion criteria does not apply to participants enrolled from version 4.0 of the protocol onwards
- Continued use of anticoagulants, such as coumarins and related anticoagulants (for example, warfarin) or new oral anticoagulants (for example, apixaban, rivaroxaban, dabigatran and edoxaban);
- Any other significant illness, disorder or finding that may significantly increase the risk for the participant, affect his/her ability to participate in the study or impair the interpretation of the study data.

6.3.3 Re-vaccination exclusion criteria (two-dose groups only)

The following AEs associated with any vaccine, or identified on or before the day of vaccination constitute absolute contraindications to further administration of an IMP to the volunteer in question. If any of these events occur during the study, the subject will not be eligible to receive a booster dose and will be followed up by the clinical team or their regular doctor until resolution or stabilisation of the event:

- Anaphylactic reaction following administration of vaccine
- Pregnancy – if the outcome of pregnancy is termination or miscarriage, volunteers can be boosted if appropriate to do so and given they have a negative pregnancy test at the time of boosting.
- Any AE that in the opinion of the Investigator may affect the safety of the participant or the interpretation of the study results

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

6.3.4 Effective birth control for volunteers

Participants of childbearing potential must use an effective form of birth control during the 12 months of study.

Acceptable forms of birth control for participants include:

- Established use of oral, injected or implanted hormonal of birth control methods;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Complete hysterectomy;
- Bilateral occlusion of the tubes;
- Contraceptive barrier methods (condom or occlusive tampon with spermicide);
- Male sterilization, if the vasectomized partner is the participant's only sexual partner;
- True abstinence, when it is in line with the subject's preferred and usual lifestyle (periodic abstinence and withdrawal are not acceptable of birth control methods).

6.3.5 Withdrawal of participants

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

- Investigator's Decision;
- Ineligibility (both during the study and retrospectively, having been omitted in the screening);
- Significant deviation from the protocol;
- Non-adherence of the participant to the study requirements;
- An AE, which requires discontinuing participation in the study or resulting in an inability to continue to comply with the study procedures.

The reason for the withdrawal will be registered with the CRF. If the withdrawal is a consequence of an AE, appropriate follow-up visits and/or medical care will be scheduled, with the consent of the participant, until the AE is resolved, stabilized or a causality unrelated to his/her participation in the study has been attributed. Any participant who is withdrawn from the study may be replaced, if this is possible within the specified period. The DSMB or DSMB president may recommend withdrawing participants.

If a participant withdraws from the study, the data collected before their withdrawal will still be used in the analysis. The storage of blood samples will continue unless the participant specifically requests otherwise.

In all cases of withdrawal from the subject, the collection of long-term safety data, including some procedures such as a safety blood test, will continue as appropriate if individuals have received one or more doses of the vaccine, unless they refuse any additional follow-up.

6.4 Pregnancy

If a participant becomes pregnant during the trial, she will be followed up for clinical safety assessment with her continuous consent and, in addition, she will be followed up until the outcome of the pregnancy is determined. We will not routinely perform venipuncture on a pregnant participant unless there is a clinical need. In addition, full and free follow-up and assistance will be ensured, for as long as necessary for: (a) the participants who become pregnant, and (b) the fetus, if applicable.

7 CLINICAL PROCEDURES

This section describes the clinical procedures for evaluating study participants and following up after administering the study vaccine.

7.1 Visit Schedule

All participants will have visits and clinical procedures as indicated in the visit schedule below table 4. The subjects will receive the ChAdOx1 nCoV-19 or MenACWY vaccine/saline solution placebo, and will be followed up for a total of 12 months post final vaccination procedure. Additional visits or procedures may be performed at the investigators' discretion, for example, medical history and additional physical examination, or additional blood tests, if they are clinically relevant.

All participants in groups 1a and 1b will be offered a booster dose of vaccine, however if a participant declines the booster dose they will continue in group 1a or 1b and follow the planned visit schedule, as per table 4.

7.2 Observations, medical history and physical examination

Temperature will be routinely measured at the time-points indicated in the schedule of procedures. Respiratory rate, oxygen saturation, pulse, blood pressure and temperature will be measured at the COVID-19 testing visits and if clinically required. All subjects will undergo medical history and a targeted physical examination if considered necessary at screening or pre-enrolment on D0. The purpose of this examination is to assess and document the subject’s baseline health status so that any later change can be determined. Vital signs (temperature, heart rate, respiratory rate, blood pressure +/- oxygen saturation), height and weight will be measured at screening or pre-enrolment on D0 as part of baseline assessments. Further medical history, physical examination and observations may be done throughout the study based on clinical discretion.

7.3 Blood samples, nose/throat swabs and urine analysis

- **PCR process for COVID-19.** A nose andthroat swab will be collected for COVID-19 PCR.

- **Immunology.** Immunogenicity will be assessed using a variety of immunological assays. This may include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma and flow cytometry assays, neutralization and other functional antibody assays and B cell analyses. Other exploratory immunological assays, including cytokine analysis and other antibody assays, among others, may be performed at the Investigators' discretion. Immunology samples for the assays described above will be drawn as per the schedule of attendances below (table 4)
- **Urine analysis.** In the case of participants of childbearing age, urine will be tested for beta-human chorionic gonadotropin (β-HCG) at screening (when applicable) and immediately before vaccination.

Collaboration with other specialized laboratories in the UK, Europe and outside of Europe may take place for new exploratory tests and for some of the immunology testing described above. This would involve transferring serum, or plasma, PBMC and/or other study samples to these laboratories, but these would remain anonymous. For this, after evaluation and prior approval of the REC/CONEP system, the participant will be presented with a new Informed Consent Form. Only after obtaining this new consent form can the samples be used for purposes other than those specified in this protocol.

Immunological tests will be performed according to the standard operating procedures of the research sites, the University of Oxford, and collaborating international laboratories.

The subjects will be informed which blood sample (after all tests for this study are completed), will be stored in a biorepository for future use. The subjects will be able to decide whether to allow such future use of any sample. With the informed consent of the participants, blood serum and/or PBMCs will be frozen for future analysis of COVID-19 and responses related to the vaccine. If a subject chooses not to allow this, no sample will be stored beyond the storage period required to meet Good Laboratory Practices (GLP) and regulatory requirements.

7.4 Study visits

Study visits and procedures will be performed by the research sites staff. The procedures to be included in each visit are documented in the visit schedule (table 4). Each visit is assigned a time and window period, within which the visit will take place.

7.4.1 Screening visit and recruitment

All potential participants will have a screening visit, up to 7 days before vaccination for a baseline assessment. For participants who are recruited in the study before version 4.0 of the study protocol, a serological evaluation of baseline antibodies against SARS-CoV-2 is performed. The results of the serology should be available within this period, no later than 7 days after collection. Volunteers with negative serology for IgG antibodies to SARS-CoV-2 may participate in the study (applicable to previous protocol versions only and not from version 4.0 onwards).

Having established that there is a low baseline seropositivity in the study population, the remaining participants can be included without baseline SARS-CoV-2 antibodies. This allows the screening visit to take place at the same day as the vaccination visit, and will precede vaccination procedure.

At the screening visit, the objectives of the study and all tests to be performed will be described to the participants. Individually, each participant will have the opportunity to question a duly trained and delegated researcher before signing the consent. The informed consent procedure will be performed before screening/recruitment procedures, as described in section 6.2. A medical history, including previous vaccinations, and targeted physical examination (when necessary) will be conducted at the screening visit. Findings will be recorded as part of baseline and eligibility assessment. A screening visit can be repeated if time from screening to vaccination is greater than the pre-specified window in the study protocol.

The research site staff may contact the subject's general practitioner/personal physician with written permission after screening to corroborate the clinical history when possible and practical to do so. The participant's doctor may be notified that the subject has been enrolled voluntarily in the study.

7.4.2 Day 0: Recruitment and vaccination visit

Participants will be considered enrolled in the trial at the time of vaccination. Before the investigational vaccination/treatment, the eligibility of the participant will be reviewed. The temperature and, if necessary, a medical history and physical examination will be performed to determine the need to postpone vaccination. The study vaccines/treatment will be administered as described below.

7.4.2.1 Vaccination

All vaccines will be administered intramuscularly according to specific standard operating procedures. The injection site will be covered with a sterile dressing and the participant will remain at the study site for observation, in case of immediate adverse events. Observations will be made at a minimum of 15 minutes after vaccination, the sterile dressing will be removed and the injection site inspected.

A sub sample of 200 participants will receive a thermometer, a metric ruler, access to the electronic diary via web, a printed diary (for use in case the electronic diary presents problems), guidelines and instructions for use, together with a contact card containing the number of 24-hour emergency telephone number to contact the research site if necessary. Participants will be instructed on how to self-assess the intensity and severity of requested adverse events (Table 3 - Requested and unsolicited AEs). There will also be space in the electronic (or paper) Symptom Diary for the participant to document unsolicited AEs for 28 days, and if a medication has been taken to relieve the symptoms. The diaries will collect information about the timing and severity of the following solicited AEs. Participants who were asked to fill out a diary post prime vaccination will be asked to fill out the same diary post booster vaccination.

Table 3. Spontaneous, requested AEs collected in the post-vaccination electronic diary (or daily card) for reactogenicity

AE spontaneous locations	AE systemic spontaneous
Pain	Fever
Sensitivity	Feeling feverish

Redness	Chills
Heat	Joint pain
Itching	Muscle ache
Swelling	Fatigue
Local hardening	Headache
	Malaise
	Nausea
	Vomiting

The use of electronic diaries allows the real-time monitoring of the safety of the study vaccines.

NB All volunteers who develop COVID-19 symptoms triggering the symptomatic pathway will be asked to fill out a symptoms diary (electronic or paper), which is separate to the vaccine reactogenity diaries described above.

7.4.3 Later visits

Follow-up visits will take place according to the visit schedule described in table 4, with their respective windows.

If the participants experience adverse events (laboratory or clinical), for which the investigator (doctor) and/or DSMB president requires more rigorous observation, the participant may be admitted to the hospital for observation and subsequent medical treatment under the care of the hospitalization team.

Table 4 Visiting schedule for participants

Groups 1a and 1b

Visit number _____	Screening	1	2	3	4	5	Test for COVID-19 (S0)	COVID-19 Testing +3-5 days (S3-5) - Only if PCR at S0 is negative	COVID-19 PCR positive + 7 days (S7)
Chronology** (days)	-7	0	28	90	182	364	As required	3-5 days post S0,	7 days after positive PCR for COVID-19
Time window (days)	±7		-7/+14	±7	±14	±30	N/A	±2	±2
Informed consent	X								
Review of contraindications, inclusion and exclusion criteria		X							
Vaccination		X							
Vital signs	X	X	X	X	X	X	X	(X)	X
Ascertainment of adverse events		X	X	X	X	X	X	X	X
COVID Hospital Admission Medical Records Review and Data Collection							If COVID-19 case results in Hospital Admission		

Electronic Diaries of Vaccine Symptoms [$] (subset of volunteers only)		X	X						
Electronic Diaries of COVID-19 Symptoms (all participants in the study that enter the symptomatic pathway)							X		
Clinical history, physical examination		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Biochemistry, hematology (mL)							5	(X) Only if clinically necessary	5
Exploratory immunology (mL)		Up to 50mL	Up to 50mL	Up to 50mL	Up to 50mL	Up to 50mL	10		10
Nose andThroat Swab							X	X [a]	
urinary bHCG (women only)	X	X							
Blood volume per visit		50	50	50	50	10	15		15
Accumulated blood volume [%]		50	100	150	200	250	265		280

(X) = if deemed necessary ^ = Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set of observations will be taken, including respiratory rate and oxygen saturation; ** Chronology is approximate only. The exact

times of the visits refer to the day of recruitment, that is, each visit must take place within the indicated interval of days after recruitment ± time window. % Accumulated blood volume for participants if blood is drawn according to schedule, and excluding any repeat safety blood tests that may be required. [a] A second PCR at 3-5 days post symptoms onset will be done if the first sample is negative. [$] Vaccine reactogenitiicy diaries are applicable to a subset of participants only, all volunteers in the trial who present COVID-19 symptoms will be asked to fill out a COVID-19 symptoms diary.

NB Participants who refuse a booster vaccination should be followed-up as per the schedule of attendances above.

Group 1c and 1d

Attendance Number (boost)	Screening	1 (prime)	2 (booster)	3	4	5	6	COVID-19 Testing (S0)	COVID-19 Testing +3-5 days (S3-5) – Only if PCR at S0 is negative	COVD-19 Positive PCR + 7 days (S7)
Timeline** (days)	-7	0	4-12 weeks post prime	28 post booster	90 post booster	182 post booster	364 post booster	As required	3-5 days post S0	7 days post COVID-19 PCR positive

Attendance Number (boost)	Screening	1 (prime)	2 (booster)	3	4	5	6	COVID-19 Testing (S0)	COVID-19 Testing +3-5 days (S3-5) – Only if PCR at S0 is negative	COVD-19 Positive PCR + 7 days (S7)
Time window (days)	±7		+14	+7	±14	±14	±30	N/A	±2	±2
Informed Consent	X		X[b]							
Review contraindications, inclusion and exclusion criteria		X	X							
Vaccination		X	X							
Vital signs^	X	X	(X)	(X)	(X)	(X)	(X)	X	(X)	X
Ascertainment of adverse events		X	X	X	X	X	X	X	X	X
COVID Hospital Admission Medical Records Review and Data Collection								If COVID-19 case results in Hospital Admission		
Electronic Diaries of Vaccine Symptoms [$]		X	X							

Attendance Number (boost)	Screening	1 (prime)	2 (booster)	3	4	5	6	COVID-19 Testing (S0)	COVID-19 Testing +3-5 days (S3-5) – Only if PCR at S0 is negative	COVD-19 Positive PCR + 7 days (S7)
(subset of volunteers only)										
Electronic Diaries of COVID-19 Symptoms (all participants in the study that enter the symptomatic pathway)								X		
Medical History / Physical Examination		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Biochemistry, Haematology (mL)								5	(X) Only if clinically necessary	5

Attendance Number (boost)	Screening	1 (prime)	2 (booster)	3	4	5	6	COVID-19 Testing (S0)	COVID-19 Testing +3-5 days (S3-5) – Only if PCR at S0 is negative	COVD-19 Positive PCR + 7 days (S7)
Exploratory immunology (mL)		Up to 50mL	Up to 50mL	up to 50	up to 50	up to 50	up to 50	up to 10		up to 10
Nose andThroat Swab								X	X [a]	
Urinary bHCG (women of childbearing potential only)	X	X	X							
Blood volume per visit		50	50	50	50	50	50	up to 15		up to 15
Cumulative blood volume (post boost)[%]		50	100	150	200	250	300	315		330

(X) = if deemed necessary ^ = Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set of observations will be taken, including respiratory rate and oxygen saturation; ** Chronology is approximate only. The exact times of the visits refer to the day of recruitment, that is, each visit must take place within the indicated interval of days after recruitment ±

time window. % Accumulated blood volume for participants if blood is drawn according to schedule, and excluding any repeat safety blood tests that may be required. [a] A second PCR at 3-5 days post symptoms onset will be done if the first sample is negative. [$] Vaccine reactogenicity diaries are applicable to a subset of participants only, all volunteers in the trial who present COVID-19 symptoms will be asked to fill out a COVID-19 symptoms diary. [b] New PIS/ICF only for participants enrolled before protocol 4.0 from groups 1c and 1d

NB Participants who accept to take part in booster dose subgroup will have their schedule of attendances replaced by above schedule. Participants who already attended their D28 visit post prime will be asked to attend a separate visit for their booster.

7.4.4 Symptomatic participants

Participants who become symptomatic during follow-up will be instructed to call the study team, who will then advise on how to proceed with clinical trials for COVID-19, if necessary, according to the trial work instructions. If a participant is symptomatic, COVID-19 testing should take place from enrolment onwards, regardless of time elapsed from vaccination to symptom onset. An isolated fever ≥37.8C is an indication for COVID-19 testing, unless this isolated fever has occurred within 48 hours of vaccination. If fever persists beyond 48 hours post-vaccination, the patient will then be eligible for COVID-19 testing. Participants will receive weekly reminders (for example, text messages - SMS or Whatsapp, surveillance APPs notifications, emailor telephone contacts) to contact the study team if they experience fever or cough or shortness of breath or anosmia/ageusia and if they are hospitalized for any reason. During the test visit for COVID-19, examination with nose/throat swab, collection of blood samples for safety will be performed (complete blood count, biochemistry, PCR and others, if considered clinically relevant) and immunology (serum and others), vital signs and other clinical data. Symptomatic participants can be regularly monitored by telephone, if appropriate. Participants who test positive for COVID-19 will continue to be followed throughout the duration of the trial, including repeated COVID-19 testing visits if symptomatic again during the course of the study and until the end of the trial. New episodes will be considered if they have a minimum 28 days interval between the previous PCR positive result.

If PCR is negative at S0 (first swab), participants will be asked to attend a follow-up visit at 3-5 days post symptoms onset (+2 days) for clinical review and further testing. Participants will be asked to record information on an electronic diary COVID-19 or a printed diary (for use in case the electronic diary presents problems), related symptoms for safety monitoring until symptom resolution or for at least 14 days if symptoms do not resolve before then. Volunteers who have 2 consecutive negative swabs may stop filling out the diaries before symptom resolution or 14 days. Participants who have a positive PCR at S0, will not be required to attend a S3-5 visit, but will be reviewed for safety at 7 days post positive swab. Clinical data, and additional blood samples for safety and immunology purposes will be taken at the S7 visit. Participants who have a positive swab at S3-5 will be reviewed for safety at 7 days post

positive swab where clinical data, and additional blood samples for safety and immunology purposes will be taken. Participants who have 2 negative PCR results from S0 and either a S3-5 visit will not be required to attend for an S7 visit. Closer follow-up and safety monitoring may be carried out by local trial teams if felt this is clinically indicated.

Participants who develop COVID-19 symptoms and have a positive PCR test after the first vaccination can only receive a booster dose after a minimum 4 weeks interval from their PCR positive test, provided their symptoms have significantly improved. The decision to proceed with booster vaccinations in those cases will be at clinical discretion of investigators. Booster vaccinations of participants are allowed to take place beyond the pre-specified 12 weeks window limit if they are required to be delayed due to PCR positivity within the preceding 4 weeks of the scheduled booster dose.

Further details and instructions on the symptomatic pathway can be found on the clinical study plan.

7.4.5 Review of the medical record

With the consent of the participant, the study team will request access to the medical records or send a data collection form to be filled out by the clinical team, in any episodes of medically attended COVID-19 . Investigators will aim to collect clinical data from medical records where participants with suspected COVID-19 have been admitted to Relevant data will be collected to verify the efficacy endpoints and disease enhancement. There is no internationally accepted definition of disease enhancement. Severity between groups will be described and compared. In addition, a proportion of serious illness/all illnesses will be constructed for recipients of the candidate and control vaccine. In case the vaccine induces increased disease, this proportion would be higher in the vaccine than in the control group. These probably include, but are not limited to information about ICU admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, blood test results and images, among others.

7.4.6 Randomization, blinding, and unblinding

Participants will be randomized to investigational vaccine or MenACWY vaccine in a 1:1 allocation ratio, using block randomization of 4 participants. The blinding scheme will be applied to the participants in relation to the arm in which they were allocated. The blinding scheme will not apply to the study team administering the vaccine. Vaccines will be prepared out of the participant's reach and the syringes will be covered with an opaque label that will guarantee the unilateral blinding of the participant.

If a participant's clinical condition requires unblinding, this will be done according to a specific study work instruction and the group allocation will be sent to the attending physician if unblinding is considered relevant and possibly changes treatment clinical.

7.5 Description of ChAdOx1 nCoV-19

ChAdOx1 nCoV-19 vaccine consists of the ChAdOx1 deficient replication monkey adenovirus vector, containing the SARS-CoV-2 structural surface glycoprotein antigen.

7.6 Storage

The vaccine manufactured by Advent is stored at -80 ^{o}C in a safe freezer at the clinics. The vaccine manufactured by Cobra Biologics Ltd is stored at 2-8°C in a secure fridge, at the clinical site. The traceability of the study vaccines will be documented according to the existing standard operating procedure (SOP). Accounting, storage, shipping, and handling of vaccines will be in accordance with relevant SOPs and forms.

7.7 Administration

On the day of vaccination, ChAdOx1 nCoV-19 will be thawed at room temperature and will be administered according to specific assay instructions. The vaccine manufactured by Cobra Biologics is a multi-dose vial which is stored at 2-8 degrees and does not require thawing. If the vaccine is stored outside of 2-8 it must be used within 6 hours. The vaccine will be administered intramuscularly in the deltoid of the non-dominant arm (preferably). All participants will be observed in the unit for a minimum of 15 minutes after vaccination. During the administration of research products, Advanced Life Support medications and

resuscitation equipment will be immediately available for the treatment of anaphylaxis. Vaccination will be performed and IMPs handled according to the relevant SOPs.

7.8 Rationale for selected dose

The dose to be administered in this study was selected based on clinical experience with the adenovirus vector ChAdOx1 expressing different inserts and other similar vectorized adenovirus vaccines (for example, ChAd63).

A first dose escalation study in humans using the ChAdOx1 vector encoding an influenza antigen (FLU004) administered ChAdOx1 NP + M1 safely at doses ranging from 5 x 10^8 to 5 x 10^{10} pv. The subsequent review of the data identified an optimal dose of 2.5 x 10^{10} pv, balancing immunogenicity and reactogenicity. This dose was later administered to hundreds of volunteers in numerous larger phase 1 studies at the Jenner Institute. ChAdOx1 vectorized vaccines have so far shown to be very well tolerated. The vast majority of AEs have been mild to moderate and there have been no SARs to date.

Another monkey adenovirus vector (ChAd63) was safely administered in doses of up to 2 x 10^{11} pv, with an optimal dose of 5 x 10^{10} pv, balancing immunogenicity and reactogenicity.

MERS001 was the first clinical trial of a vector ChAdOx1 expressing the total Spike protein from a separate, but related beta-coronavirus. ChAdOx1 MERS has been administered to 31 participants so far in doses ranging from 5x10^9 pv to 5x10^{10} pv. Despite the greater reactogenicity observed with the dose of 5x10^{10} pv, this dose was safe, with self-limiting AE and without registered SARs. The dose of 5x10^{10} pv was the most immunogenic, in terms of inducing neutralizing antibodies against MERS-CoV using a live virus assay (Folegatti et al. Lancet Infect Dis, 2020, https://doi.org /10.1016/S1473-3099(20)30160-2). Due to the immunology findings and the safety profile observed with a ChAdOx1 vector vaccine against MERS-CoV, the dose of 5x10^{10} pv was chosen for ChAdOx1 nCoV-19.

An analytical comparability assessment of ChAdOx1 nCoV-19 (AZD1222) manufactured by CBF, Advent and Cobra Biologics was conducted using a comprehensive set of physiochemical and biological release and characterization tests. In order to support the analytical comparability assessment, A260 testing of Advent's process (K.0007, K.0008, and K.0009 lots)

was performed, where corrections to the absorbance due to excess polysorbate 80 were made to compensate for polysorbate 80 concentrations above the formulation target of 0.1% (w/v).

Differences in strength related attributes (ie, virus particle concentration, virus genome concentration, and infectious virus concentration) are noted. These differences in strength is further examined for potential impact on clinical dosing. The target clinical dosage of CBF's product is 5×10^{10} viral particles per dose based on vp/mL concentration determined by UV spectroscopy (A260), whereas that of Advent's product is 5×10^{10} viral genome copies per dose based on vg/mL concentration determined by qPCR. The target clinical dosage of Symbiosis' product is $3.5 – 6.5 \times 10^{10}$ viral particles per dose based on the vp/mL concentration determined by A260, with a 0.5 mL dosing volume. This dosing range is based on a target 5×10^{10} viral particles per dose and a ± 30% range to take into account process and method variabilities. The planned clinical dosage of Symbiosis' product is compared to that of CBF and Advent products, the resulting Symbiosis' product dosage at 0.5 mL for lot 20481A is somewhat lower in total viral particle per dose (20% from the lower range limit), slightly higher in total viral genome copies per dose (12% from the higher range limit), and slightly lower in total infectious particle per dose (8% from the lower range limit). These differences are considered to be comparable to or within the variabilities from the analytical methods used in concentration determination (A260, qPCR, and infectivity) and the dosing volumes during clinical administration. In summary, with a 0.5 mL dosing volume for Symbiosis' product, strength difference from CBF and Advent products is not expected to have significant clinical impact in terms of reactogenicity and immunogenicity/efficacy

Table 12 Clinical Strengths of ChAdOx1 nCoV-19 (AZD1222) Drug Product

Strength Attribute	CBF		Advent			Cobra
	Lot 02P20-01	Lot 02P20-02	Lot K.0007	Lot K.0008	Lot K.0009	Lot 20481A
Concentration						
Virus particle concentration (A_{260}) (vp/mL)	1.49×10^{11}	1.22×10^{11}	3.12×10^{11}	3.16×10^{11}	2.45×10^{11}	0.8×10^{11}

Table 12 Clinical Strengths of ChAdOx1 nCoV-19 (AZD1222) Drug Product

Strength Attribute	CBF		Advent			Cobra
	Lot 02P20-01	Lot 02P20-02	Lot K.0007	Lot K.0008	Lot K.0009	Lot 20481A
Virus genome concentration (qPCR) (vg/mL)	1.7×10^{11}	Not tested	1.7×10^{11}	2.1×10^{11}	1.4×10^{11}	1.3×10^{11}
Infectious particle concentration (ifu/mL) [a]	2.6×10^{9}	Not tested	2.9×10^{9}	3.0×10^{9}	2.4×10^{9}	1.3×10^{9}
Target Clinical Dosage						
Equivalent DP volume per dose (mL)	0.34	0.41	0.294	0.235	0.356	0.50
Dosing of virus particle (vp/dose)	5.1×10^{10}	5.0×10^{10}	9.2×10^{10}	7.4×10^{10}	8.7×10^{10}	4.0×10^{10}
Dosing of viral genome (vg/dose)	5.8×10^{10}	NA	5.0×10^{10}	4.9×10^{10}	5.0×10^{10}	6.5×10^{10}
Dosing of infectious particle (ifu/dose)	8.8×10^{8}	NA	8.5×10^{8}	7.1×10^{8}	8.5×10^{8}	6.5×10^{8}

ifu = infectious units; NA = not applicable; vp = virus particle; vg = virus genome

[a] Testing performed using the Advent infectivity assay.

7.9 Environmental contamination control (GMO)

The possibility of environmental contamination with genetically modified organisms (GMOs) will be appropriately controlled. The study will be performed in accordance with the relevant local regulations regarding GMO products, following the recommendations of CTNBio. The approved SOPs will be followed to minimize the spread of the recombinant vector vaccine virus in the environment. GMO residues will be inactivated according to the approved SOPs. All material used during vaccination and by vaccination personnel will be autoclaved and incinerated later.

7.10 Control vaccine

Participants who are allocated to control groups will receive an injection of the MenACWY vaccine instead of ChAdOx1 nCoV-19. Either of the two MenACWY vaccines of authorized quadrivalent protein-polysaccharide conjugate – will be used, i.e.:

- Nimenrix (Pfizer). The authorized dosage of this vaccine for those over 6 months of age is a single intramuscular dose (0.5 mL), containing 5 mcg each of a polysaccharide from group A, C, W and Y of *Neisseria meningitidis*, each conjugated with 44 mcg of tetanus toxoid carrier protein.
- Menveo (Glaxo Smith Kline). The authorized dosage of this vaccine for those aged 2 years or older is a single intramuscular dose (0.5 mL), containing
    - 10 mcg of group A meningococcal polysaccharide, conjugated with 16.7 to 33.3 mcg of CRM protein$_{197}$ of *Corynebacterium diphtheriae*.
    - 5 mcg of group C meningococcal polysaccharide, conjugated with 7.1 to 12.5 mcg of CRM protein$_{197}$ of *Corynebacterium diphtheriae*.
    - 5 mcg of group W meningococcal polysaccharide, conjugated with 3.3 to 8.3 mcg of CRM protein$_{197}$ of *Corynebacterium diphtheriae*.
    - 5 mcg of group Y meningococcal polysaccharide, conjugated with 5.6 to 10.0 mcg of CRM protein$_{197}$ of *Corynebacterium diphtheriae.*

The summary of product characteristics for both vaccines allows the administration of a booster dose, if indicated by ongoing risk. Prior administration of a vaccine (or a quadrivalent simple meningococcal polysaccharide vaccine in groups A, C, W and Y) is not a contraindication to receiving another vaccine in this study.

The masking of the participants regarding the injection they are receiving will be maintained.

A vaccination accounting record from MenACWY will be maintained at each study site.

MenACWY will be stored in a locked (or controlled access) refrigerator (2 °C to 8 °C) at the research site, according to the package insert.

7.11 Placebo

Participants who were allocated to the control group will receive a placebo injection of 0.9% saline instead of MenACWY at the time of boosting. The volume and site of injection will be the same as for the intervention arm and participants will be blinded as to which injection they are receiving. A vaccine accountability log of the saline will be maintained at each trial site, similar to what is done for the study intervention (ChAdOx1 nCoV-19) and the comparator used as the prime dose (MenACWY).

7.12 Compliance with the investigational treatment

All vaccines will be administered by the research team and registered with the CRF. The study medication will not be in the participant's possession at any time and, therefore, compliance will not be a problem.

7.13 Investigational treatment accounting

IMP accounting and control vaccines will be performed in accordance with the relevant SOPs.

7.14 Concomitant medication

As established by the exclusion criteria, participants cannot be enrolled in the study if they have received: any vaccine within 30 days prior to enrollment or if any other vaccine is expected to be administered within 30 days after each vaccination, any research product within 30 days prior to recruitment or if administration is planned during the study period, or if there is any chronic use (> 14 days) of any immunosuppressive medication in the 6 months prior to enrollment or if administration is planned at any time during the study period (topical steroids are allowed).

Participants who make continuous use of oral anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or new oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban), and/or who received immunoglobulins and/or any blood products in the three months prior to the planned administration of the candidate vaccine, will be excluded from this study, according to the exclusion criteria.

Participants will be advised to take paracetamol, unless contraindicated (in which case they will be excluded from the study), for 24 hours after vaccination. Paracetamol will be stored according to the package insert. There will be no additional labeling beyond its authorized packaging.

7.15 Provision of treatment for controls

If the efficacy of the candidate vaccine is proven, after analysis of the primary endpoint and approval by the DSMB (Data and Safety Monitoring Committee), as established in the study protocol, the sponsor will make the candidate vaccine available to participants in the research allocated to the comparator group (MenACWY vaccine).

8 SAFETY ASSESSMENT

Safety will be assessed by the frequency, incidence and nature of the Aes and SAE emerging during the study.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any unexpected medical occurrence in a participant, which can occur during or after the administration of an IMP and does not necessarily have a causal relationship to treatment. An AE can therefore be any unfavorable and unintended sign (including any clinically significant abnormal finding or change from baseline), symptom or disease temporally associated with study treatment, even if it is considered to be related to study treatment or not.

8.1.2 Adverse Reaction (AR)

An AR is any unexpected or unintended response to an IMP. This means that the causal relationship between the IMP and the AE is at least reasonable, that is, the relationship cannot be ruled out. All cases judged by the medical investigator to have a reasonable causal relationship with an IMP (that is, possibly, probably, or definitely related to an IMP) will qualify as AR.

Adverse events that may be related to the IMP are listed in the Investigator's Brochure for each product.

8.1.3 Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following endpoints, considered or unrelated to the study treatment.

- Death;
- Life-threatening event (i.e., the participant was, in the Investigator's view, at immediate risk of death from the event);
- Persistent disability or disability or significant disability (i.e., substantial disruption of the ability to perform normal life functions);
- Hospitalization or extension of existing hospitalization, regardless of length of stay, even if it is a precautionary measure for continuous observation;
    - Note: Hospitalization (including hospitalization or outpatient hospitalization for an elective procedure) for a pre-existing condition that has not unexpectedly worsened does not constitute a serious AE.
- An important clinical event (which cannot cause death, be life-threatening or require hospitalization) that may, based on appropriate clinical criteria, harm the participant and/or require medical or surgical treatment to avoid one of the outcomes listed above. Examples of such clinical events include an allergic reaction that requires intensive treatment in an emergency room or clinic, blood dyscrasias or seizures that do not result in hospitalization;
- Congenital anomaly or birth defect.

8.1.4 Serious Adverse Reaction (SAR)

A serious AE that, in the opinion of the investigator or sponsor, is believed to be possibly, probably, or definitely related to IMP or any other treatment of the study, based on the information provided.

8.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SAR, whose nature and severity are not consistent with the information on the drug in question set out in the IB.

8.2 Expectation

IMP-related SAE is not expected in this study. All SARs will therefore be reported as SUSAR.

8.3 Predicted/expected adverse reactions:

Predictable/expected AR after vaccination with ChAdOx1 nCoV-19 include pain at the injection site, tenderness, erythema, heat, swelling, induration, itching, myalgia, arthralgia, headache, fatigue, fever, feverish feeling, chills, malaise, and nausea.

8.4 Adverse Events of Special Interest

The potentiation of the disease after vaccination with ChAdOx1 nCoV-19 will be monitored. Serious COVID-19 disease will be defined by clinical criteria. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These probably include, but are not limited to oxygen saturation, need for oxygen therapy, respiratory rate, need for ventilatory support, results of blood tests and images, among other clinically relevant parameters. As there is no internationally accepted definition of ADE, differences in the severity of the disease between the groups will be described. If the proportion of serious illness is similar between the two groups, this would support the lack of effectiveness and not the improvement of the illness.

Acute respiratory failure, pneumonitis, acute cardiac injury, arrhythmia, septic shock syndrome and acute kidney injury related to COVID-19 disease will be monitored based on the review of medical records of hospitalized participants.

Eosinophilia as a marker of deviated Th2 responses will be monitored routinely in participants who attend their study visits and follow-up of COVID-19. Marked eosinophilia of ≥ 1.5 $x10^9$/L will be reported as SAE.

AESI relevant to vaccination in general will also be monitored, such as: generalized seizure, Guillain-Barre Syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), Thrombocytopenia, Anaphylaxis, Vasculitides, in addition to the requested serious Aes.

8.5 Causality

For each AE, an assessment of the relationship between the event and the administration of the vaccine will be performed by the clinician delegated by the IC. An interpretation of the causal relationship of the treatment with the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of vaccine therapy. Alternative causes of AE will be considered and investigated, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination. The causality assessment will take place during planned safety reviews and in the final safety analysis, except for SAEs, which must be designated immediately by the investigator reporting the events.

0	Not related	No temporal relationship with the product under study ***and*** alternative etiology (clinical, environmental, or other treatments) ***and*** Does not follow known pattern of response to the product under study
1	Unlikely	Unlikely temporal relationship with the product under study ***and*** alternative etiology (clinical, environmental, or other treatments) ***and*** It does not follow the typical or plausible pattern of response to the product under study.
2	Possible	Reasonable temporal relationship with the product under study; ***or*** Event not produced immediately by clinical, environmental, or other treatments; ***or*** Response pattern similar to that seen with other vaccines
3	Probable	Reasonable temporal relationship with the product under study; ***and*** Event not produced immediately by clinical, environmental, or other treatments ***or*** Known response pattern seen with other vaccines

4	Definitive	Reasonable temporal relationship with the product under study; ***and*** Event not produced immediately by clinical, environmental, or other treatments; ***and*** Known response pattern seen with other vaccines

Table 5. Guidelines for assessing the relationship between vaccine administration and an AE.

8.6 Reporting procedures for all adverse events

All local and systemic AE that occur within 28 days after vaccination observed by the Investigator or reported by the participant, whether or not attributed to the study medication, will be recorded by the participants in the Diary of Symptoms and by the Investigators in the study CRF. All Aes that result in the withdrawal of a participant from the study will be followed up until a satisfactory resolution occurs, or until a causality unrelated to the study is assigned (if the participant agrees to do so). SAE and Adverse Events of Special Interest will be collected throughout the study period.

8.7 Evaluation of severity

The severity of adverse events will be assessed according to toxicity rating scales adapted from the FDA for healthy volunteers recruited in preventive vaccine clinical trials, listed in the specific study work instructions and tables 6-8 below.

Adverse Event	Grade	Intensity
Injection site pain	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that impairs daily activity
	4	Hospitalization or A/E visit
Sensitivity	1	Mild discomfort to touch

	2	Discomfort with movement
	3	Significant discomfort at rest
	4	Hospitalization or A/E visit
Injection site erythema	1	2.5 – 5 cm
	2	5.1 – 10 cm
	3	>10 cm
	4	Exfoliating dermatitis or necrosis
Injection site induration/swelling	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 – 10 cm or interferes with activity
	3	> 10 cm or impairs daily activity
	4	Necrosis

Table 6. Severity criteria for local adverse events

*erythema ≤2.5cm is an expected consequence of skin puncture and therefore will not be considered an adverse event

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (serious)	Grade 4 Potentially fatal
Fever (oral)	38, 0°C- 38, 4°C	38.5°C – 38.9°C	39.0°C – 40°C	> 40°C
Tachycardia (bpm)*	101 – 115	116-130	>130	A/E visit or hospitalization for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A/E visit or hospitalization 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	>1100	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

Table 7. Severity rating criteria for physical observations (applies to adults only).

*Measured after ≥10 minutes at rest ** When the resting heart rate is between 60 to 100 beats per minute. Use the clinical criterion when characterizing bradycardia among some populations of healthy subjects, for example, conditioned athletes. *** Only if symptomatic (for example, dizziness/vertigo)

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (<48 hours); There was no interference with routine activity; no medical treatment/therapy was needed
GRADE 2	Moderate: Mild to moderate limitation in routine activity – some assistance may be required; minimal medical treatment/therapy was required or none
GRADE 3	Serious: Marked limitation in routine activity, some assistance is usually required; medical treatment/therapy was required.
GRADE 4	Potentially fatal: requires assessment in A/E or hospitalization

Table 8. Severity classification criteria for local and systemic AE.

8.8 Serious AE reporting procedures

To comply with the rules in force on reporting SAE to regulatory authorities, the event will be accurately documented and the notification deadlines respected. Serious adverse events will be reported on the SAE forms to members of the study team as soon as the Investigators become aware of their occurrence. Copies of all reports will be forwarded for review by the Principal Investigator (as Sponsor's representative) within 24 hours after the Investigator becomes aware of the alleged SAE. The DSMB will be notified of SAE that are considered to be possibly, probably or definitely related to the study treatments; the DSMB president will be notified immediately (within 24 hours) as soon as the Sponsor become aware of the occurrence. Normally, SAE will not be reported immediately to the Ethics Committee, unless there is a clinically significant increase in the rate of occurrence, an unexpected endpoint, or a new event that may affect the safety of study participants, at the discretion of the Principal Investigator and/or DSMB. In addition to the expedited report above, the Investigator will include all SAE in the annual Development Safety Update (DSUR) report. In addition, all local reporting requirements apply.

Cases falling under the Hy's Law should be reported as SAEs. A Hy's Law Case is defined by FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (2009). Any study participant with an increase in Aspartate Aminotransferase (AST) or Alanine

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

8.9 Procedures for reporting SUSARs

All SUSARs will be communicated by the sponsor's delegate to the Competent Authority and 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.

8.10 Safety assessments

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, safety, and efficacy data every 4-8 weeks and/or as needed. The DSMB will make recommendations regarding the conduct, continuation or modification of the study.

The Sponsor may put the study on hold and pause recruitment if SUSARs reported in other international trials within the ChAdOx1 nCoV-19 programme are considered to pose a significant safety concern to all participants in the programme. The DSMB will review such events and will make a recommendation as to whether or not recruitment can continue. Study procedures other than vaccinations (e.g. safety follow-ups, immunogenicity assessments, and COVID-19 testing procedures) will continue as normal, regardless of length of study pause.

8.11 Data Safety Monitoring Committee

The Data Safety Monitoring Committee that is in force for the British studies COV001 and COV002 will also oversee this study and review the safety data for this study.

At least one properly qualified clinician/scientist from each international study site will be invited to attend meetings of the existing trial's DSMB.

The DSMB president can be contacted for independent advice and review by the Researcher or study sponsor in the following situations:

- Follow-up on any SAE considered possibly, probably or definitely related to a study treatment;
- Any other situation in which the Investigator or Study Sponsor feels that independent advice or review is important.

The DSMB will review the SAE considered to be possibly, probably, or definitely related to the study treatments. The DSMB will be notified within 24 hours after the Sponsor become aware of the occurrence. The DSMB can recommend stopping recruitment into the study, if necessary, to follow up on an SAE related to a study treatment. It will also recommend restarting the study, when appropriate, following review of such safety events (i.e. SUSARs associated with ChAdOx1 nCoV-19).

The DSMB will review safety data from volunteers aged 56 and above recruited as part of the COV002 UK study. Recruitment of older adults will only be allowed following advice from the DSMB.

9 STATISTICS

9.1 Description of statistical methods

Both a fully detailed study level statistical analysis plan (SAP) as well as a separate Statistical Analysis Plan for the Marketing Authorisation Application (MAA SAP) will be written and signed off before any interim data analyses are conducted.

The data from this study will be included in prospective pooled analyses of studies for efficacy and safety of ChAdOx1 nCoV-19 to provide greater precision of both efficacy and safety outcomes

9.2 Efficacy Outcomes

The primary efficacy endpoint is PCR positive symptomatic COVID-19.

This is defined as a participant with a PCR+ swab and at least one of the following symptoms: cough, fever > 37.8, shortness of breath, anosmia, or ageusia.

Where possible, sensitivity analyses will be conducted using common alternative definitions of virologically-confirmed COVID-19 disease, including those in use in other phase 3 protocols (including but not limited to: USA AstraZeneca phase 3 trial, South Africa COV005 trial, WHO solidarity trial, CEPI definition). This will aid in comparisons between various studies and meta-analyses. These alternative definitions will be detailed in the statistical analysis plan as exploratory analyses.

Due to the vaccine-induced disease mitigation potential, the inclusion of all positive PCR infections as a primary result may lower the vaccine's estimated effectiveness and reduce its accuracy. COVID-19 disease, positive for PCR and symptomatic, is a more specific primary outcome and may lead to an earlier demonstration of vaccine efficacy, although it includes fewer cases.

Regarding the differentiation of ADE and the lack of effectiveness of the vaccine: there is no internationally accepted definition of ADE. Differences in disease severity between groups will be described. If the proportion of serious illness is similar between the two groups, this would support the lack of effectiveness and not the improvement of the illness.

9.2.1 Efficacy

The primary and secondary analysis will be conducted on participants who are seronegative at baseline. A sensitivity analysis will be conducted including all participants regardless of baseline serostatus.

The screening of the participants will be based on the serological exam with IgG antibodies negative for SARs-CoV-2. However, for the analysis of the primary outcome, a validated assay detecting antibodies against SARS-CoV-2 nucleoprotein will be used to exclude any remaining participants who were seropositive at baseline.

Analysis of the primary endpoint will be computed as follows:

1. **Efficacy of two doses of ChAdOx1 nCoV-19**. Participants will be included who received two doses of ChAdOx1 nCoV-19. Events will be included if they occurred more than 14 days after the booster dose.

   Participants who are symptomatic up to 14 days after the second dose of vaccine will be excluded from the analysis. In addition, those with less than 14 days follow up post-second dose will also be excluded.

Secondary analyses of the primary outcome:

2. **Efficacy of at least one dose of vaccine**. Cases occurring more than 21 days after the first vaccination will be included.

   Participants who are symptomatic up to 21 days from vaccination will still attend site for PCR testing and blood samples but will be excluded from the analysis as these participants may have been exposed to SARS-CoV-2 prior to vaccination or before the immune system has had time to mount a response to the vaccine. In addition, those with less than 21 days follow up post-vaccination will also be excluded.

The proportions of participants meeting the primary outcome definition will be compared between groups of recipients of ChAdOx1 nCoV-19 and MenACWY using a Poisson regression model with robust variance (Zou 2004). The model will contain terms including treatment group, and age group at randomization if there is a sufficient sample size within each age category. The logarithm of the period at risk for primary endpoint will be used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occur. Vaccine efficacy (VE) will be calculated as (1 – RR) x 100%, where RR is the relative risk of symptomatic infection (ChADOx1 nCoV-19: Control) and 95% confidence intervals will be presented.

If the Poisson regression model with robust variance fails to converge, the exact conditional method for stratified poisson regression will be used.

The cumulative incidence of symptomatic infections will be presented using the Kaplan-Meier method.

Secondary efficacy endpoints will be analysed in the same way as the primary efficacy endpoint.

Analyses will conducted for all adults combined as well as conducting analyses stratified by age cohorts.

All data from participants with PCR-positive swabs will be assessed for inclusion in the efficacy analyses by two blinded assessors who will independently review each case according to pre-specified criteria as detailed in the statistical analysis plan, to classify each for inclusion in the primary and secondary outcomes. A separate CRF will be designed for this purpose.

All PCR-positive results will be assessed for the primary outcome, including those with symptoms who were swabbed by trial staff and other potential sources of information such as health-care workers who are tested at their workplace as either a routine test procedure or due to developing symptoms.

9.2.2 Safety and Reactogenicity

For each group, the counts and percentages of each local and systemic adverse reaction requested from the daily cards, and all unsolicited AEs and SAEs will be presented..

9.2.3 Immunogenicity

Highly deviated antibody data will be transformed logarithmically before analysis. The geometric mean of the concentration and the associated 95% confidence interval will be summarized for each group at each timepoint, calculating the anti-log of the average difference of the logarithmically transformed data.

The geometric means of concentration on day 28 and the proportion of participants with serum conversion to S-spike protein from day 0 to day 28 will be computed. Comparisons between the ChAdOx1 nCoV-19 vaccine and control groups will be made using a Mann Whitney U test due to the low titers expected in the control group that will cause non-normal distribution.

9.3 Subgroup analyses

Subgroup comparisons of efficacy, and safety will be conducted by incorporating vaccine-group by subgroup interaction terms into appropriate regression models. Subgroup comparisons will only be conducted if there are at least 5 cases in all subgroups.

Comparisons will include:

1. Males vs females
2. Age (18 to 55 years vs 56-<70 years vs 70+ years)
3. Seropositive to S-spike or non-spike proteins at baseline vs not seropositive
4. Health care workers and highly-exposed participants versus others
5. Ethnicity
6. BMI (< 30 / >= 30 kg/m2)

9.4 Number of Participants

The research sites will include up to 10,300 participants (with a margin of 1%).

9.5 Interim and primary analyses of the primary outcome

It is planned that the primary evidence of efficacy and safety for the ChADOx1 nCoV-19 vaccine will be based on global analyses utilizing studies COV001 (the UK P1/2 study), COV002 (the UK P2/3 study), COV003 (the Brazil P3 study) and COV005 (the South Africa P1/2 study) including a pooled analysis across the studies. As such the interim and primary analyses for the primary outcome will be based on cases accumulated across multiple studies, details of which will be specified within the MAA SAP rather than for each individual study. Interim and primary data cuts from this study will therefore be carried out to support the pooled analysis.

The global MAA SAP allows for interim and primary analyses to be conducted once sufficient eligible cases have accumulated, where the overall type 1 error is controlled at the 5% level using a flexible alpha–spending approach that accounts for the incorporation of data from this study into pooled interim analyses under the global MAA SAP.

Evidence of efficacy will be determined if the lower bound of the multiplicity adjusted confidence interval is greater than a 20% threshold. The primary analysis will have approximately 90% power assuming a vaccine efficacy of 60%. A flexible alpha spending approach will be implemented to allow an earlier primary analysis in the situation where accumulation of eligible cases were lower than expected.

Evidence of efficacy at an interim or primary analysis of pooled data will not be considered a reason to stop the trial, but instead will be interpreted as early evidence of efficacy. However if an interim analysis demonstrates evidence of efficacy then a study level analysis according to the study SAP may be used to support study level evidence of efficacy.

9.6 Final Analysis

A final analysis will be conducted at the end of the study. The final study-specific analysis will incorporate all data from the study, including data that has previously contributed to global efficacy estimates under the pooled analysis strategy. The final analysis will be considered a supportive analysis to the global efficacy analysis.

9.7 Inclusion in the analysis

All vaccinated participants will be included in the analysis, unless otherwise specified

9.8 Data and Safety Monitoring Committee

The independent DSMB will meet regularly to review safety data from all available studies of ChAdOx1 nCoV-19. Additionally the independent DSMB will make recommendations based on the interim analyses to assess evidence of efficacy. The DSMB works according to the DSMB statute and/or follows the trigger points of the different protocols of the global clinical development plan, allowing the different steps to be achieved with respect to safety.

10 DATA MANAGEMENT

10.1 Data processing

The Principal Investigator will be responsible for all data that accumulates in the study.

All study data, including the participant's diary, will be recorded directly in an Electronic Data Capture (EDC) system (for example, OpenClinica, REDCap or similar) or in a paper source document for later insertion in EDC if the direct entry is not available. This includes safety data, laboratory data and endpoints data. All documents will be stored securely and in confidential conditions.

Participants will be identified by a unique number and code specific to the study in any database. The name and any other identifying details will NOT be included in any electronic study data file.

The EDC system (CRF data) uses a relational database (MySQL/PostgreSQL) through a secure web interface with data checks applied during data entry to ensure data quality. The database includes a full set of features that comply 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 databases and the web server will be hosted on servers that are kept secure. The backups will be stored according to the IT department's schedule on a daily, weekly, and monthly basis and retained for one month, three months and six months, respectively. IT servers provide a stable, secure, well-maintained, high-capacity data storage environment. RedCap and OpenClinica are widely used, powerful, reliable and well supported systems. Access to the study database will be restricted to members of the study team with a username and password.

10.2 Record keeping

Investigators will maintain adequate medical and research records for this trial, in accordance with the GCP and regulatory and institutional requirements to protect the confidentiality of participants. The principal investigator, sub investigators and clinical research nurses will have access to the records. Investigators will allow Sponsor's authorized representatives, as well as ethical and regulatory agencies, to examine (and when required by applicable law, copy)

clinical records for the purposes of quality assurance reviews, audits and evaluation of the safety and progress of the study.

10.3 Source data and technical data sheets (CRFs)

All information required by the protocol will be collected in CRFs designed by the Sponsor. All source documents will be archived. The source documents are documents, data and original records from which the participant's CRF data is obtained.

For this study, these will include, but are not limited to, the Informed Consent Form, blood test results, and response letters from the general practitioner, laboratory records, diaries, medical records and correspondence. In this study, this will include, but is not limited to, medical history, medication records, vital signs, physical exam records, urine tests, blood test results, adverse event data and vaccine details. All source data and CRFs of the participants will be safely stored.

Where data are recorded directly onto the electronic data system these will be considered source documents. However, if local regulations require these electronic case report forms to be printed, they will be printed and filed in the participants

10.4 Data protection

The study protocol, documentation, data, and all other information generated will be kept strictly confidential. No information about the study or its data will be disclosed to unauthorized third parties without prior written approval from the sponsor.

Identifiable details, such as contact details, will be stored for a minimum of 5 years. Unidentified search data may be stored indefinitely. If participants agree to be contacted for future research, information about their Informed Consent Form will be recorded, retained and stored securely and separately from the research data.

10.5 Data quality

The data collection tools will undergo proper validation to ensure that the data is collected accurately and completely. The datasets provided for analysis will be subject to quality control processes to ensure that the data analyzed is a true reflection of the source data.

Study data will be managed in accordance with local data management SOPs. If an additional study of specific processes is necessary, an approved Data Management Plan will be implemented.

10.6 Archiving

Study data can be stored electronically on a secure server, and paper notes will be kept in a filing cabinet locked with a key in the site. All essential documents will be retained for a minimum of 5 years after the end of the study. The need to store study data for a longer time in relation to vaccine authorization will be subject to continuous review. For effective vaccines that can be authorized, we can safely store research data in the sites at least 15 years after the study ends, subject to adjustments to clinical trial regulations. Where participants' relevant bank details will be stored for 7 years, in accordance with the sites's financial policy. Unidentified search data may be stored indefinitely.

11 QUALITY CONTROL PROCEDURES AND QUALITY ASSURANCE

11.1 Investigator's Procedures

The approved standard operating procedures (SOPs) will be used in the research sites and in all laboratory centers.

11.2 Monitoring

Regular monitoring will be performed in accordance with the GCP by the monitor. When proceeding in accordance with the written SOPs, the monitor will verify that the clinical trial is performed and the data are generated, documented and reported in accordance with the protocol, GCP and applicable regulatory requirements. The sites will provide direct access to all data/documents and source reports related to the study for the purpose of monitoring and auditing by the Sponsor and to inspect by local and regulatory authorities.

11.3 Deviation from the protocol

Any deviations from the protocol will be documented on a protocol deviation form and filed in the study's master file.

Each deviation will be assessed for its impact on the safety of the participants and the conduct of the study. Significant deviations from the protocol will be listed at the end of the study report.

11.4 Audit and inspection

The QA manager conducts internal systems-based audits to verify that trials are being conducted in accordance with local procedures and in accordance with study protocols, departmental SOPs, GCP and applicable regulations.

The Sponsor, the study sites, the Research Ethics Committee, and the Regulatory Agencies may conduct audits to ensure compliance with the appropriate protocol, GCP, and regulations.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Declaration of Helsinki

Investigators will ensure that this study is being conducted in accordance with the principles of the current revision of the Declaration of Helsinki.

12.2 Guidelines for good clinical practices

The Investigator will ensure that this trial is being conducted in accordance with the relevant standards and good clinical practices.

12.3 Ethical and regulatory approvals

After the Sponsor's approval, the Protocol, the Informed Consent Form, the participant's information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities and host institutions for written approval. No changes to this protocol will be made without consulting the Sponsor and without its consent.

The Investigator is responsible for ensuring that changes in an approved study, during the period for which the approval of the Research Ethics Committee and Regulatory Agency has

already been given, are not initiated without their review and approval, except to eliminate immediate risks apparent to the subject (i.e., as an urgent safety measure).

12.4 Volunteers confidentiality

The study will comply with the EU General Data Protection Regulation (GDPR) and the UK Data Protection Act of 2018, as well as local data protection regulations, which require data not to be identified, whenever and when practical to do so. The processing of participants' personal data will be minimized by using only a single study number of the participant in all study documents and in any electronic database, with the exception of informed consent forms and participant identification records. All documents will be stored securely, and accessible only by study staff and authorized personnel. The study team will protect the privacy of participants' personal data. A separate confidential file containing personally identifiable information will be stored in a secure location in accordance with current data protection legislation. The photographs taken at the vaccination sites (if necessary, with the written and informed consent of the participant) will not include the face of the participant and will be identified by the date, study code and the subject's unique identifier. Once developed, the photographs will be stored as confidential records, as above. This material can be shown to other professionals, used for educational purposes, or included in a scientific publication.

If participants are diagnosed with COVID-19 during the course of the study, the study team will pass on their details to the local health protection team, if necessary, in accordance with the relevant notifiable disease legislation. Samples collected for the purpose of diagnosing COVID-19 can be sent to reference laboratories together with your personal data. This would be in line with national guidance and the policy of sending samples for testing in reference laboratories.

13 FUNDING AND INSURANCE

13.1 Funding

University of Oxford and external donors (Fundação Lemann, Fundacao Brava, Fundacao Telles, Instituto D'or de Ensino e Pesquisa and AstraZeneca Brasil).

13.2 Insurance

Global Insurance

Insured Party: University of Oxford

Exclusive market reference B 1526 CSHLC1900662

Research participants who suffer direct damage as a result of their participation in the study are entitled to claim compensation from the sponsor and the institutions involved in this study, covered by global and local insurance for research protocols.

13.3 Publication Policy

Researchers will be involved in reviewing draft manuscripts, abstracts, press releases and any other publications resulting from the study. The study data can also be used as part of a doctoral or master's thesis.

14 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR INTELLECTUAL PROPERTY GENERATION

The IP title generated by University employees belongs to the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations. Researchers in this study can benefit from the University's royalty-sharing policy if new intellectual property is generated from the study. Several investigators are applicants or co-inventors of past patent registrations or patents related to ChAdOx1 vaccines. University of Oxford, which is a partner of Oxford University Hospitals NHS Foundation Trust at the NIHR Oxford Biomedical Research Centre, is committed to translational progress and the commercial development of healthcare products potentially

serving medical and global healthcare needs, and works and will work with business partners for these purposes.

References

1 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).

2 Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England)* **395**, 565-574, doi:10.1016/S0140-6736(20)30251-8 (2020).

3 Li, F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annual review of virology* **3**, 237-261, doi:10.1146/annurev-virology-110615-042301 (2016).

4 Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, doi:10.1038/s41586-020-2012-7 (2020).

5 Alharbi, N. K. *et al.* ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice. *Vaccine* **35**, 3780-3788, doi:10.1016/j.vaccine.2017.05.032 (2017).

6 Tseng, C. T. *et al.* Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PloS one* **7**, e35421, doi:10.1371/journal.pone.0035421 (2012).

7 Weingartl, H. *et al.* Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *Journal of virology* **78**, 12672-12676, doi:10.1128/jvi.78.22.12672-12676.2004 (2004).

8 Liu, L. *et al.* Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI insight* **4**, e123158, doi:10.1172/jci.insight.123158 (2019).

9 Agrawal, A. S. *et al.* Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. *Human vaccines & immunotherapeutics* **12**, 2351-2356, doi:10.1080/21645515.2016.1177688 (2016).

10 Munster, V. J. *et al.* Protective efficacy of a novel simian adenovirus vaccine against lethal MERS-CoV challenge in a transgenic human DPP4 mouse model. *NPJ vaccines* **2**, 28, doi:10.1038/s41541-017-0029-1 (2017).

11 Alharbi, N. K. *et al.* Humoral Immunogenicity and Efficacy of a Single Dose of ChAdOx1 MERS Vaccine Candidate in Dromedary Camels. *Scientific reports* **9**, 16292, doi:10.1038/s41598-019-52730-4 (2019).

12 Antrobus, R. D. *et al.* Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. *Mol Ther* **22**, 668-674, doi:10.1038/mt.2013.284 (2014).

13 Coughlan, L. *et al.* Heterologous Two-Dose Vaccination with Simian Adenovirus and Poxvirus Vectors Elicits Long-Lasting Cellular Immunity to Influenza Virus A in Healthy Adults. *EbioMedicine*, doi:https://doi.org/10.1016/j.ebiom.2018.02.011 (2018).

14 Wilkie, M. *et al.* A phase I trial evaluating the safety and immunogenicity of a candidate tuberculosis vaccination regimen, ChAdOx1 85A prime – MVA85A boost in healthy UK adults. *Vaccine* **38**, 779-789, doi:10.1016/j.vaccine.2019.10.102 (2020).

15 Modjarrad, K. MERS-CoV vaccine candidates in development: The current landscape. *Vaccine* **34**, 2982-2987, doi:10.1016/j.vaccine.2016.03.104 (2016).

16 She, J., Liu, L. & Liu, W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol*, doi:10.1002/jmv.25807 (2020).

17 Dong, Y. *et al.* Epidemiology of COVID-19 Among Children in China. *Pediatrics*, doi:10.1542/peds.2020-0702 (2020).

18 Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*, doi:10.1111/apa.15270 (2020).

19 Zimmermann, P. & Curtis, N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. The Pediatric Infectious Disease Journal 39, 355-368, doi:10.1097/inf.0000000000002660 (2020).

APPENDIX A: AMENDMENTS HISTORY

Amendment No.	Version of the protocol No.	Date issued	Amendment author(s)	Details of Amendments made
N/A	1.0	May 27th, 2020	N/A	First version
1	1.0	May 31st, 2020	Sue Ann & Lily	Ethical requirements of the Brazilian Ethics Committee/CONEP system
2	2.0	June 10th, 2020	Pedro Folegatti	Ethical requirements of the English Ethics Committee (OxTREC) – updated data according to IB 6.0
3	3.0	June 14th, 2020	Sue Ann & Lily, Peter O'Reilly	ANVISA requests, updating of participating centers, electronic ICF, correction of sample size and exclusion of assistance to pregnant partners of research participants.
4	4.0	July 28th, 2020	Pedro Folegatti, Peter O'Reilly, Susan Tonks Merryn Voysey	Added booster groups. Removed requirement for negative COVID-19 serology prior to enrollment; Added details on COBRA batch; clarified process around data entry/source data; updated statistical analysis section to reflect

				changes in trial procedures (e.g. addition of booster doses); added cellular immune responses in a subset of individuals as exploratory objective; added clarifications to swabbing procedures; added Hy's law cases as part of the requirement for SAE reporting; added clarifications to DSMB composition and their role in advising stopping recruitment.
5	4.1	August 11th, 2020	Pedro Folegatti	Clarify boosting dose windows; include placebo as comparator; update abbreviations; clarify the cellular immune response volunteers selection; clarify study groups; clarify non-hospitalized volunteers shall not take part in covid-19 treatment clinical trials; clarify serology criteria before/after protocol 4.0; update table 4
6	5.0	August 16th, 2020	Pedro Folegatti, Merryn Voysey	Increased sample size to up to 10,000; Changes to statistical analysis section, including changes to how the primary endpoint will be analysed; changes to the symptomatic pathway;

				clarifications to the inclusion and exclusion criteria
7	6.0	September 30th 2020	Pedro Folegatti, Sue Ann Clemens, Lily	Increased time from vial piercing to vaccine administration from 4 to 6 hours; clarifications to inclusion and exclusion criteria and removal of one of the exclusion criteria (participation in serological surveys); clarification and minor changes to symptomatic pathway in line with clinical study plan (requirements on visit S3-5, diaries, COVID-19 hospitalisation data collection); clarifications to vital signs collected at different timepoints; additional funders;
8	7.0	October 29th 2020	Pedro Folegatti, Sue Ann Clemens	Increase in sample size to up to 10.300 people to account for the competitive and simultaneous recruitment strategy at multiple sites.
9	8.0	12 Nov 2020	Pedro Folegatti, Sue Ann Clemens, Merryn Voysey	Clarifications to vital signs and physical measurements required at different visits; Updated Statistical Analysis section in line with global programme and with references to study level SAP and a separate SAP

				for Marketing Authorisation Application Increased number of subset of individuals for CMI assessment from 50 to 60.

List details of all protocol amendments here whenever a new protocol version is produced.