Full title: A phase I study to determine the safety and immunogenicity of a new vaccine against Middle East Respiratory Syndrome Coronavirus in Adults aged 50 to 70

Short Title: A study of a new vaccine against MERS Virus in adults aged 50 to 70

Study Code: MERS003

Internal Reference Number: OVG2022/02

Protocol Version: 4.1

Date: 18 July 2025

Chief Investigator: Prof Maheshi Ramasamy

Lead Scientific Investigator: Prof Dame Sarah Gilbert

Sponsor: University of Oxford

Funder: CEPI

REC Details: South Central - Oxford A Research Ethics Committee

REC Number: 23/SC/0047

EudraCT Number: 2022-002159-21

IRAS Reference: 1006223

ISRCTN Registry Number: ISRCTN17936606

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1 KEY TRIAL CONTACTS

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2 LAY SUMMARY

This is a trial of a new vaccine (ChAdOx1 MERS) against Middle East Respiratory Syndrome (MERS) in volunteers aged between 50 and 70 years.

MERS has been identified as one of the most worrying outbreak diseases by global agencies including the World Health Organization (WHO). It is a viral respiratory illness that can cause severe pneumonia and even death. MERS-Coronavirus, the virus that causes MERS, was identified in 2012 in Saudi Arabia. 2,300 cases and over 800 deaths have occurred so far. It continues to cause a small number of cases each year in Saudi Arabia. Currently, there is no treatment and no approved vaccine.

This study is of a vaccine against MERS, called ChAdOx1 MERS vaccine, which has been developed by The University of Oxford. The vaccine used in this study is very similar to the Oxford/AstraZeneca COVID-19 vaccine and is made using the same technology. However, the trial vaccine targets a component of the MERS virus rather than a component of the virus that causes COVID-19.

We have already completed two small clinical trials using ChAdOx1 MERS at different doses in healthy adults aged between 18 to 50 years.

The purpose of this new study is to:

1. Assess the safety and the immune response to the ChAdOx1 MERS vaccine in older adults, and
2. Investigate whether having previously received doses of the Oxford/AstraZeneca COVID-19 vaccine has any effect on the immune response generated by the ChAdOx1 MERS vaccine.

We plan to recruit up to 84 people aged between 50 and 70 years to take part in this study, half of whom will have previously been vaccinated with at least 2 doses of the Oxford/AstraZeneca COVID-19 vaccine. Participants will be screened for eligibility with an initial online questionnaire followed by a phone call and an in-person medical assessment.

Eligible participants will be invited to attend the first vaccination visit when and where they will be assigned at random to get two doses (given approximately 12 weeks apart) of either the study vaccine or a 'placebo' injection (sterile salt water). For every 6 participants recruited, 5 participants will receive the trial vaccine and 1 participant will receive the placebo. Neither the participants nor the study team will know which injections (vaccine or placebo) were given until the end of the study (apart from the researchers responsible for the randomisation, preparation and administration of the vaccine; who will not be involved in assessing any of the study outcomes).

Participants will be followed up for 1 year to monitor their safety and immune responses.

3 SYNOPSIS

<table>
<tr><td>Trial Title</td><td>A phase I study to determine the safety and immunogenicity of a new vaccine against Middle East Respiratory Syndrome Coronavirus in Adults aged 50 to 70</td></tr>
<tr><td>Trial Sites</td><td>Site 1: Liverpool Vaccine Group, Accelerator Research Clinic, Liverpool Life Sciences Accelerator Building, Liverpool School of Tropical Medicine, 1 Daulby Street, Liverpool L7 8XZ
Site 2: Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford OX3 7LE</td></tr>
<tr><td>Trial code</td><td>MERS003</td></tr>
<tr><td>Clinical Phase</td><td>Phase I</td></tr>
<tr><td>Study Design</td><td>Participant-observer blinded, 5:1 randomised, saline placebo-controlled, 12-week interval two-dose regimen phase I trial</td></tr>
<tr><td>Population</td><td>Non-immunosuppressed adults aged 50-70 years with stable comorbidities. Half of the volunteers will have previously received at least 2 doses of the ChAdOx1 nCov-19 (Oxford/AstraZeneca COVID-19 vaccine) and half will not.</td></tr>
<tr><td>Planned Sample Size</td><td>Up to 84 volunteers consisting of approximately 42 participants who have previously received at least 2 doses of the ChAdOx1 nCov-19 (Oxford/AstraZeneca COVID-19 vaccine) and approximately 42 participants who have no previous history of receiving ChAdOx1 nCov-19.</td></tr>
<tr><td>Follow-up duration</td><td>12 months</td></tr>
<tr><td>Study Groups</td><td>
<table>
<tr><th rowspan="2">Group / previous ChAdOx1 nCov-19 (Oxford/AZ COVID-19 vaccine status)</th><th rowspan="2">Allocation ratio</th><th>Intervention 1</th><th>Intervention 2</th></tr>
<tr><th>Week 0</th><th>Week 12</th></tr>
<tr><td rowspan="2"><u>Group 1</u>
Previous ChAdOx1 nCov-19 recipients approximately n=42</td><td>5</td><td>5×10^{10} vp ChAdOx1 MERS</td><td>5×10^{10} vp ChAdOx1 MERS</td></tr>
<tr><td>1</td><td>Saline placebo</td><td>Saline placebo</td></tr>
<tr><td rowspan="2"><u>Group 2</u>
ChAdOx1 nCov-19 naïve approximately n=42</td><td>5</td><td>5×10^{10} vp ChAdOx1 MERS</td><td>5×10^{10} vp ChAdOx1 MERS</td></tr>
<tr><td>1</td><td>Saline placebo</td><td>Saline placebo</td></tr>
</table>
</td></tr>
<tr><td>Planned Trial Period</td><td>Q2 2023 to Q1 2026</td></tr>
<tr><td>Primary Objective</td><td>To assess the safety, tolerability and reactogenicity profile of ChAdOx1 MERS vaccine in adult volunteers aged 50 to 70 years</td></tr>
<tr><td>Secondary Objective</td><td>To assess the cellular and humoral immunogenicity of ChAdOx1 MERS vaccine in adult volunteers aged 50 to 70 years</td></tr>
<tr><td>Investigational Products</td><td>1. ChAdOx1 MERS 5×10^{10} viral particles (vp) dose per administration
2. Placebo comparator: 0.9% sodium chloride (saline) injection</td></tr>
</table>

Route	Intramuscular
Vaccine Schedule	2 doses given at 0 and 12 weeks
Funder	Coalition for Epidemic Preparedness Innovations (CEPI)

4 SCHEDULE OF PROCEDURES TABLE

4.1 Schedule of Procedures: Screening Visit (all volunteers)

Visit Number	S
Visit Type	Screening
Timeline	0 to 90 days before D0
Visit Procedures	
Informed Consent	X
Review inclusion and exclusion criteria	X
Record Demographic Data	X
Medical History*	X
Vital signs (Heart rate, Temperature, Blood Pressure)	X
Screening Physical Examination	X
TOPS Registration *www.tops.org.uk*	X
Urine Samples	
Urinary HCG (WOCBP only)	X
Stool Samples (Optional)	
Sample containers and instructions provided	X
Blood Samples**	
HBsAg, HCV Ab, HIV serology (mL)	Up to 5
Biochemistry, Haematology (mL)	Up to 5
Blood volume per visit (mL)	Up to 10
Cumulative blood volume (mL)	Up to 10

Table 1: Schedule of Procedures: Screening Visit

*Medical history may be initially assessed by a telephone call prior to screening (Section 9.2.1)**Minor differences in blood volumes may occur depending on the collection tubes and equipment used.

4.2 Schedule of Procedures Table: Vaccination and Follow up Visits

	Trial Period						
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Type	Vac1	f/u	f/u	Vac2	f/u	f/u	f/u
Timeline	D0	D14	D28	D84 (V2)	V2+14	V2+28	V2+281
Time window (days)		±3	-3/ +5	±14	±3	-3/ +5	±60
Visit Procedures							
Review contraindications, inclusion and exclusion criteria	X			X			
Randomisation	X						
Vaccination (and immediate post-vaccination observation period)	X			X			
Vital signs (Heart rate, Temperature, Blood Pressure)	X	X	X	X	X	X	
Targeted Medical History, Physical Examination if required	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Record any COVID-19 infections and vaccinations	X	X	X	X	X	X	X
Adverse Event Collection							
Solicited AE collection	D0-D6			V2 to V2+6			
Unsolicited AE collection	D0 to D27			V2 to V2+27			
SAEs & AESI collection	X	X	X	X	X	X	X
Review Ongoing AEs		X	X	X	X	X	X
Electronic diary (eDiary)							
Electronic diary started	X			X			
Electronic diary review**		X	X		X	X	
Electronic diary closed			X			X	
Urine Samples							
Urinary HCG (WOCBP only)	X			X			
Stool Samples (Optional)							
Home collection of stool samples	(X)	(X)			(X)		(X)
Nasal Samples (Optional)							
Nasosorption Strips	(X)		(X)	(X)		(X)	(X)
Blood Samples*							
HLA typing (mL)	up to 4	-	-	-	-	-	-
Biochemistry, Haematology (mL) [LFTs, U+Es, FBC]	up to 5	up to 5	up to 5	up to 5	up to 5	up to 5	-
Immunology (mL)	up to 50	up to 50	up to 50	up to 50	up to 50	up to 70	up to 50
Blood volume per visit (mL)	up to 59	up to 55	up to 55	up to 55	up to 55	up to 75	up to 50
Cumulative blood volume (mL)***	up to 69	up to 124	up to 179	up to 234	up to 289	up to 364	up to 414

Table 2: Schedule of Procedures Table: Vaccination and Follow up Visits () = Optional. *Minor differences in blood volumes may occur depending on the collection tubes and equipment used. ** eDiaries are remotely monitored in (near) real-time for the occurrence of grade ≥3 AEs and daily for non-completion. ***including screening blood volumes

5 BACKGROUND & RATIONALE

5.1 Impact of MERS

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has been identified as one of the most worrying emerging outbreak pathogens by the World Health Organization (WHO), the National Institute of Allergy and Infectious Diseases (NIAID), the Centre for Disease Control and Prevention (CDC), Public Health England (PHE) and many other global agencies and expert groups. The disease was first described in 2012 and is now endemic in Saudi Arabia. It has since spread to different countries in the Middle East and other regions, including a recent outbreak in South Korea. More than 2500 cases of MERS with 894 deaths in 27 countries have been reported until this date[1].

MERS is a betacoronavirus, like SARS-COV and SARS-COV-2, and can be transmitted via zoonotic or human-to-human routes. MERS is suspected to have originated in bats, although dromedary camels are thought to be the major source of zoonotic infections. Occupational exposure to dromedary camels, which are used as livestock animals on the Arabian Peninsula and in north Africa, is a major risk factor for infection. Sustained human-to-human transmission has been observed in hospital environments and small household clusters but not outside of these settings to date.

The clinical spectrum of MERS-CoV infection varies from asymptomatic or mild respiratory symptoms to severe acute respiratory disease and death. The case fatality rate, approximately 35%, and rate of severe cases appears to be higher for MERS than COVID-19. Clinical symptoms include fever, cough and shortness of breath. Severe illness can cause respiratory failure that requires mechanical ventilation and support in an intensive care unit. Gastrointestinal symptoms, including diarrhoea, have also been reported. The virus appears to cause more severe disease in the elderly, immunosuppressed and those with chronic diseases such as cardiovascular disease and diabetes[2-5].

MERS-CoV viral fusion is mediated by interaction of the MERS-CoV spike protein with the dipeptidyl peptidase 4 (DPP4) host receptor, contrasting with SARS-COV and SARS-COV-2 spike proteins which target the ACE2 receptor. The MERS-CoV spike (S) protein is a characteristic structural component of the virion membrane and binding to DDP4 is mediated by the S1 domain. Due to its role in viral fusion, the MERS-CoV spike protein has been chosen as the target antigen for use in ChAdOx1 MERS and by all other MERS vaccines that are currently in clinical development (section 5.5).

5.2 Rationale for Vaccination

No vaccines or specific treatments have been approved for the prevention or treatment of MERS. This coupled with the potential for future outbreaks, high mortality rate, and risk presented to healthcare workers mean that MERS remains a major threat to global health. The need for vaccines against MERS is recognised by multiple global health organisations. To this end we have developed ChAdOx1 MERS, a simian adenoviral-derived replication incompetent viral vector encoding the MERS spike protein.

Adenovirus vaccines are highly scalable, with a well-developed existing manufacturing capability and supply chains that support a continuous uninterrupted supply of vaccine and the potential for rapid production in public health emergencies. Wild type replication competent oral human adenovirus vaccines, to protect against acute respiratory illness caused by adenovirus serotype 4 and 7, have been administered to millions of military personnel over decades in the USA with no safety issues[6]. ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine) has been shown to be safe, immunogenic and efficacious against COVID-19 disease in a number of clinical trials[7-10] and has been approved in many countries. Additionally, it has been administered to over 1 billion individuals, including those with

serious medical co-morbidities across diverse populations. Experience with ChAdOx1 nCoV-19 has shown the vaccine can be rapidly manufactured at high volume for low cost, with storage conditions amenable to use in the developing world. Safety surveillance of ChAdOx1 nCoV-19 has demonstrated very rare associations with some serious adverse reactions (e.g. thrombosis and thrombocytopenia syndrome). The vaccine continues to be recommended for use as the benefits against COVID-19 outweigh the risks of its use for the majority of populations.

5.3 ChAdOx1 MERS Vaccine

ChAdOx1 MERS consists of the ChAdOx1 vector encoding MERS-CoV spike glycoprotein. ChAdOx1 is a recombinant simian adenovirus viral vector developed by the University of Oxford. It was derived from wildtype serotype Y25 adenovirus which has been rendered replication-deficient through deletion of the E1 gene region which is essential for viral replication. The spike protein sequence used in the vector consists of a codon optimised sequence from MERS-CoV isolate Camel/Qatar_2_2014 (GenBank:KJ650098.1).

5.4 ChAdOx1 MERS Preclinical studies

ChAdOx1 MERS preclinical studies are summarised in the ChAdOx1 MERS investigator brochure. Briefly, ChAdOx1 MERS has been shown to be immunogenic in BALB/c mice, dromedary camels and non-human primates. A repeat dose GLP toxicology study (QS18DL) using a two-dose schedule with a 14-day interval concluded that ChAdOx1 MERS was well tolerated and not associated with adverse events.

5.5 ChAdOx1 MERS Previous clinical experience

Two clinical trials using ChAdOx1 MERS have been performed previously. MERS001 was a first-in-human study conducted in the UK and sponsored by the University of Oxford employing ChAdOx1 MERS[11]. MERS002 was a phase I study, similar to MERS001, conducted in Saudi Arabia and Sponsored by the King Abdullah International Medical Research Center[12]. To date, 53 participants received ChAdOx1 MERS at doses ranging from $5x10^9$ vp to $5x10^{10}$ vp as part of MERS001 (UK) and MERS002 (Saudi Arabia), primarily as a single dose schedule. No safety concerns and no serious adverse reactions related to vaccination were reported in either trial. Solicited adverse events were common but short-lived.

In both MERS001 and MERS002 ChAdOx1 MERS was found to be immunogenic, inducing seroconversion (Figure 1A) and T-cell responses (Figure 1B) in the majority of participants, with responses demonstrating good durability up to 1 year after vaccination. Neutralising antibodies were assessed using a live MERS-CoV neutralisation assay (MERS001 only) or by several lentiviral-based pseudo-neutralisation assays (both trials). Pseudo-neutralising antibody levels were detected in the majority of participants in MERS001 and MERS002 after a single dose of ChAdOx1 MERS (ChAdOx1 MERS Investigator Brochure). Live MERS-CoV neutralising antibodies were less readily detectable, although were observed in 4/9 single-high-dose volunteers at day 28 (Figure 1C).

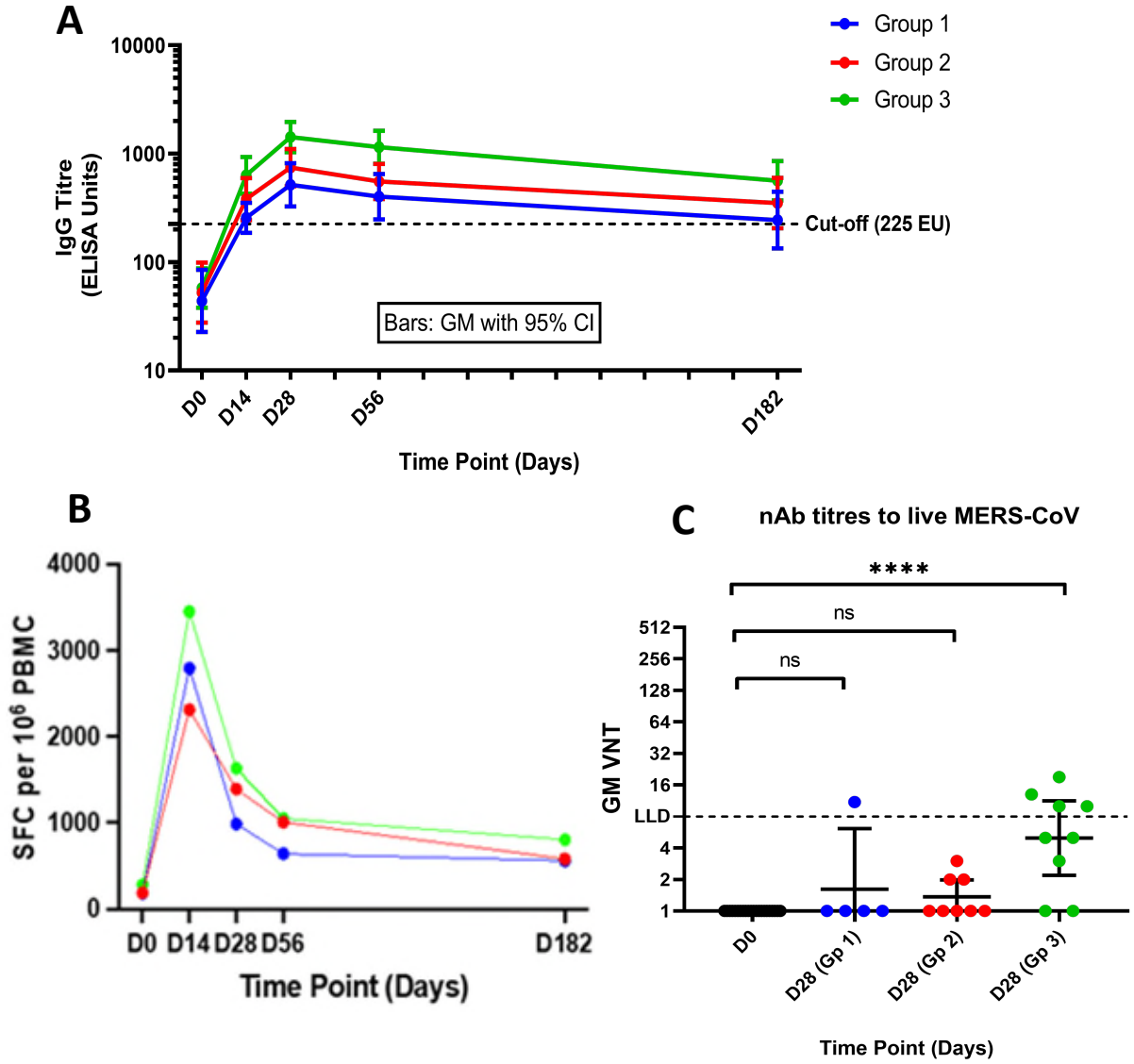

Figure 1: A. Binding antibodies induced by ChAdOx1 MERS measured by MERS-CoV spike protein antibody ELISA (MERS001 and MERS002 data combined). **B**. Cellular immunogenicity to ChAdOx1 MERS assessed by MERS-CoV spike protein ex-vivo ELISpot (MERS001 and MERS002 data combined). **C**. MERS-CoV Live Neutralising antibody results at day 0 and day 28. (MERS001 data only). Group 1 = single dose 5x10^9 vp, Group 2 = single dose 2.5x10^10 vp, Group 3 = single dose 5x10^10 vp.

3 participants in MERS001 also received a homologous two-dose schedule ($2.5x10^{10}$ vp x 2) using either a 4 week (n=2) or 6 month interval (n=1) before the trial was prematurely terminated due to the COVID-19 pandemic. The small number of individuals who received a second dose showed evidence of substantial boosting measured by anti-MERS-spike ELISA (further details within ChAdOx1 MERS investigator brochure).

5.6 Other MERS Vaccines in Clinical Testing

The International Clinical Trials Registry Platform was searched on 11th Jul 2022 for "MERS" and several experimental MERS vaccines in phase I or II clinical trials were identified. These are summarised in **Table 3**. Other than ChAdOx1 MERS, several other vaccine candidates are in clinical

development including adenoviral (BVRS-GamVac and BVRS-GamVac-Combi) and MVA vectored (MVA-MERS-S) vaccine candidates and a DNA vaccine candidate (INO-4700 / GLS-5300). All of the candidate MERS vaccines in current clinical trials target the MERS spike protein. A phase 1 trial using MVA-MERS-S has been published, which demonstrated an acceptable safety profile and showed that the vaccine can elicit humoral and cellular responses to the MERS-CoV spike protein following a homologous two-dose regimen[13]. Results for other trials are not yet available.

Type	**Vaccine Name**	**Manufacturer**	**Trial Phase, (Year of Registration), Registration Number**	**Results**
Adenoviral Vector	BVRS-GamVac	Gamaleya Research Institute	Phase 1/2: (2019) NCT04130594	n/a
Adenoviral Vector (heterologous combination)	BVRS-GamVac-Combi	Gamaleya Research Institute	Phase 1/2: (2019) NCT04128059	n/a
Adenoviral Vector	ChAdOx1	University of Oxford	Phase 1: (2018) NCT03399578, (2019) NCT04170829	[11,12]
DNA plasmid Vaccine	INO-4700 / GLS-5300	GeneOne Life Science / Inovio Pharmaceuticals	Phase 1/2: (2018) NCT03721718 Phase 2: (2020) NCT04588428	n/a
Modified Vaccinia Ankara Vector	MVA-MERS-S	IDT/ MERS-CoV Vaccine Consortium	Phase 1: (2018) NCT03615911, (2019) NCT04119440	[13]

Table 3: MERS Vaccines in Registered Clinical Trials (as of 11th July 2022)

5.7 Clinical experience with other ChAdOx1 vaccines

A number of other ChAdOx1 vectored vaccines have also been developed, including most notably ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine) which has been approved in many countries and administered to over one billion individuals[8-10,14,15].

Early phase clinical trials have also been performed for a number of other ChAdOx1 vectored vaccines encoding antigens for Influenza (fusion protein NP+M1), Tuberculosis (85A), Prostate Cancer (5T4), Malaria (LS2), Chikungunya (structural polyprotein), Zika (prM and E), group B Meningococcus (outer membrane protein) and others with positive safety and immunogenicity results[16,17]. Further details of other ChAdOx1 studies are contained within the ChAdOx1 MERS investigator brochure.

5.8 Rationale for Selected Doses

Clinical and non-clinical data of ChAdOx1 MERS and other ChAdOx1-vectored vaccines support the use of ChAdOx1 MERS at a 5 x 10^{10} vp dose with a 12-week interval in this study. Participants in MERS001 and MERS002 received a single dose of ChAdOx1 MERS at a dose of between 5x10^{9} vp - 5x10^{10} vp. A small number of participants in MERS001 received two doses of 2.5 x 10^{10} vp ChAdOx1 MERS prior to the early termination of that study due to the COVID-19 pandemic. The vaccine was found to be immunogenic and well tolerated with no safety concerns in these trials. A repeat dose pre-clinical toxicology study of ChAdOx1 MERS in mice showed no safety concerns (section 5.4). Multiple other ChAdOx1-vectored vaccines have been used safely in clinical trials at a dose of 5 x 10^{10} vp (ChAdOx1 MERS Investigator Brochure).

Experience with ChAdOx1 nCoV-19 has shown that a second 5 x10^{10} vp dose of vaccine significantly boosts binding and neutralising antibody responses to SARS-CoV-2 and vaccine efficacy[8,18,19]. Additionally, a longer interval 12-week schedule has been shown to be more immunogenic than a 4-week schedule[10]. A second 5 x10^{10} VP dose of ChAdOx1 nCoV-19 is well tolerated and produces lower rates of adverse reactions compared with the initial dose[8,18,19].

5.9 Potential Risks

Trial related risks are summarised below. Potential risks associated with ChAdOx1 MERS are also discussed in further detail within the ChAdOx1 MERS Investigator Brochure.

ChAdOx1 MERS Administration

The main risks that recipients of ChAdOx1 MERS are likely to experience are common short lived local (primarily injection site tenderness or pain) and systemic vaccine reactions (fatigue, headache, malaise, feverishness) that resolve completely within days.

Very rare serious reactions have been identified as part of post-marketing surveillance of ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine). These include thrombosis with thrombocytopenia (TTS), immune thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), transverse myelitis, capillary leak syndrome (CLS) and anaphylaxis. It is currently unknown whether these very rare reactions may occur with other ChAdOx1 vaccines. As ChAdOx1 MERS is highly similar to ChAdOx1 nCoV-19, participants will be informed about these conditions as part of the informed consent process for the trial. Investigators should be aware of potential signs of these conditions.

Other Potential Trial Related Risks

Blood sampling during the trial may cause slight pain, bruising, light-headedness or fainting. The volume of blood taken in the trial is less than that given by regular blood donors over the same period.

The medical tests carried out during the trial screening and afterwards may find incidental medical problems that might require referral of volunteers for further investigation. Participants will be informed of these and, with their consent, their GP.

Intramuscular injections carry a risk of bleeding in patients with very low platelet counts or coagulopathies.

Although there is no reason to believe ChAdOx1 MERS would be harmful during pregnancy there is no data on the use of ChAdOx1 MERS in pregnancy yet. Therefore, pregnant women will be excluded from the trial and women of childbearing potential will be required to use effective contraception to take part (section 8.4).

5.10 Potential Benefits

The recruitment population in this study will not benefit directly from participation in the study as they are highly unlikely to be at direct risk of MERS infection currently. Additionally, efficacy against MERS virus infection has not been established and will not be established by this study.

Participants will be informed that they should not anticipate any protection from potential future MERS infection by participating in this study.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives, Outcome Measures and Evaluation Timepoints

Outcome	Objective	Outcome measure	Evaluation Timepoints*
Primary	To assess the safety and tolerability of ChAdOx1 MERS vaccine in healthy volunteers aged 50-70.	a) Occurrence of solicited local reactogenicity signs and symptoms	Within 7 days of each vaccination
		b) Occurrence of solicited systemic reactogenicity signs and symptoms	Within 7 days of each vaccination
		c) Occurrence of unsolicited adverse events (AEs)	Within 28 days of each vaccination
		d) Change from baseline for safety laboratory measures	Within 28 days of each vaccination
		e) SAEs and AESIs	Whole duration of the study follow up period (D0 to V2+281)
Secondary	To assess the immunogenicity of ChAdOx1 MERS vaccine in healthy adult volunteers aged 50-70	a) MERS spike protein specific serological response as measured by ELISA	D0, D14, D28, V2, V2+14, V2+28, V2+281
		b) MERS spike protein T cell response measured by IFN-γ ELISPOT	D0, D14, D28, V2, V2+14, V2+28, V2+281
Exploratory**	Immunological Profiling	a) MERS virus neutralising antibodies (using either live or pseudoneutralisation assays) b) Cellular immune response to MERS virus measured by ICS, proliferation and/or whole blood assays c) Describe immunological outcomes grouped by presence or absence of previous ChAdOx1 nC0V-19 vaccination	Timepoints will be detailed in the lab analysis plan
		d) Assessment of mucosal immunogenicity	D0, D28, V2, V2+28, V2+281
	To assess anti-vector immunity following vaccination	a) Binding and/or neutralising antibody responses against ChAdOx1	Timepoints will be detailed in the lab analysis plan
	To investigate a potential relationship between the composition of the gut microbiota and vaccination outcomes	Characterisation of the gut microbiome composition and function	Baseline, D14, V2+14, V2+281

*Visit and procedure timepoint windows are defined in section 4.2 (schedule of procedures table);
**Sample analysis for the completion of exploratory endpoints may be performed under the ethically approved Oxford Vaccine Centre (OVC) Biobank protocol (REC 21/SC/0161). Further exploratory assays/analyses may be carried out (see section 9.5.7).

7 TRIAL DESIGN

This is a multi-site, participant-observer blind, randomised, placebo-controlled, phase I trial to assess the safety, tolerability and immunogenicity of two administrations of an intramuscular ChAdOx1 MERS vaccine in adults aged 50 to 70 years. Participants will be considered enrolled in the study once their first vaccination has been administered (D0).

Volunteers will be recruited and vaccinated at the designated study sites. The trial aims to recruit up to 84 volunteers consisting of approximately 42 participants with no prior history of receiving ChAdOx1 nCoV-19 and approximately 42 participants who have previously received at least 2 doses of ChAdOx1 nCoV-19.

Participants will be grouped on the basis of previous ChAdOx1 exposure and subsequently randomised to receive either ChAdOx1 MERS or saline placebo with a 5:1 allocation ratio.

7.1 Study Groups

Group / previous ChAdOx1 nCov-19 (Oxford/AZ COVID-19) vaccine status	Allocation ratio	n	Intervention 1	Intervention 2	Follow up period
			Week 0	Week 12	
Group 1 previous ChAdOx1 nCov-19 (Oxford/AZ vaccine) recipients approximately n=42	5	approx. n=35	5×10^{10} vp ChAdOx1 MERS	5×10^{10} vp ChAdOx1 MERS	1 year
	1	approx. n=7	Saline placebo	Saline placebo	1 year
Group 2 ChAdOx1 nCov-19 (Oxford/AZ vaccine) naïve approximately n=42	5	approx. n=35	5×10^{10} vp ChAdOx1 MERS	5×10^{10} vp ChAdOx1 MERS	1 year
	1	approx. n=7	Saline placebo	Saline placebo	1 year

7.2 Trial Duration

The total duration of the study will be 12 months from the day of enrolment for each volunteer.

7.3 Definition of Start and End of Trial

The start of the trial is defined as the date of the first vaccination of the first volunteer. The end of the trial will be complete when all assays providing data for primary and secondary endpoints have been completed.

7.4 Group allocation

Allocation to each group will be decided on the basis of prior ChAdOx1 nCoV-19 vaccination status. Recruitment to group 1 and group 2 will occur concurrently with the aim of having balanced numbers across groups 1 and 2.

7.5 Blinding

This study will be conducted in an observer and participant blind fashion. Blinding of treatment allocation will remain until the defined end of the study (defined in section 7.3).

There will be dedicated blinded and unblinded study teams. Blinded staff will include clinical study doctors (including the CI), study nurses, administrative and laboratory staff who will be directly managing participants and participant samples. Steps to maintain blinding of the IMP are detailed in section 10.3. Access to the randomisation and vaccination eCRF of the study database will be password protected and access restricted.

In the unlikely event that accidental unblinding (i.e. for reasons not outlined in this protocol) of any blinded study team member occurs, this would be recorded as a protocol deviation, and the study team member will be quarantined from taking part in further blinded study activities, so that the study progress is not compromised.

Participants and their General Practitioners will receive written notification by letter or email of whether they have received the vaccine or placebo at the time of full study unblinding.

Unblinding may also occur at an earlier time point in the event of the occurrence of SAEs, SARs or SUSARs on discussion with the CI and/or Data Safety and Monitoring Committee.

In the case of medical emergency the study site investigator will have direct access to unblinding of the participant(s) by opening of the participant(s) sealed envelope containing their vaccine record. This will be confirmed by electronic unblinding via the REDCap database, which can be performed in the first instance to avoid any delay in unblinding due to a medical emergency, or out of hours.

8 PARTICIPANT IDENTIFICATION

8.1 Inclusion and exclusion criteria

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

8.1.1 Inclusion criteria

The volunteer must satisfy all the following criteria to be eligible for the study:

- Adults aged between 50 to 70 years (inclusive) at the time of screening
- Medically stable, such that according to investigator judgement hospitalisation within the study period is not anticipated, and the participant appears likely to be able to remain a study participant through the end of protocol-specified follow-up. Planned elective procedures for pre-existing conditions are allowable. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 90 days prior to enrolment.
- Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of diary cards.
- Willing to allow confirmation of their past medical history either through: provision of or access to medical record summary, allowing investigators to obtain a copy of their medical history from their GP practice or accessed via the electronic patient record or other medical documentation provided by the participant.
- Agreement to refrain from blood donation during the course of the study.
- Willing and able to give informed consent for participation in the study.
- *For women of childbearing potential only* (As defined by protocol section 8.4)*:* Willing to use effective contraception as defined from one month prior to receiving the first vaccine and for the duration of the study AND a negative pregnancy test on the days of screening and vaccination.
- Willing to provide their national insurance number or passport number to be registered on The Over-Volunteering Prevention System (TOPS).
- Willing to allow his or her General Practitioner and/or Consultant, if appropriate, to be notified of participation in the study.
- *Group 1 specific inclusion criteria:* a confirmed history of receiving at least TWO doses of the ChAdOx1 nCov-19 (Oxford/AZ COVID-19) vaccine prior to enrolment.
- *Group 2 specific inclusion criteria*: no previous history of receiving ANY doses of the ChAdOx1 nCov-19 (Oxford/AZ COVID-19) vaccine prior to enrolment.

8.1.2 Exclusion criteria

The volunteer may not enter the study if any of the following apply:

- Participation in another research study involving an investigational product or that which may compromise the integrity of the study (e.g. significant volumes of blood already taken in previous study) in the past 12 weeks, or are planning to do so within the trial period.
- Planned receipt of another adenoviral vectored vaccine (e.g. Oxford/AstraZeneca or Janssen COVID-19 vaccines) within 90 days of any study vaccine.

- Previous immunisation with an investigational MERS vaccine.
- History of prior confirmed or suspected MERS infection.
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
- Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; severe infections or receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic corticosteroid therapy (including for more than 7 days consecutively within the previous 3 months).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine including hypersensitivity to the active substance or to any of the excipients of the IMP or Vaxzevria (i.e. the Oxford/AstraZeneca COVID-19 vaccine).
- History of allergic reaction to aminoglycoside antibiotics.
- History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
- History of anaphylaxis in relation to vaccination.
- History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition likely to affect participation in the study.
- Female participants who are pregnant, breastfeeding/lactating or planning pregnancy during the course of the study.
- Bleeding disorder (e.g. Factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- History of confirmed major thrombotic event (including cerebral venous sinus thrombosis, deep vein thrombosis, pulmonary embolism), history of antiphospholipid syndrome, or history of heparin induced thrombocytopenia.
- Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria (i.e. the Oxford/AstraZeneca COVID-19 vaccine).
- Individuals who have previously experienced episodes of capillary leak syndrome.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, or neurological illness, as judged by the Investigator (note, mild/moderate well-controlled comorbidities are allowed)
- Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week.
- Suspected or known injecting drug abuse in the 5 years preceding enrolment.
- Detectable circulating hepatitis B surface antigen (HBsAg).
- Seropositive for hepatitis C virus (antibodies to HCV).
- Any clinically significant finding on screening investigations, that are either unlikely to resolve or do not resolve on repeat testing (at the discretion of an Investigator) within the recruitment timeline of the study.
- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

8.2 Temporary Exclusion Criteria

The following applies to both **initial enrolment** and **subsequent vaccination** visits. If the temporary exclusion resolves within the time constraints of the trial, they can be enrolled and/or progression in the trial can continue.

1. Receipt of any systemic corticosteroid (or equivalent) treatment within 14 days prior to vaccination, or for more than 7 days consecutively within the previous 3 months.
2. Febrile illness (oral temperature ≥37.5°C) or systemically unwell on the day of vaccination.
3. If a participant is taking systemic antibiotics then the vaccination is postponed until 7 days after the last dose. This does not apply to topical antibiotic preparations.
4. Use of antipyretics in the 4 hours prior to vaccination.
5. A laboratory AE considered, in the opinion of the Investigator, requiring of further time and/or investigation to resolve or stabilise prior to a dose of vaccine being administered.
6. Confirmed (on lateral flow test or PCR) symptomatic COVID-19 infection within 10 days prior to the vaccination visit.
7. Any illness / AE considered, in the opinion of the investigator, requiring of further time and/or investigation to resolve or stabilise prior to a dose of vaccine being administered.
8. Planned or actual receipt of any vaccines administered within 30 days of study vaccines (before or after) EXCEPT for influenza and non-adenoviral COVID-19 vaccines which may be given up until 14 days of the study vaccines.

8.3 Absolute contraindications to further vaccinations

If any of these events occur during the study, the participant must not receive additional doses of vaccine but will continue to be followed up within the study.

1. Hospitalisation with COVID-19 (WHO Clinical progression scale 4 or above) during the study follow up period will preclude further vaccinations
2. Any SAR

8.4 Pregnancy and Contraception

The possible adverse effects of the ChAdOx1 MERS vaccine on the outcome of pregnancy are unknown; therefore, pregnant women will be excluded from the study. Women of childbearing potential will be required to use an effective contraceptive measure. Contraception should be maintained during the vaccination period and for the duration of the study. Should a volunteer become pregnant during the trial, she will be followed up for clinical safety assessment until the pregnancy outcome is determined with her ongoing consent. Her baby will be followed up for up to 3 months post delivery. Venepuncture will not be performed in a pregnant volunteer unless there is clinical need. Male participants with female partners are not required to use barrier methods for the purposes of contraception, as the risks of vaccine excretion are negligible.

The viral vector component of the ChAdOx1 MERS vaccine lacks the E1 gene region necessary for replication in vivo. No safety signal related to pregnancy has been observed with the ChAdOx1 nCov-19 vaccine. The risk of human teratogenicity/fetotoxicity with ChAdOx1 MERS is therefore unlikely.

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post- menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophrectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using

hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhoea, a single FSH measurement is insufficient.

Female volunteers of childbearing potential are required to use an effective form of contraception from 1 month prior to the first vaccination visit until their last follow-up visit. Acceptable forms of contraception for female volunteers include:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. intrauterine device (IUD)
3. intrauterine hormone-releasing system (IUS)
4. Barrier methods of contraception (condom or occlusive cap)
5. bilateral tubal occlusion
6. vasectomised male partner, if the vasectomised partner is the sole partner for the participant.
7. sexual abstinence when this is in line with the preferred and usual lifestyle of theparticipant . Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception.
8. Exclusive sex with a female partner(s)

9 TRIAL PROCEDURES

9.1 Recruitment

All potential participants may be contacted by methods including but not limited to email, telephone, posters, leaflets, websites, advertisements in newspaper, radio and on social media, public engagement events and/or mail using a REC approved invitation letter or other advertising material using wording from REC approved study documents in the first instance to invite them to participate in the study.

Where mail-outs are used, participants may be identified via the electoral open register, or through National Health Service databases using data extracts. For the NHS databases initial contact to potential participants will not be made by the study team. Instead, study invitation material will be sent out on behalf of the study team by an external company, CFH Docmail Ltd (or equivalent company), in order to preserve the confidentiality of potential participants. CFH Docmail Ltd (or equivalent company) is accredited as having exceeded standards under the NHS Digital Data Security and Protection Toolkit (ODS ID – 8HN70).

For mail-outs via the electoral register, the study team will obtain access to the names and addresses of individuals who are on the open electoral register (only contains the names of registered voters who have not opted out). In this instance, the study team will upload the mailing list to the CFH Docmail system (or equivalent company), and the study invitation pack will be sent out by CFH Docmail (or equivalent company).

The details of other recruitment methods that may be used are outlined below:

1. Email campaign: We will contact representatives of local tertiary education establishments and local employers and ask them to circulate posters and link to study website by email or hard copy.
2. Healthy volunteers databases: Direct email and link to members of the public who have registered their interest in potentially volunteering for clinical trials. These are secure databases where members of the public have registered and have given consent to have their details recorded to be contacted expressly for the purpose of being notified when a trial opens for recruitment.

They understand this is not a commitment to volunteering for any trial they are contacted about. The study may be also advertised on an electronic newsletter sent out to the potential participants signed up to the healthy volunteer databases.

3. Media advertising: Local media, newspaper and website advertisement placed in locations relevant for the target age group with brief details of the study and contact details for further information.
4. Website advertising: Description of the study and copy of information booklet on study team websites and other appropriate platforms for vaccine trial advertising.
5. Social media: Advertisements placed on trial site media accounts or targeted social media platform advertisements including, but not restricted to, Twitter, Facebook and Instagram
6. Exhibitions: Advertising material and/or persons providing information relating to the study will exhibit using stalls or stands at exhibitions and/or fairs, such as University Fresher's Fairs.
7. Volunteers may also be recruited using direct SMS/text message, or emails to potential participants identified by GPs from their databases (PIC agreements to be set up with the GP surgeries as required).
8. Royal Mail Leaflet: Royal Mail door-to-door service with delivery of invitation letters in site envelopes to every household within certain postcode areas.

Potential participants who are interested in study participation will be able to contact the sites by telephone, email, online or a reply slip.

9.2 Screening and Eligibility Assessment

9.2.1 Initial Eligibility Assessment of Potential Study Participants

Once an expression of interest has been received, an information sheet will be sent via mail, email or downloaded from the website by potential participants to read. If potential participants are willing to proceed, they will be initially screened by a website questionnaire and/or telephone before they are invited for a screening and consent visit, where their eligibility will be assessed by a member of the clinical research team. Permission to access the volunteer medical records either via the electronic records system or GP will be sought (if possible) prior to the screening visit. Participants will be asked to sign a secure electronic document (hosted by the REDCap database) which will then be counter-signed by a study team member. Alternatively, written permission to access medical records will be sought at the volunteers screening and consent visit.

9.2.2 Baseline Assessments at Screening

Once informed written consent is obtained, the following baseline assessments and information is collected as part of the assessment of inclusion/exclusion criteria:

1. Participant demographics: age, sex and ethnicity
2. Medical history
3. Contraception: female participants of childbearing potential are asked if they are willing to use effective contraceptive measures one month prior to vaccination and for the remainder of the study
4. Use of concomitant medication (including over the counter medications, vitamins, illicit drug use and herbal supplements)
5. Recording of resting pulse, blood pressure, temperature, weight and height
6. Physical examination; cardiovascular, respiratory, abdominal and gross neurological examination
7. Urine pregnancy test (females of childbearing potential only)
8. Blood samples for: full blood count, urea and electrolytes, liver function tests and serology for HIV, hepatitis C and hepatitis B
9. Collect emergency contact details

The medical, vaccination and prescribed medication history are initially based on participant recall. However, with prior participant approval, patient medical summary, vaccination and prescribed medication history will be formally requested from the GP or accessed via the electronic patient record (if available) at the screening visit if not already requested or accessed in advance. In addition, all participant GPs will be notified of their participation in the study.

9.2.3 Prevention of Over-Volunteering

Consent will be taken to register the participant on The Over-volunteering Prevention System (TOPS) database to guard against the potential for harm that can result from excessive volunteering in clinical trials involving IMPs and blood donations. This will be done using the participant's National Insurance number or Passport Number. The TOPS database will be checked for any conflicts at screening, however formal registration will be done at enrolment.

9.2.4 Screen Failures

Participants who have signed the informed consent form but are not subsequently enrolled in the trial will be regarded as screen failures. For each of these participants, a minimal set of screen failure data will be recorded including demographic details and the reason for screening failure. These details will be reported as required by Consolidated Standards of Reporting Trials (CONSORT) publishing standards.

9.3 Informed consent

All volunteers will sign and date the informed consent form before any study specific procedures are performed. The information sheet will be made available to the volunteer at least 24 hours prior to the screening visit. At the screening visit, the volunteer will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

1. Participation in the study is entirely voluntary.
2. Decision not to participate involves no penalty or loss of medical benefits.
3. The volunteer may withdraw from the study at any time.
4. The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved.
5. The study involves research into an investigational vaccine.
6. There is no direct benefit to individuals from participating.
7. The volunteer's General Practitioner (GP) will be informed of their participation in the study.
8. Confirmation of their medical history will be required e.g. through a medical history summary from their GP practice or equivalent.
9. The volunteer's samples may be sent outside of the UK and Europe to laboratories in collaboration with the University of Oxford. These samples will be de-identified.
10. That long term storage of samples after the trial is over is optional and will be covered under the Oxford Vaccine Centre Biobank Study protocol which will be consented to separately.

The participant will have the opportunity to discuss the study with a medically qualified investigator. Written informed consent will be obtained by means of a dated signature of the participant and a signature of the appropriately trained and delegated clinician. A copy of the signed informed consent will be given to the participant and the original signed form will be retained at the study site.

9.4 Randomisation

Participants that have completed all screening assessments and who have been assessed as eligible for the study will be invited to the D0 visit. Randomisation will only take place after a final eligibility assessment at the D0 visit.

Participants will be randomised within their group (which is based on past vaccination with ChAdOx1 nCov-19) to receive either ChAdOx1 MERS or saline placebo in a 5:1 ratio. Randomisation will be performed using an electronic system within the RedCAP database.

9.5 Study visits

The procedures to be included in each visit are documented in the schedule of procedures tables (Section 4). Each visit is assigned a time-point and a window period, within which the visit will be conducted.

9.5.1 Vaccination visits

Vaccination visits are held at the study site. The visit procedure for the vaccination visits will be as follows:

1. Ensure that participant consent remains valid and confirm continued consent.
2. (first vaccination visit) Obtain and document interim medical history since the screening visit and check eligibility criteria, specifically temporary exclusion to vaccination
3. (Subsequent vaccination visits) Review for AEs and SAEs since the last visit
4. Participant is provided access and training to use the electronic diary card using their personal email address for the set-up
5. Provide participant with a medic alert contact card with 24 hour emergency telephone number to contact a study clinician
6. Record temperature, pulse and blood pressure
7. Perform urinary pregnancy test for females of childbearing potential (section 8.4)
8. Perform blood draw
9. Optional collection of nasal mucosal sample using nasosorption strips
10. Optional collection of stool sample and supply ‘By Post’ stool collection kit, as required
11. Administer vaccine by IM injection into non-dominant deltoid muscle
12. Post-vaccination observation of volunteer for a minimum of 30 minutes following vaccine administration
13. Schedule next visit and re-iterate participant requirements such as return of the Diary Card entries

9.5.2 Follow up Visits

Other visits may require the following procedures:

1. Review for AEs/AESIs/SAEs, as appropriate, since the last visit
2. Review eDiary entries and laboratory blood tests
3. Record oral temperature, pulse and blood pressure
4. Perform blood draw
5. Optional collection of nasal mucosal sample using nasosorption strips
6. Optional collection of stool sample and supply ‘By Post’ stool collection kit, as required
7. Schedule next visit and re-iterate participant requirements such as eDiary entries

9.5.3 Unscheduled Visits

Additional visits or procedures may be performed at the discretion of investigators, e.g. further medical history and physical examination, additional blood tests or other investigations if clinically relevant, including testing for COVID-19.

9.5.4 Missed Visits

In exceptional circumstances, where follow up visits would otherwise be missed entirely, visits may alternatively be conducted remotely via phone or video calling. This will allow a minimum set of safety and adverse event data to be collected.

9.5.5 eDiary

Following each vaccination, participants will have access to an electronic diary (eDiary) system using their personal email address to allow them to self-report solicited and unsolicited AEs. Each participant will be given unique log-in details associated with their study number. Local site (blinded) clinical teams will have access to the eDiary in order to review data inputted by participants. Training for this will be given at the first visit as described above. A paper copy of the diary will be provided to allow for completion in the event of inability to access the online version for whatever reason. The study team will be following up on compliance.

9.5.6 Clinical Laboratory Blood Samples

Blood will be drawn for the following laboratory tests. These will be carried out at an accredited local clinical laboratory:

- **Haematology:**
  - Full Blood Count (Including: Haemoglobin, platelet count, total white cell count, neutrophil count, lymphocyte count, eosinophil count)
- **Biochemistry:**
  - Urea and Electrolytes (Including: Sodium, Potassium, Urea and Creatinine)
  - Liver Function Tests (Including: ALT, ALP, Bilirubin, Albumin)
- **Diagnostic serology (Screening Only):**
  - Screening tests for Hep B, Hep C and HIV infection (Including: HBsAg, HCV antibodies, HIV antibodies)
- **Immunology:**
  - Human Leukocyte Antigen (HLA) typing

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigators.

9.5.7 Immunology Samples

9.5.7.1 University of Oxford research laboratories:

Immunogenicity will be assessed by a variety of immunological assays. This may include ELISpot assays for interferon gamma and flow cytometry assays, functional antibody assays and B cell analyses. Other exploratory immunological assays including cytokine analysis and other antibody assays, production of monoclonal antibodies, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed.

9.5.7.2 Other research laboratories:

Collaboration with other specialist laboratories in the UK (including laboratories at trial sites), Europe and outside of Europe for further exploratory immunological tests may occur. This would involve the transfer of serum, plasma and PBMC to these laboratories, but these would remain de-identified. Informed consent for this will be gained from the volunteers. Immunological assays will be conducted according to local SOPs.

9.5.7.3 Nasosorption

Synthetic absorptive matrix (SAM) strips are small pieces of absorbent material which are designed for sampling mucosal fluid and will be used in this study to sample fluid from the nasal mucosa. Sampling will take place using CE marked SAM strips for their intended purpose of nasal sampling, in line with manufacturer instructions. Briefly the absorbent tip is inserted into the participant's nostril and the participant presses against the side of that nostril for 60 seconds. It is then removed from the nostril and returned to the tube and stored for subsequent immunological analysis. This may be carried out in clinic by an appropriately trained and delegated member of clinical staff. Samples will be used to investigate mucosal immunogenicity.

9.5.8 Stool Sample Collection

Stool samples will optionally be collected for the study of gut microbiota. Participants will collect faecal samples at home, following an established SOP for stool collection and using specific containers provided by the trial team. Sample return instructions will be provided to participants.

9.5.9 Urine Samples

For female volunteers of childbearing potential only, urine will be tested for human chorionic gonadotrophin (HCG) at screening and immediately prior to each vaccination. β-HCG blood sampling may also alternatively be acceptably used to confirm a female participant is not pregnant.

9.5.10 Retention of Samples

Participants will be informed that they may opt-in to the Oxford Vaccine Centre Biobank study (REC 21/SC/0161) to allow long-term storage of biological samples collected under the MERS003 protocol for use in possible future research. The OVC Biobank study is covered by a separate study protocol and consent process. Participants will be informed that declining to take part in the OVC Biobank study will not affect their participation in this study. If a participant elects to decline to take part in the OVC Biobank, all of their leftover samples will be destroyed after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

9.14. Discontinuation/Withdrawal of volunteers

Each participant can exercise their right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for participant safety including, though not exclusive to, the following:

1. Significant non-compliance with study requirements
2. Consent withdrawn
3. Lost to follow up

Withdrawal from the study will not result in exclusion of the data generated by that participant from analysis. The reason for withdrawal, if given, will be recorded in the CRF. Participants who withdraw from the trial after randomisation but prior to receipt of any vaccine doses may be replaced by a further volunteer who will be randomised separately.

Furthermore, in circumstances pertaining to the safety of the participant, the DSMC chair, DSMC committee or investigator may choose to discontinue further vaccination +/- specific study procedures, however participants should otherwise continue to attend the follow up visit schedule

and applicable follow up procedures unless they withdraw consent for this.. Such circumstances may include, though may not be exclusive to, the following:

4. Pregnancy (further details on management of volunteers who become pregnant are provided in section 8.4)

5. An adverse event which requires discontinuation of the study vaccinations or results in an inability to continue to comply with study procedures

6. Ineligibility (either arising during the study or in the form of new information not declared or detected at screening)

Withdrawal from the study will not result in exclusion of the data generated by that participant from analysis. All data and participant samples obtained up to the point of withdrawal will be used in the analysis.

9.6 Special Circumstances: COVID-19

9.6.1 Study Conduct / Risk Assessment

It is difficult to predict the time course of the COVID-19 pandemic. At all times the safety and welfare of study participants remains paramount.

The Chief Investigator may perform a risk assessment as necessary with relevant parties (e.g. DSMC, Regulatory Authorities) on the basis of the current UK COVID-19 situation, to determine:

1. Appropriateness to initiate vaccinations
2. Appropriateness to continue the trial once started
3. Necessity to extend trial duration

Dependant on the prevailing COVID-19 situation, the conduct of the trial may be modified in line with national policy in effect at the time in the interests of participant safety. Such measures may include but are not limited to:

1. Pausing further vaccinations
2. Modifying study visits and procedures (as detailed in the MERS003 Clinical Study Plan)
   e.g.: study visits conducted by phone or video calling where appropriate.

Any deviation from this protocol required due to national policy in effect at the time, will require a non-substantial/substantial amendment unless specifically permitted to do otherwise by the Sponsor, MHRA and REC.

9.6.2 COVID-19 Infection Control Measures at Visits

Infection control procedures including the safe handling of clinic visits, a COVID-19 secure workplace, maintaining staff safety will be included in local SOPs. If appropriate, these will be updated in line with NHS/UK Government policies.

9.6.3 Participants Under Quarantine

Given the evolving epidemiological situation both globally and in the UK, should a participant be under quarantine and unable to attend any of the scheduled visits, a telephone/video consultation may be arranged in order to obtain safety and the visit may be re-scheduled, depending on the timelines.

9.6.4 Participants Invited For COVID-19 Vaccination During the Trial

Participants would not be impeded in taking up an offer of a COVID-19 vaccine if offered through the national rollout. If a rollout offer coincides with a planned trial vaccine, the trial vaccine would be rescheduled to at least 14 days before or after the COVID-19 vaccine, within the allowable visit windows. This is in line with the UK Green Book COVID-19 vaccination recommendations for other

vaccines which recommends “at least 7 days” interval. It would also minimise the risk of any cross-attribution of reactogenicity, and minimise impact on immunology investigations.

9.6.5 Recording of COVID-19 infections and vaccinations

To facilitate interpretation of immunology outcomes, participants will be asked to report episodes of COVID-19 and COVID-19 vaccinations to the study team.

10 INVESTIGATIONAL PRODUCTS

All participants will receive the interventions as scheduled for their allocated group, as detailed in section 7.1. The term "investigational products" applies to either ChAdOx1 MERS or 0.9% saline placebo in this study.

10.1 ChAdOx1 MERS

ChAdOx1 MERS has been formulated and vialed under Good Manufacturing Practice conditions at the Clinical Biomanufacturing Facility (CBF), University of Oxford. At the CBF the vaccine will be certified and labelled for the trial by a Qualified Person (QP) before transfer to the clinical sites. The vaccine is supplied as a liquid in glass vials for intramuscular administration and will be stored at nominal -80°C in a secure freezer at the clinical sites.

Batch number 01N17-01 (used for this trial) is presented in A438 formulation buffer (10mM Histidine, 7.5% sucrose, 35mM NaCl, 1mM MgCl2, 0.1% PS80, 0.1mM Edetate Disodium, 0.5% ethanol, pH 6.6). The appearance of ChAdOx1 MERS is a slightly opaque frozen liquid, essentially free from visible particulates. During the manufacturing process of ChAdOx1 MERS an antibiotic named Geneticin (G418) is used.

The dose of ChAdOx1 MERS to be used in trial will be 5×10^{10} virus particles per administration.

Administration of Two Doses of Vaccine Drawn from Three Vials, with One Vial Being Shared

Minimal overage of ChAdOx1 MERS vials is available for this trial. Therefore, vial sharing may exceptionally be used such that two doses (of 5×10^{10} vp) are drawn up from three vials, with one vial being shared. This may only take place if both doses are administered within 1 hour of removal of each of the three vials from -80 degree storage. Vials will not re-enter storage and must be discarded if not used within this time. This method of using the second vial contents for two doses may only be used if two doses of ChAdOx1 MERS are planned to be given in a narrow time window. Full ChAdOx1 MERS administration details are covered by the relevant section of the MERS003 clinical study plan.

10.2 Saline Placebo (0.9% Sodium Chloride)

The placebo consists of 0.9% sodium chloride for injection acquired from an appropriate commercial medical supplier which will be stored in accordance with manufacturer's instructions.

10.3 Blinding of IMPs

ChAdOx1 MERS and saline placebo will not be supplied to sites in a blinded form. Instead, to maintain blinding they will be drawn up and prepared by unblinded staff out of sight of participants and blinded study staff. As ChAdOx1 MERS and 0.9% sodium chloride have a potentially different appearance, vaccine syringes will be obscured using an opaque covering. The administration equipment will have the same appearance and the same volume will be used for both ChAdOx1 MERS and placebo.

10.4 Storage of ChAdOx1 MERS

ChAdOx1 MERS requires storage at -80C throughout and will be transported to the study sites after authorised release for use in the clinical trial by the CBF Qualified Person (QP) and study approval by REC and MHRA. All movements of study medication between CBF and study sites, will be documented in accordance with relevant SOPs.

The study vaccine will be stored throughout the study in temperature monitored freezers with an auditable temperature record in accordance with the manufacturer's instructions and relevant SOPs.

Study freezers are connected to a monitoring system with 24-hour access to staff that are able to move the product in the event of significant temperature deviation.

10.5 Compliance with Trial Treatment

The study investigational product and placebo will be administered by trained unblinded study personnel and will be documented according to GCP guidelines and relevant SOPs. Issues related to compliance are therefore the responsibility of study personnel who have received appropriate training.

10.6 Accountability of The Trial Treatment

The ChAdOx1 MERS vaccine will be manufactured, packaged, labelled and supplied by CBF. All vaccines (vials and boxes) are labelled with a label specifying 'for clinical trial use only'.

The vaccine will be delivered and stored at the study sites pending authorised release for use in the clinical trial.

10.7 Concomitant Medication

The use of all concomitant medication prescribed or over-the-counter, will be recorded in the CRF. Concomitant medication that will result in temporary exclusion or withdrawal of volunteers from further vaccination are detailed in section 8.2. There is otherwise no restriction on the use of concomitant medication.

10.8 Emergency Medication and Procedures

All clinical staff are trained and can provide evidence of competency in the acute management of anaphylaxis reactions including the use of intra-muscular adrenaline. This is detailed in relevant SOPs and adrenaline is available at all times of vaccine administration and subsequent observation.

10.9 Post-Trial Treatment

Study medication will not be continued beyond the trial period.

10.10 Other Treatments (non-IMPs)

No other treatments other than those specified in the protocol above will be administered to trial participants.

10.11 Other Interventions

No other interventions other than those specified in the protocol above will be administered to trial participants.

11 SAFETY REPORTING

11.1 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of

a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

11.2 Adverse Events of Special Interest (AESI)

AESIs will be monitored and recorded throughout the study period. These will include the list below (Table 4 **AESIs**). Additionally, other adverse events (i.e. not listed below) may also be categorised by investigators as AESIs if scientifically warranted.

Table 4 AESIs

Respiratory	Acute Respiratory Distress Syndrome (ARDS)
	Pneumonitis
Neurological	Transverse Myelitis
	Generalised convulsion
	Guillain-Barre Syndrome (GBS)
	Acute Disseminated Encephalomyelitis (ADEM)
	Encephalopathy
	Encephalitis
	Stroke
Haematological / Vascular	Thrombocytopenia
	Thrombosis with Thrombocytopenia Syndrome (TTS)
	Major thrombosis (without thrombocytopenia)
	Heparin-Induced Thrombocytopenia
	Immune thrombocytopenic purpura
	Disseminated intravascular coagulation (DIC)
Immunological	Anaphylaxis
	Vasculitis
	Capillary Leak Syndrome
	Other Immune-Mediated Conditions
Other	Acute renal failure

11.3 Causality assessment

The relationship of each adverse event to the trial vaccine(s) or study procedures must be determined by a PI-delegated blinded clinician / investigator. The relationship of the adverse event with the study procedures will be categorized as not related, possibly related, probably related or definitely related. The delegated clinician will use clinical judgement to determine the relationship using the following definitions (Table 5):

Table 5 Guidelines for assessing the relationship of vaccine administration to an AE.

No Relationship		No temporal relationship to study product; ***and*** Alternate aetiology (clinical state, environmental or other interventions); ***and*** Does not follow known pattern of response to study product.
Related	Possible	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines.
	Probable	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***or*** Known pattern of response seen with other vaccines.
	Definite	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines.

11.4 Expectedness assessment

As no expected SARs are recorded in the reference safety information section of the ChAdOx1 MERS IB any SARs associated with ChAdOx1 MERS will be classified as unexpected and reported as SUSARs in this trial.

11.5 Severity Assessment

The severity of clinical and laboratory adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy and adolescent volunteers enrolled in preventive vaccine clinical trials. Severity scales will be listed in the trial specific clinical study plan. Site-specific laboratory adverse event severity gradings will be used.

11.6 Procedures For Collecting And Recording Adverse Events

Abnormal clinical findings from medical history, examination or blood tests, will be assessed by a blinded delegated clinician / investigator as to their clinical significance.

All AEs that are observed by the investigator or reported by the participant irrespective of their relatedness to the study medication will be recorded from the day of vaccination and until 28 days after each vaccination. These will be recorded in either the e-diary and/or eCRF. Outside of this window (i.e. from 28 days after each vaccination and until the point of a subsequent vaccination or until the final visit if vaccination course completed), non-serious AEs will only be recorded if they require medical attention (contact with GP, visit to emergency department). These will be recorded in the eCRF. All AEs will be collected via participant eDiaries and/or recorded by the blinded study team.

11.7 Solicited Adverse Events

Predefined local and systemic solicited AEs for reactogenicity assessment, as listed below (Table 6 Solicited Adverse Events), will be collected in an electronic diary for 7 days following administration of the vaccine. Participants will measure and record their temperature and the diameter of any injection site redness or swelling with the provided thermometer and tape measure and AE severity gradings will be calculated based on these measurements. For all other solicited AEs, solicited AE severity will be self-assessed by participants according to severity grading scales provided to them as defined in the trial specific clinical study plan.

Table 6 Solicited Adverse Events

Local solicited AEs	Systemic solicited AEs
Redness at the injection site (measured)	Fever (measured)
Warmth at the injection site	Chills
Itch at the injection site	Feverishness
Pain at the injection site	Joint pains
Swelling at the injection site	Muscle pains
	Fatigue
	Headache
	Nausea
	Malaise

11.7.1 Unsolicited Adverse Events

Unsolicited adverse events i.e. those collected through open questioning e.g. “did you experience any new illnesses?” (that are not solicited adverse events) and do not constitute SAEs or AESIs will be collected for 28 days following administration of the IMP. These will be recorded in the participant eDiary and relevant eCRF.

11.7.2 eDiary AEs

11.7.2.1 eDiary Collection of Solicited Adverse Events

Solicited adverse events will be recorded by the participant in an electronic diary and graded by the participant alone from the time of each vaccine administration for 7 days post-vaccination (day of vaccination and six subsequent days). Solicited adverse events will be reviewed daily by the clinical study team. If further action is required including face-to-face medical review, and/or prescribed medication this will be recorded by the study team in the eCRF. Causality will be assigned by blinded PI-delegated clinician / investigator. Any solicited AE which meets the definition of a SAE will be managed and reported as per Section 11.8.

1. eDiary Collection of Unsolicited Adverse Events

Unsolicited adverse events will be collected using the eDiary and reviewed at clinic visits. If clarification of any event is required then the study nurse or doctor will seek this from the participant during a clinical visit or by telephone call. These unsolicited adverse events will be recorded in the AE section of the eCRF. Unsolicited adverse events recorded in the eDiary will be severity graded by the

participant. Causality will also be assigned by the PI-delegated clinician / investigator as per section 11.2.

11.7.3 Observation Related AEs

Physical observations (e.g. temperature, blood pressure) of the patient will be taken at each visit These will be recorded in the eCRF. If abnormal, a severity grading will be assigned as per the trial specific clinical study plan.

11.7.4 Visit Elicited AEs

Participants will be asked about the occurrence of AEs and if any are elicited they will be recorded in the eCRF and graded by a blinded PI-delegated clinician / investigator.

11.7.5 Laboratory AEs

Severity grading for laboratory AEs are site specific and will be defined in the MERS003 clinical study plan. All changes in laboratory values will be recorded as AEs if they are of Grade 2 severity or above. Changes of laboratory values of Grade 1 severity may be recorded as AEs if they are judged to be clinically significant by a blinded PI-delegated clinician / investigator.

If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and advised with regards appropriate medical care. If abnormal laboratory values are the result of pathology for which there is an overall diagnosis then this diagnosis should be reported as one AE only.

A Grade 4 laboratory AE will be considered a SAE.

11.7.6 Notes on Recording AEs

Pre-existing medical conditions (present prior to enrolment into the study) are considered “concurrent medical conditions” and should not be recorded as AEs. However, if the participant experiences a worsening or complication of the condition, the worsening or complication should be recorded as an AE. Study staff will ensure that the AE term recorded captures the change in the condition (e.g., “worsening of”).

Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms (including abnormal laboratory values) should not be recorded as additional AEs.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect at which point it would fall within the definition of “serious” and the congenital abnormality of birth defect would be reported as an SAE. Pregnancy notification and follow-up reports on pregnancy outcome will be provided to the DSMC with ongoing consent of the participant.

11.7.7 Following Up of AEs

AEs considered related to the active vaccine or placebo will be followed until resolution, the event is considered stable or until non-study causality is assigned. At the end of the study all other ongoing/open AEs will be assessed by a blinded PI-delegated clinician / investigator, to ensure if not already done so, adequate medical follow-up (if required) has been arranged, e.g. referral to participant’s general practitioner.

All AEs that result in a participant’s withdrawal from the study will be, subject to participant consent, followed up where possible until a satisfactory resolution occurs, or until a non-study related causality is assigned. This will involve an end of study assessment at which the requirement for further appropriate care under medical supervision will be determined. If required the participant will be

referred to their GP for ongoing medical supervision, until symptoms cease or the condition is deemed resolved or stable.

11.8 Reporting Procedures for Serious Adverse Events

SAEs will be collected throughout the entire trial period (from first vaccination to the final study visit or withdrawal).

All SAEs must be reported on the SAE form (paper or electronic) to the CI (as delegated by the Sponsor) immediately (or within 24 hours at the latest) of the site study team becoming aware of the event being defined as serious. Causality of SAEs will be assessed by the blinded investigator.

The CI on behalf of the Sponsor will be responsible for unblinding in the event of serious adverse reactions and will be responsible for the reporting of any SUSARs (as detailed in section 11.9).

All SAE will be reported to the DSMC Chair (or nominated designee) within 24 hours of discovery or notification of the event.

Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form emailed to the CI and DSMC Chair (or nominated designee).

The chair of the DSMC (or nominated designee) will perform an independent review of SAEs and request any further information required in a manner adherent to the procedures and timelines of the DSMC Charter. Documentation of this review will be kept in the TMF. The DSMC will provide independent real-time safety assessment throughout the study as described below.

11.8.1.1 Events exempt from reporting as SAEs

Hospitalisation (including inpatient or outpatient hospitalisation) for an elective procedure for a pre-existing condition that has not worsened unexpectedly does not constitute an SAE. Emergency department attendances should not routinely be reported as SAEs unless they meet the SAE definition described in section 11.1.

11.9 SUSAR Reporting

All SUSARs will be reported to the Sponsor, relevant Research Ethics Committee and to the MHRA. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. Any additional relevant information should be sent within eight days of the report.

The CI or Co-Investigator will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

11.10 Development Safety Update Report

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

The Development International Birth Date (DIBD) for ChAdOx1 MERS is 20th December 2017 and the data lock point of each DSUR will be the last day of each one-year reporting period (19th December).

11.11 Safety Profile Review

The safety profile will be reviewed on a day to day basis by the investigators using a blinded electronic diary, adverse events CRF and safety bloods to date. Any concerns will be referred to the blinded CI.

If the CI remains concerned they may consider unblinding and/or escalation to the unblinded DSMC as required.

11.12 Trial Management Group

The CI and study site investigators will form the trial management group (TMG) and will provide on-going management of the trial.

11.13 Data Safety Monitoring Committee (DSMC)

For this study, an independent DSMC will be appointed. There will be a minimum of three appropriately qualified committee members of whom one will be the designated chair. The DSMC will operate in accordance with the trial specific DSMC charter, which will be established before recruitment starts. The Chair of the DSMC may also be contacted for advice where the Chief Investigator feels independent advice or review is required.

11.14 Safety reviews

11.14.1 Sequence of enrolment and vaccination

An initial cohort of 12 participants (consisting of the first 6 participants in group 1 and first 6 participants in group 2) will be enrolled and receive their first vaccine prior to the enrolment of further volunteers. Enrolment of the remaining participants in the trial will only continue after a positive decision from the DSMC following the first DSMC safety review (detailed below in section 0).

Administration of the second doses of vaccine will also initially be limited to 12 participants (6 participants in group 1 and 6 participants in group 2). Administration of second doses to the remaining participants will only continue after a further DSMC safety review (detailed below in section 0).

11.14.2 DSMC Safety Reviews

DSMC data review will be done as follows:

1. Formal review of the safety profile after 7 days of safety data has been collected from the first 6 participants in Group 1 and first 6 participants in Group 2 to receive the first dose of vaccine. This review will decide on progression to enrolling and administering the first vaccine to the remaining volunteers in the trial.
2. Formal review of the safety profile after 7 days of safety data has been collected from the first 6 participants in Group 1 and first 6 participants in Group 2 to receive the second dose of vaccine. This review will decide on progression to administering the second dose to the remaining volunteers in the trial.
3. Formal review of the safety profile including safety data up to 28 days after the second dose of vaccine has been administered to all participants.
4. Independent review following any SAE deemed to be related to the trial active vaccine or placebo.
5. Unscheduled reviews on request of the study management committee at a demand and frequency determined by the severity of reported adverse events.

From these reviews the DSMC will make recommendations to the study investigators on whether there are any ethical or safety reasons why the trial should not continue. A summary of all blinded and unblinded AEs and SAEs to date will be provided to the DSMC on request.

The outcome of each DSMC review will be communicated directly to the TMG and documentation of all reviews will be kept in the TMF.

11.15 Procedures to be followed in the event of abnormal findings

Laboratory parameters for inclusion/exclusion in the trial will be considered on an individual basis, with investigator discretion for interpretation of results and the need for repeated tests. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator.

11.16 Safety Holding Rules

11.16.1 Group holding rules

The group holding rules are as follows;

1 Solicited local adverse events:

If 2 or more participants in a group experience the same grade 3 solicited local adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at grade 3 for >48 hrs.

2 Solicited systemic adverse events:

If 2 or more participants in a group experience the same grade 3 solicited systemic adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at grade 3 for >48 hrs.

3 Unsolicited adverse events:

If 2 or more participants in a group experience the same grade 3 unsolicited adverse event (including the same laboratory adverse event) that is considered possibly, probably or definitely related to vaccination and persists at grade 3 for > 48hrs.

4 A serious adverse event considered possibly, probably or definitely related to vaccination occurs

5 Death occurs

6 A life-threatening reaction occurs

If a holding rule has been met the sponsor will inform the regulatory authority. The DSMC will be asked to review relevant safety data and provide a recommendation on further dosing. If the DSMC recommend to restart dosing, the request (with pertinent data) must be approved by the regulatory authority prior to restarting dosing. The DSMC review would consider:

- The relationship of the AE or SAE to the vaccine.
- The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.
- If appropriate, additional screening or laboratory testing for other volunteers to identify those who may develop similar symptoms and alterations to the current Participant Information Sheet (PIS).
- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The vaccine manufacturer (CBF) will also be notified if a holding rule is activated or released. All vaccinated volunteers will be followed for safety until the end of their planned participation in the

study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

In addition to these pre-defined criteria, the study can be put on hold upon advice of the DSMC, CI, Study Sponsor, Regulatory Authority or Ethical Committee(s), for any single event or combination of multiple events which they deem jeopardise the safety of the volunteers or the reliability of the data.

11.16.2 Individual Holding Rules

In addition to the above stated group holding rule, stopping rules for individual volunteers will apply (i.e. indications to withdraw individuals from further vaccinations):

1. Local reactions: Injection site ulceration, abscess or necrosis
2. Systemic solicited adverse events: the volunteer develops a Grade 3 systemic solicited adverse event considered possibly, probably or definitely related to vaccination within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for > 48hrs
3. Laboratory AEs: the volunteer develops a Grade 3 laboratory adverse event considered possibly, probably or definitely related to vaccination within 7 days after vaccination and persisting at Grade 3 for > 48hrs (site-specific laboratory AE reference ranges as per protocol section Appendix C: Severity Grading Scales).
4. Unsolicited adverse events:
    1. the volunteer has a Grade 3 adverse event considered possibly, probably or definitely related to vaccination, persisting continuously at Grade 3 for >48hrs.
    2. the volunteer has a serious adverse event considered possibly, probably or definitely related to vaccination.
    3. the volunteer has an acute allergic reaction or anaphylactic shock following the administration of an investigational product.

If a volunteer fulfils any of the temporary exclusion criteria at the scheduled time of a second administration of investigational product, the volunteer will not receive the vaccine at that time. The vaccine may be administered to that volunteer at a later date within the time window specified in the protocol or they may be withdrawn from the study at the discretion of the Investigator.

All vaccinated volunteers will be followed for safety until the end of their planned participation in the study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

12 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

The investigators will populate the content of participants' CRFs, which will be in a paper and/or electronic format using a REDCap database. This database is stored on a secure University of Oxford server and has restricted access and is password-protected with accountability records. These data include safety data, laboratory data (both clinical and immunological) and outcome data. All information transcribed to and from the REDCap database is by encrypted (Https) transfer.

Each study participant will have a unique screening number which will be allocated following the taking of informed consent and all names and/or identifying details are not included in any study data electronic file. After enrolment the participants will be identified by a study specific participant number which will be determined by enrolment order. Samples sent to laboratories for processing will be identified by a trial number and participant number only.

12.1 Data Integrity

Data collection and storage will be inspected throughout the study by internal (performed by the Oxford Vaccine Group) monitoring. The Sponsor may also audit the trial data.

12.2 Data Archiving and Storage

Study data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 5 years after the study has finished. Volunteers who complete online screening or telephone screening only (before informed consent) will not have data kept beyond the end of the trial. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the site at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. Participants' bank details will be stored in line with the site financial policy. De-identified research data maybe be stored indefinitely.

12.3 Source Data

Source documents are original documents, data, and records from which participants' CRF data are populated. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. In this study CRF entries will be considered source data where it is the site of the original recording. All documents will be stored safely under strict confidentiality and with restricted access. On all study-specific documents, other than the signed consent and the participant contact sheet, the participant will be referred to by the study participant number/code only.

12.4 Access to Data

Direct access will be granted to authorised representatives from the sponsor/host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.5 Data Recording and Record Keeping

The investigators will populate the content of participants' CRFs and all the study data will be recorded directly into an Electronic Data Capture (EDC) system (e.g. REDCap, or similar) or onto a paper source

document for later entry into EDC if direct entry is not available. Any additional information that needs recording but is not relevant for the CRF (such as signed consent forms etc.) will be recorded on a separate paper source document. All documents will be stored safely and securely in confidential conditions.

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

Each study participant will have a unique participant number which will be allocated at the time a screening visit is booked and all names and/or identifying details are not included in any study data electronic file, with the exception of the electronic diaries, for which consent will be obtained to store the participant email address, which is necessary for the system to function. Only site research staff and sponsor data managers have access to view the email address. After enrolment the participants will be identified by a study specific participants number and/or code. With the exception of clinical safety blood samples which are sent to local clinical laboratories and follow local sample labelling requirements, samples sent to laboratories for processing will be identified by trial number and participant number only.

The study team will use names and contact details to contact participants about the research study, and make sure that relevant information about the study is recorded for their care, in relation to their health during the study and to oversee the quality of the study. At the completion of the study, unless participants consent otherwise (e.g. requesting to be informed of other trials), participant's personal details will not be used to contact them other than exceptional circumstances concerning their safety. If consent is provided by participants to take part in another study carried out by the study site, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition. If participants provide specific consent, we will use personal identifiable data to invite participants for future research.

Bank details will be stored for time limited periods set by local site financial policies.

13 STATISTICS

13.1 Study Analyses

13.1.1 Descriptive Statistical Methods

The analyses for this study will be descriptive in purpose and will not include any hypothesis testing or presentation of p values for group comparisons or power calculation.

13.1.2 The Number of Participants

Up to 84 participants will be recruited to the study and allocated to groups 1 or 2. Participants will be replaced only if they have not received a dose of vaccine. There has been no formal power calculation to determine this figure as the study is primarily descriptive. The number of participants has therefore been chosen to pragmatically reflect logistical and budgetary constraints.

13.1.3 The Level of Statistical Significance

There will be no statistical significance testing. All confidence intervals for descriptive analyses will be set at 95%.

13.1.4 Criteria For Termination of the Trial

The Chief Investigator and Data Safety Monitoring Committee will have the right to terminate the study at any time on grounds of participant safety. If the study is prematurely terminated the investigator will promptly inform the participants and will ensure appropriate therapy and follow-up. If the study is halted, the MHRA, and relevant Ethics Committee will be notified within 15 days of this occurring.

In the event of the trial being terminated early, follow-up of enrolled participants will still continue as detailed in section 2 for safety reasons, with the exception that further vaccination will not be given and study procedures will be modified to monitor safety only.

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

All available data will be used in the analyses and there will be no imputations for missing data. Participants will be analysed according to the group to which they were assigned.

13.1.6 Inclusion in Analysis

All participants with any available data will be included in the analyses.

13.1.7 Interim Analysis

An interim analysis of safety outcomes will occur at the interim safety reviews as described in Section 11.14 Interim safety reviews.

14 ETHICS AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

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

14.2 Guidelines for Good Clinical Practice

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

14.3 Approvals

Following sponsor approval, the protocol, informed consent form, participant information sheet and required material will be submitted to an appropriate Research Ethics Committee (REC), HRA (if relevant), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4 Transparency in Research

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

14.5 Reporting

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

14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which requires data to be anonymised as soon as it is practical to do so.

14.7 Participant Financial Compensation

Each participant is compensated for their time and inconvenience based on the following figures:

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

Remuneration is on a *pro rata* basis should a participant not complete all visits and/or study requirements. Each participant can therefore receive a maximum of £360. Additional reimbursement for unscheduled visits at £45 per visit will also be provided.

15 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

15.1 Investigator procedures

Approved site-specific standard operating procedures (SOPs) will be used at all clinical and laboratory sites.

15.2 Risk Assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and Standard Operating Procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities. Approved and relevant SOPs will be used at all clinical and laboratory sites.

15.3 Monitoring

Monitoring will be performed according to GCP by OVG. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Trial sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

15.4 Protocol deviation

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

15.5 Audit & inspection

The QA manager at OVG conducts systems based internal audits to check that trials are being conducted according to local procedures and in compliance with GCP and applicable regulations.

The Sponsor, trial sites, and ethical committee(s) may carry out audits to ensure compliance with the protocol, GCP and appropriate regulations.

GCP inspections may also be undertaken by the MHRA to ensure compliance with protocol and the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. The Sponsor will assist in any inspections and will support the response to the MHRA as part of the inspection procedure.

16 FINANCING AND INSURANCE

16.1 Financing

The study is funded by the Coalition for Epidemic Preparedness Innovations (CEPI).

16.2 Insurance

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

16.3 Contractual Arrangements

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

17 SERIOUS BREACHES

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

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

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

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor will be informed within one working day.

18 PUBLICATION POLICY

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

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

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University’s technology transfer office, Oxford University Innovations.

20 ABBREVIATIONS

Abbreviations	
AdC	Chimpanzee adenovirus
AdC68	Chimpanzee Adenovirus serotype 68
ADEM	Acute Disseminated Encephalomyelitis
AdHu	Human adenovirus
AdHu5	Human adenovirus serotype 5
AE	Adverse event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
BAC	Bacterial artificial chromosome
CBF	Clinical Biomanufacturing Facility
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
CDC	Centers for Disease Control and Prevention
ChAd63	Chimpanzee Adenovirus serotype 63
ChAdOx1	Chimpanzee Adenovirus Ox1
ChAdOx2	Chimpanzee Adenovirus Ox2
ChAdOx1 MERS	Recombinant simian adenovirus ChAdOx1 vector expressing the MERS spike protein
ChAdOx1 nCov-19	The ChAdOx1 nCov-19 vaccine against COVID-19. Also known as: The Oxford/AstraZeneca COVID-19 vaccine, AZD1222, Vaxzevria, COVID-19 Vaccine AstraZeneca
CI	Chief Investigator
CMV	Human cytomegalovirus
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
EBV	Epstein Barr virus
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunospot assay
EMA	European Medicines Agency
ePRO	Electronic participant reported outcomes
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
GP	General Practitioner
HBsAg	Hepatitis B surface antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HEK	Human embryonic kidney

Abbreviations	
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
IB	Investigators Brochure
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IFN	Interferon
IM	Intramuscular/intramuscularly
IMP	Investigational medicinal product
ISF	Investigator Site File
IU	Infectious units
IUD	Intrauterine device
IUS	Intrauterine system
JCVI	Joint Committee on Vaccination and Immunisation
LVLV	Last volunteer last visit
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome-Related Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
MVA	Modified Vaccinia Virus Ankara
NCT Number	National Clinical Trial number
NHP	Non-human primate
OVC	Oxford vaccine centre
OVG	Oxford vaccine group
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PEP	Post-exposure prophylaxis
PHE	Public Health England
PrEP	Pre-exposure prophylaxis
PIS	Participant information sheet
PT	Preferred terms
QP	Qualified Person
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance (Formerly named Clinical Trials and Research Governance)
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SFC	Spot forming cells
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TOPS	The Over-Volunteering Prevention System
VAERS	Vaccine Adverse Event Reporting System

Abbreviations	
VNA	Virus neutralising assay
vp	Viral particles
WHO	World Health Organisation
WOCBP	Women of Childbearing Potential

21 REFERENCES

1 WHO. MERS Situation update, June 2022. (2022).

2 Badawi, A. & Ryoo, S. G. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *International Journal of Infectious Diseases* **49**, 129-133, doi:http://dx.doi.org/10.1016/j.ijid.2016.06.015 (2016).

3 Assiri, A. *et al.* Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis* **13**, 752-761, doi:10.1016/s1473-3099(13)70204-4 (2013).

4 WHO. Fact Sheet: Middle East respiratory syndrome coronavirus (MERS-CoV). (WHO, 2015).

5 Mackay, I. M. & Arden, K. E. MERS coronavirus: diagnostics, epidemiology and transmission. *Virology journal* **12**, 222, doi:10.1186/s12985-015-0439-5 (2015).

6 McNeil, M. M. *et al.* Adverse events following adenovirus type 4 and type 7 vaccine, live, oral in the Vaccine Adverse Event Reporting System (VAERS), United States, October 2011–July 2018. *Vaccine* **37**, 6760-6767, doi:https://doi.org/10.1016/j.vaccine.2019.08.087 (2019).

7 Folegatti, P. M. *et al.* Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* **396**, 467-478 (2020).

8 Ramasamy, M. N. *et al.* Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *The Lancet* **396**, 1979-1993 (2020).

9 Voysey, M. *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet* **397**, 99-111 (2021).

10 Voysey, M. *et al.* Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *The Lancet* **397**, 881-891 (2021).

11 Folegatti, P. M. *et al.* Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. *The Lancet Infectious Diseases* **20**, 816-826 (2020).

12 Bosaeed, M. *et al.* Safety and immunogenicity of ChAdOx1 MERS vaccine candidate in healthy Middle Eastern adults (MERS002): an open-label, non-randomised, dose-escalation, phase 1b trial. *The Lancet Microbe* **3**, e11-e20 (2022).

13 Koch, T. *et al.* Safety and immunogenicity of a modified vaccinia virus Ankara vector vaccine candidate for Middle East respiratory syndrome: an open-label, phase 1 trial. *The Lancet Infectious Diseases* **20**, 827-838 (2020).

14 Emary, K. R. *et al.* Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial. *The Lancet* (2021).

15 Folegatti, P. M. *et al.* Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet (London, England)* **396**, 467-468 (2020).

16 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).

17 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).

18 MHRA. Public Assessment Report National procedure Vaxzevria (previously COVID-19 Vaccine AstraZeneca, suspension for injection) COVID-19 Vaccine (ChAdOx1-S [recombinant]) PLGB 17901/0355 AstraZeneca UK Limited 24 June 2021.

19 Barrett, J. R. *et al.* Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. *Nat Med* **27**, 279-288, doi:10.1038/s41591-020-01179-4 (2021).

20 Public Health England 2020 Publications approval reference: 001559 Clinical guidance for healthcare professionals on maintaining immunisation programmes during COVID-19 First published: June 2020. Last updated: November 2020.

22 Appendix A: Investigator Signature and Declarations

Statement of Compliance

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

Chief Investigator Approval, Agreement and Conflict of Interest statement

I have read the trial protocol V4.1, dated 18th July 2025 and agree to conduct the trial in compliance with the protocol, the principles of Good Clinical Practice and all applicable regulatory requirements.

Conflict of interest statement: Nil

Chief Investigator Prof Maheshi Ramasamy	**Signature**	**Date:**

Lead Statistician Approval, Agreement and Conflict of Interest statement

I have read the trial protocol V4.1, dated 18th July 2025 and agree to conduct the trial in compliance with the protocol, the principles of Good Clinical Practice and all applicable regulatory requirements.

Conflict of interest statement: Nil

Lead Statistician Dr Merryn Voysey	**Signature**	**Date:**

Principal Investigator Approval, Agreement and Conflict of Interest statement

I have read the trial protocol V4.1, dated 18 July 2025 and agree to conduct the trial in compliance with the protocol, the principles of Good Clinical Practice and all applicable regulatory requirements.

Conflict of interest statement:

Principal Investigator (Print name)	**Signature**	**Date:**

23 Appendix B: Document History

Amendment no.	Protocol version	Date issued	Authors	Changes
n/a	1.0	04 JAN 2023	Daniel Jenkin, Ilsa Haeusler, Bilyana Stoilova, Maheshi Ramasamy	Document created
n/a	2.0	15 MAR 2023	Daniel Jenkin, Ilsa Haeusler, Bilyana Stoilova, Maheshi Ramasamy	Response to MHRA grounds for non acceptance. • Section 10.7 Concomitant Medications. This section now cross-references the temporary exclusion criteria section which provides instruction for investigators on concomitant medication that lead to temporary exclusion from further vaccination. • Section 11.14.3 Other Safety Reviews which detailed the CI safety review following second dose administration has been removed and replaced with an additional scheduled DSMC review detailed in Section 11.14.2 DSMC Safety Reviews. • Section 11.16.1 Group Safety Holding rules thresholds updated. • Section 11.16.2 Inividiual Holding Rules thresholds updated. • Section 11.8 SAE reporting. Clarified that the Sponsor is respsonible for unblinding in the event of SARs. Clarified that SAEs must be reported to the sponsor immediately or within 24 hours at the latest. Response to REC Queries: • Section 8.2 Temporary Exclusion Criteria updated to clarify that *non-adenoviral* COVID-19 vaccines may be given up to 14 days of the study vaccines • Section 12 Data Management and Section 14.6 Participant Confidentiality –

				removed references to participant initials being included on case report forms
Amendment 01 - NSA01	2.1	21 APR 2023	Bilyana Stoilova, Daniel Jenkin, Ilsa Haeusler, Maheshi Ramasamy	Non-substantial changes to the protocol: • Clarification on end of trial results reporting (Section 14.4) and bank details retention time (Section 12.2) • Correction of typographical error in eligibility criteria about contraception (Section 8.1) • Listing of Oxford University Hospitals NHS Foundation Trust as a non-recruiting NHS site, which was already listed in the IRAS but omitted from the protocol in error Section 4.2, Table 2 D14, D28 and V2+28 correction of visit window errors
Amendment 02 - NSA02	2.2	25 MAY 2023	Bilyana Stoilova	Non-substantial changes to the protocol: • Addition of Liverpool University Hospitals NHS Foundation Trust as Other Trial Site, as per the HRA Hub and Spoke study delivery model
Amendment 03 - SA1	3.0	02 JUN 2023	Daniel Jenkin, Ilsa Haeusler, Bilyana Stoilova	• (Section 4.2 - Schedule of procedures, Section 6.1 – Outcomes, Section 9.5 - Study visits, Section 9.5.7.3 – Nasosorption) Addition of optional nasal sampling using nasosorption strips • Section 3 Planned Trial Period Updated • Section 9.5.1 Vaccination visits: listed the provision of Medic Alert Contact Card with 24 hour emergency telephone number, which document has been submitted in the initial document package and process outlined in the PIS but omitted from the protocol in error • Section 10.1 ChAdOx1 MERS updated to include “Administration of Two Doses of Vaccine Drawn from Three Vials, with One Vial Being Shared” details • 22 Appendix A: Investigator Signature and Declarations: protocol version and date added

Amendment 06 - NSA04	3.1	30 Dec 2024	Bilyana Stoilova	Non-substantial changes to the protocol: • Section 3 Planned Trial Period Updated
Amendment 07 - SA03	4.0	19 Feb 2025	Bilyana Stoilova, Daniel Jenkin	Substantial changes to the protocol: • Section 7.3 End of trial definition has been updated
Amendment 08 – NSA05	4.1	18 July 2025	Thejaswini Madupuri	Non-substantial changes to the protocol: Section 3 Planned Trial Period Updated

24 Appendix C: Severity Grading Scales

Table 7. Severity grading criteria for local adverse events *erythema measured at point of greatest diameter. Note erythema <2.0cm is an expected consequence of skin puncture and will therefore not be considered an adverse event. ****graded using functional scale as well as actual measurement

Adverse Event	Grade	Intensity
Pain at injection site	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.0 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Induration/Swelling at injection site**	1	2.0 – 5 cm and does not interfere with activity
	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis

Table 8. Severity grading criteria for systemic AEs. NB: A&E assessment in itself does not constitute a SAE. Refer to Section 11.1 for SAE definition

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	A&E visit or hospitalisation for hypotensive shock
Diarrhoea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	A&E visit or hospitalisation
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	A&E visit or hospitalisation
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	A&E visit or hospitalisation
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	A&E visit or hospitalisation
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	A&E visit or hospitalisation

Table 9. Severity grading criteria for physical observations (applies to adults only). *Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
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 hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalisation for malignant hypertension
Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalisation for malignant hypertension
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80	A&E visit or hospitalisation for hypotensive shock
Respiratory Rate (breaths per minute)	17 - 20	21-25	>25	Intubation

Table 10 Liverpool Vaccine Group Site Specific Severity Grading Scale for Laboratory AEs

Blood Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	g/L	31 - 28	27 - 25	≤ 24	-
Alkaline phosphate	U/L	143 - 260	261 - 390	391 - 1300	≥ 1301
ALT (female)	U/L	36 - 83	84 - 165	166 - 330	≥ 331
ALT (male)	U/L	45 - 103	104 - 205	206 - 410	≥ 411
Bilirubin – (abnormal ALT/ALP)	µmol/L	23 - 26	27 - 32	33 - 37	≥ 38
Bilirubin – (normal ALT/ALP)	µmol/L	23 - 32	33 - 42	43 - 63	≥ 64
Creatinine (female)	µmol/L	92 - 126	127 - 252	≥ 253	-
Creatinine (male)	µmol/L	114 - 156	157 - 312	≥ 313	-
Eosinophils	cells/µL	0.65 - 1.50	1.51 - 5.00	≥ 5.01	-
Hemoglobin (female)	g/l	113 - 105	104 - 90	89 - 80	≤ 79
Hemoglobin (male)	g/l	125 - 115	114 - 100	99 - 85	≤ 84
Lymphocytes	cell/mm3	0.99 - 0.75	0.74 - 0.50	0.49 - 0.25	≤ 0.24
Neutrophils	cell/mm3	1.99 - 1.5	1.49 - 1	0.99 - 0.51	≤ 0.5
Platelets	cell/mm3	140 - 125	124 - 100	99 - 25	≤ 24
Potassium	mEq/L	5.4 - 5.5	5.6 - 5.7	5.8 - 6.8	≥ 6.9
Potassium	mEq/L	3.3 - 3.2	3.1 - 3	2.9 - 2.6	≤ 2.5
Sodium	mmol/L	132 - 130	129 - 128	127 - 123	≤ 122
Sodium	mmol/L	147 - 148	149 - 150	151 - 156	≥ 157
Urea	mmol/L	8.2 - 9.3	9.4 - 11.0	≥ 11.1	-
WBC	cells/µL	3.49 - 2.50	2.49 - 1.50	1.49 - 1.00	≤ 0.99
WBC	cells/µL	11.50 - 15.00	15.01 - 20.00	20.01 - 25.00	≥ 25.01

Table 11 Oxford Vaccine Group Site Specific Severity Grading Scale for Laboratory AEs

Blood Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	g/L	31 - 28	27 - 25	≤ 24	-
Alkaline phosphate	U/L	143 - 260	261 - 390	391 - 1300	≥ 1301
ALT (female)	U/L	49 - 112	113 - 225	226 - 450	≥ 451
ALT (male)	U/L	No difference between male and female			
Bilirubin – (abnormal ALT/ALP)	µmol/L	23 - 26	27 - 32	33 - 37	≥ 38
Bilirubin – (normal ALT/ALP)	µmol/L	23 - 32	33 - 42	43 - 63	≥ 64
Creatinine (female)	µmol/L	No difference between male and female			
Creatinine (male)	µmol/L	114 - 156	157 - 312	≥ 313	-
Eosinophils	cells/µL	0.65 - 1.50	1.51 - 5.00	≥ 5.01	-
Hemoglobin (female)	g/l	113 - 105	104 - 90	89 - 80	≤ 79
Hemoglobin (male)	g/l	125 - 115	114 - 100	99 - 85	≤ 84
Lymphocytes	cell/mm3	0.99 - 0.75	0.74 - 0.50	0.49 - 0.25	≤ 0.24
Neutrophils	cell/mm3	1.99 - 1.5	1.49 - 1	0.99 - 0.51	≤ 0.5
Platelets	cell/mm3	140 - 125	124 - 100	99 - 25	≤ 24
Potassium	mEq/L	5.4-5.5	5.6-5.7	5.8-6.8	≥ 6.9
Potassium	mEq/L	3.3 - 3.2	3.10	3 - 2.5	≤ 2.4
Sodium	mmol/L	132 - 130	129 - 128	127 - 123	≤ 122
Sodium	mmol/L	146 - 147	148-149	150-155	≥ 156
Urea	mmol/L	8.2 - 9.3	9.4 - 11.0	≥ 11.1	-
WBC	cells/µL	3.49 - 2.50	2.49 - 1.50	1.49 - 1.00	≤ 0.99
WBC	cells/µL	11.50 - 15.00	15.01 - 20.00	20.01 - 25.00	≥ 25.01